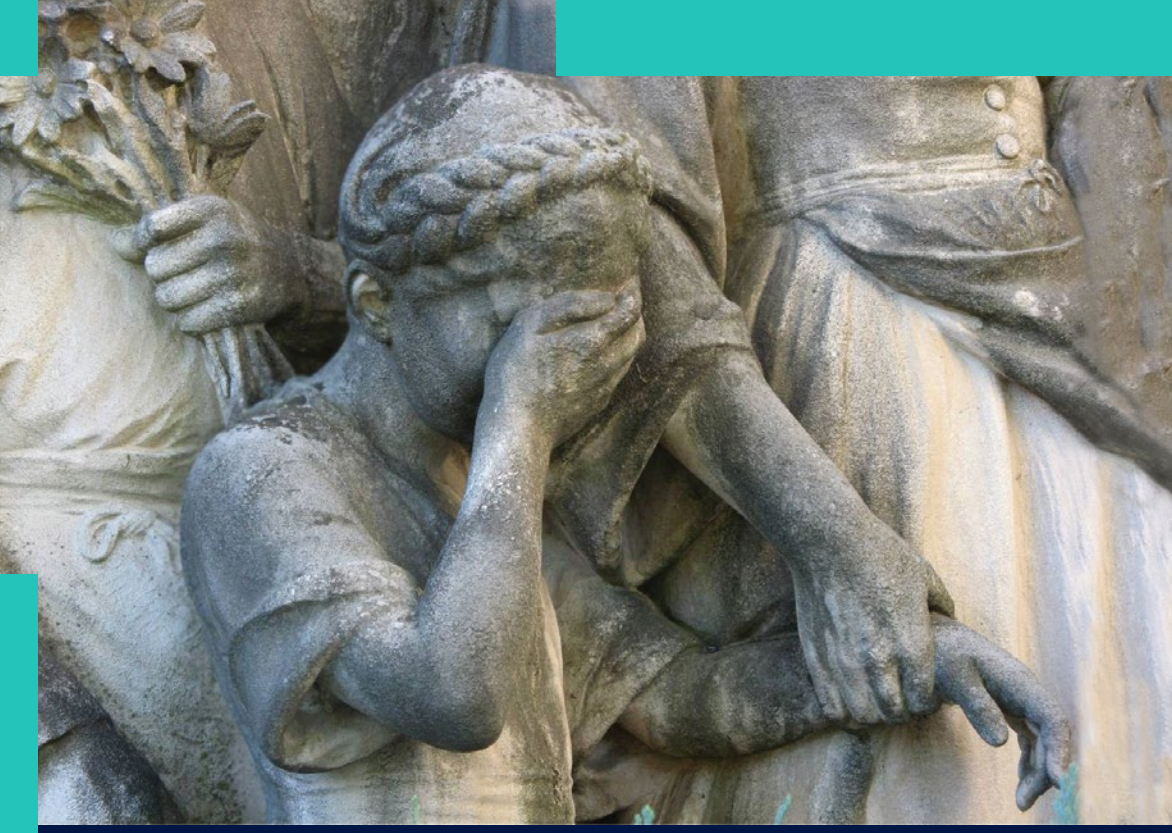

Forensic Pathology of Infancy and Childhood

Kim A. Collins · Roger W. Byard
Editors

Springer Reference

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With 686 Figures and 123 Tables

Springer Reference

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To David and Dontrell
Kim A. Collins

To Renée and Lucy
Roger W. Byard

Preface

The field of pediatric forensic pathology and medicine has been repeatedly discussed and evaluated in recent years with a number of concerns being raised about the quality of opinions and diagnoses. Although it is easy to define, as the study of injury and disease in children and how this applies to the law, problems have arisen in determining how it should be taught, certified, and practiced. Studies and commentaries that have evaluated the quality of autopsy investigations of childhood deaths have often identified inadequacies and omissions.

These deficits have been dealt with to some extent by the development of international protocols and codes of practice. However, as the number of cases being handled by individual institutions may be low, full-time specialized pediatric forensic pathologists may not be employed, leaving other pathologists to take on responsibility for these cases. Unfortunately, it is not always appropriate to extrapolate from adult to pediatric practice, as an understanding of the effects of normal growth and development are required, in addition to knowledge of the range of sometimes very rare disorders that may manifest in the young, and an awareness of the type of ancillary testing that is required. The ability to then synthesize and interpret these results is a vital part of pediatric forensic practice. All of this is not helped by the fact that our understanding of a number of childhood entities is still in evolution.

It was against this background that a decision was taken to provide a state-of-the-art text that would cover many facets of the forensic pathology of infancy and childhood, with contributions from experts from a wide variety of backgrounds and number of different countries. As the reader will see, the following chapters concentrate on inflicted and accidental trauma in the young in addition to covering the very variable manifestations of natural conditions resulting in unexpected death from *in utero* life through to adolescence. The pathological diagnosis of pediatric conditions is discussed in some detail with additional chapters dealing with scene examinations, the biomechanics of injury, toxicological issues, ancillary testing, death certification, and expert evidence.

Given the very eclectic and dynamic nature of many areas within pediatric forensic practice, the authors fully realize that not every topic will have been covered. In addition some authors may have presented interpretations and opinions that not all readers will agree with. This is, however, the very foundation of

academic debate that is so important in the advancement of knowledge. It is hoped, therefore, that both general and specialist readers will find something of use between the covers of these two volumes that will enhance their daily practice and so improve the quality of the care of our children.

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A History of Pediatric Forensic Pathology

1

Harold Sanchez

Contents

Abstract

In contemporary society, few news items provoke the shock and outrage that follow reports of child abuse and murder. So visceral is this response that it would be easy to assume that all peoples throughout history have felt the same way. This is not the case. Throughout much of history, children in almost all societies have been exploited, abused, conscripted, and murdered often by those closest to them and often without any consequences. Prior to the advent of effective public health measures, vaccination programs, and antibiotics, the high rate of infant and child mortality caused by natural diseases provided cover for the widespread practice of infanticide. Society and the medical community were painfully slow to recognize the problem. It is telling that charitable organizations created to protect the welfare of animals predate

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societies for the prevention of cruelty to children. If pediatrics is a relatively new medical specialty (the American Academy of Pediatrics was established in 1930), then pediatric pathology (Paediatric Pathology Society, founded in 1955) is very recent, and pediatric forensic pathology is still in its infancy. Much has been accomplished in a very short time, but recent reviews of the field (e.g., the Goudge Report) highlight how much remains to be done to firmly establish pediatric forensic pathology as a mature specialty.

Introduction

Although physicians have recognized common childhood illnesses since the beginning of recorded history, pediatrics as a specialty separate from internal medicine and obstetrics and gynecology is a fairly recent development. While pediatricians have treated the natural diseases of children since the 1850s, the role of physicians in recognizing, treating, and preventing violent injuries and deaths in infants and children (and distinguishing those from natural disease) is much more recent. The history of pediatric forensic pathology is a story of recognizing what has been right before our eyes, energetically compensating for long periods of neglect, and then contritely correcting for overcompensation. The tendency for vigorous response is understandable. There are few things that ignite passions more than matters that involve the welfare of children. Pediatric forensic pathology deals with suspected violent child deaths. The written opinions issued by pathologists and their expert testimony in court are often crucial factors in court decisions about the custody of surviving children and the liberty of accused parents.

In some ways the history of pediatric forensic pathology is very much like any other medical history. Developments in the field depend not just on the academic work of physicians, but also on the social and political environment. Without the confidence of the public and the financial and legal support of the government, no medical field can hope to get very far. What is somewhat unusual about pediatric forensic pathology is the extent to which actors outside the medical establishment (parents, social workers, journalists, social reformers, etc.) have influenced the development of the field. Equally surprising (especially given the male dominance that has characterized most of medical history) is that the number of key figures in the history of pediatric forensic pathology are women.

The field is still in its infancy. In an ideal world, unexpected pediatric deaths would be investigated by board-certified pediatric forensic pathologists with specialty training in pediatrics, pediatric pathology, and forensic pathology. As of the writing of this chapter, there are only a handful of such physicians in the world. Pediatric forensic pathology has no dedicated journals, no recognized credentialing board, and only a handful of dedicated texts. This lack of expertise has almost certainly led to the failure to recognize instances of abuse and, equally importantly, has clearly been shown to play a crucial role in mistaken diagnoses of abuse and wrongful convictions.

To understand the brief but colorful history of forensic pathology, it is important to place the development of the field in the context of the history of children in society, the history of medicine, and the relationship of medicine to law. This chapter will attempt to trace this development by separating the discussion into four loosely defined time periods: antiquity, the Middle Ages and the Renaissance, the period from the French Revolution to the Industrial Revolution, and finally the twentieth century.

Antiquity

The Status of Children in Antiquity

Few issues elicit the sort of universal public horror and outrage that accompany reports of violent crimes against infants and children. Every bit as powerful as this visceral response, and intimately related to it, is the primal parental drive to love and protect one's children. So strong and pervasive are such feelings that it would be easy to believe that all people at all times have felt this way. But a review of history shows that this is not the case. Throughout much of human history, children have been conscripted, enslaved, abused, and killed, often by family members and, until comparatively recently, often with impunity. Throughout antiquity and until surprisingly recently, there has been little need for the expert medicolegal investigation of infant and child deaths because such deaths were not unexpected, not criminal, and not covert.

While no age group has been immune, infants, especially newborns, have been particularly vulnerable. Anthropologists estimate that in prehistoric cultures, anywhere from 15 % to 20 % of newborns were killed by their parents. In the absence of effective methods of family planning, the number of children was methodically kept in line with the available means of sustenance. Neonaticide was not the shameful act of desperate or deranged parents, but rather a primitive recognition of Malthusian principles. And it was not just a matter of numbers. Newborns with obvious birth defects and newborn girls were more likely to be quietly killed at birth. (Evidence of the selective killing of newborn girls is supported by the striking male-to-female ratio of some ancient civilizations). The same was true for children born out of wedlock. Twins were thought to be a particularly disastrous event, and one or both were often killed (as was the mother in some societies).

The method of neonaticide varied from place to place (Brockington 1996). In China, newborns were held in a bucket of water and drowned. In Japan, they were smothered with wet paper. In India, there were reports of mothers smearing opium on the breast and then nursing. Parents in many ancient societies took the more passive approach of simply "exposing" the newborn, that is, leaving the child exposed to the elements. Builders of bridges and castles in antiquity would sometimes entomb a child in the foundation to appease the local deities and ensure the structure's integrity. Evidence of this practice, referred to as foundation sacrifice,

has been found in archeological ruins in Jericho that date from 7000 BCE. It is known to have continued as late as 1843 in Germany (Montag and Montag 1979).

The decision to kill a child was typically made in private and without any fear of government interference. When governments did insert themselves into these matters, it was almost never on behalf of the child. Some societies, for example, ancient Rome, simply *promoted* eugenic neonaticide. Under Roman law the father as head of the household had extraordinary power (*pater potestas*) over the lives of his children. In this capacity he was not merely permitted but encouraged to kill sickly or deformed newborns for the good of the state. Other societies went a step further and actually *performed* eugenic neonaticide. In Sparta, for example, all newborn children were examined by a group of elders, and those judged to be feeble or deformed were thrown into Ceadas, a chasm on Mount Taygetus, and left to die (Abt and Garrison 1965). Ritual sacrifice of healthy children, perhaps the most extreme form of official state involvement in child homicide, was performed to appease deities, to commemorate momentous occasions, or to celebrate certain annual holidays in ancient societies in the Old World (e.g., by the Carthaginians) and the New World (e.g., by the Aztecs and Incas). Of the well-studied ancient Western civilizations, only the Thebans and Jews appear to have forbidden infanticide.

Monotheistic religions would exert an ameliorating effect. Judaism, Christianity, and Islam all expressly forbid infanticide. As the influence of Christianity grew in Rome, a more benevolent attitude toward children gradually found its way into public policy and law. In 318 CE, Emperor Constantine I declared infanticide a crime, and in 360 CE the Council of Constantinople went a step further and equated infanticide with homicide.

Medicine in Antiquity

Children born into families who were willing and able to raise them were hardly out of the woods. Even for children with adequate nutrition and relatively safe living and working conditions, there was a formidable array of childhood infectious diseases to survive. What Caulfield said about the health of children in colonial New England could be said with slight modifications about children almost anywhere in the world well into the nineteenth century:

> In addition to diphtheria, dysentery, measles, and scarlet fever, smallpox, influenza, and tuberculosis should certainly be included in the list of common diseases of colonial children. A surprisingly large proportion of them had worms. Deaths from falls, burns, and poisonings were frequent. It seems a little surprising that any of them survived (Pearson 2006).

From earliest recorded history, women looked to other women (relatives and midwives) for help in all matters related to childbearing and rearing. The intervention of healing professionals, typically men, was unusual and sought only in dire circumstances, a very rational approach. Prior to the advent of vaccines and antibiotics, many childhood diseases fell into one of the two categories: (1) trivial

self-limited diseases, which required no treatment and (2) serious life-threatening diseases, for which no treatment existed.

This is not to say that physicians were completely ignorant of childhood diseases. Hippocrates of Cos (460–370 BCE) and other Greek physicians wrote about them as part of larger works on contagious diseases or in works on obstetrics and gynecology. They did an excellent job of cataloguing such diseases. Hippocrates described cases that are easily recognizable as some of the common infectious diseases of childhood such as malaria, mumps, and dysentery. There are also descriptions of more exotic infections. For example, he writes (in an obvious reference to vertebral tuberculosis) that children who acquire humped backs from asthma or cough before puberty will die (Abt and Garrison 1965). But while ancient Greek physicians could make reasonably sound diagnoses and offer prognoses, their treatment options were few.

The heir to the Hippocratic mantle was Galen of Pergamum (129–179 CE), a remarkably prolific author and an imaginative theoretician. He adapted the work of the Hippocratic school and elaborated upon it to create what would become the most authoritative body of medical work in the Western world. He covered almost every topic known to medicine and put together a modified humoral system that was so complete and well thought out that he predicted that nothing more of consequence would ever be added to it. He was very nearly right. Galenic medicine would be embraced, embellished, and commented upon by generations of Roman, Arab, and European physicians but would remain essentially unchanged for over 1,000 years. His authority was so complete that generations of physicians settled all medical arguments, including anatomical disputes, by referring to his writings.

Every bit as durable as the stranglehold of Galenic medicine was the societal prohibition on human dissection. Like the Greek authorities, Roman, Jewish, Christian, and Muslim authorities were opposed to dissecting the dead for centuries. An exception occurred in Alexandria during the Ptolemaic dynasty in Egypt. For the span of about a generation around 300 BCE, Alexandrian Greek physicians such as Herophilus and Erasistratus conducted anatomical dissections with the approval of the king and at times with the king in attendance (Von Staden 1992). Great strides were made in human anatomy, many of which were subsequently ignored or forgotten.

Medicine and Law in Antiquity

At this point in history, there was only a rudimentary understanding of human anatomy, there was nothing that resembled the modern field of anatomic pathology, and there was no forensic medicine as such. However, Roman law did provide for expert testimony in cases that involved technical issues. A physician could be called as a friend of the court (*amicus curiae*) to explain complex medical issues. This practice, like much of Roman law, was adopted throughout Europe and incorporated into common law after the fall of Rome.

The Middle Ages and the Renaissance

Society and Children

Infanticide and child abandonment continued largely unabated into the Middle Ages. In Europe, the Catholic Church and local governments tried to address the issue of abandonment by establishing foundling hospitals. The first dedicated foundling hospital opened in Milan in 787, and others followed in Montpelier (1010), in Florence (1168), and across Europe. Turntables were placed in the doors of some foundling hospitals and churches so that distraught parents could abandon their children to the care of these institutions anonymously. At one point, a third of all newborns in Paris ended up in foundling hospitals (Brockington 1996). Another option was the so-called baby farms, privately owned organizations that for a fee would care for infants.

The issue of infanticide was also addressed. A decision by Henry VIII in 1538 to require the registration of all births, christenings, and deaths in England not only provided valuable census data, but also made it more difficult to conceal an undesired pregnancy and birth (Rudolph 1987). Holy Roman Emperor Charles V in 1532 (Montag and Montag 1979) and English Parliament in 1623 (Oberman 1996) both took a step further by enacting laws that made it a capital crime for an unwed mother to conceal the birth of an illegitimate child by hiding its body. With the encouragement of reformers like St. Vincent de Paul (1581–1660), noble patrons across Europe began to take an interest in the plight of abandoned children. Foundling hospitals became a favorite charity of monarchs with lavish endowments. The foundling hospital in St. Petersburg, for example, occupied two palaces in the center of town (Brockington 1996). By the Middle Ages, the lives of infants were protected by religious precepts and by criminal laws with severe penalties for transgressors.

In fact none of these well-intentioned measures dramatically improved the lot of children. The very harshness of the laws made many courts reluctant to enforce them. When such laws against concealing pregnancy and infanticide were invoked, they were most often used to punish unmarried women (with little concern for the role of the father of the dead infant). The result was that in much of Europe, married women could dispose of unwanted infants with little fear of reprisal.

For children who made it to the foundling hospitals, the outcome was often no better. These hospitals were crowded, and wet nurses were in short supply, so nutrition was often poor. Outbreaks of infectious diseases claimed many of these children and malnutrition many others. It was rare for a child in a foundling hospital to survive to adulthood. The situation was often worse for infants in "baby farms." Nutrition was poor. Sick children, if they were treated at all, were typically managed by sedation with opiate-containing remedies like Daffy's elixir or Godfrey's cordial. For the majority of these infants, the baby farms were only a small step up from exposure and most died within months of their arrival.

Medicine

The study of anatomy would remain confined to the classroom for centuries until animal dissection was revived in the Italian port city of Salerno around 1200.

In a momentous decision in 1241, the Holy Roman Emperor Frederick II granted permission for medical students to see at least one human dissection per year. The influence of Salerno's medical school and its graduates quickly spread throughout Europe, and their model of medical education was adopted in schools in Montpelier, Paris, Bologna, and Padua (Catholic Encyclopedia 2011). These schools would perform anatomic dissections on the bodies of executed criminals with some of the dissections open to the public as well as medical students. Because of the available pool of bodies, female cadavers were rare and children even more so. The limited knowledge of normal childhood anatomy would prove important centuries later in early theories of sudden infant death.

The early 1300s in Italy also saw the first dissections that can be truly called autopsies and not simply demonstrations of normal anatomy. Family members requested autopsies from the treating physician to ascertain the cause of death and, in the case of childhood deaths, to look for signs of hereditary diseases that might be of concern to future children. It should be noted that even in these examinations, as forward-thinking as they were, what was seen could not help but be influenced by what was known. These early postmortem examinations would sometimes ascribe the patient's death to causes such as an abundance of blood collected in the great "chilic" vein, multiple round, hard uterine tumors (most likely fibroids), or demonic possession (Park 1995).

Despite this historically unprecedented interest in anatomy, medical progress remained slow, burdened as it was by the weight of Galenic tradition. The study of normal anatomy would take an enormous step forward with the work of Andreas Vesalius. As a professor at Padua, Vesalius took the unusual step of performing his own dissections and was struck by the irreconcilable differences between his own observations and Galenic anatomy texts. In 1543, at the age of 28 years, he would publish his own anatomy, *De Humani Corporis Fabrica*. It was the first textbook of human anatomy based almost entirely on human dissection and the first real challenge to medical dogma in centuries. Others would follow. In 1628, William Harvey, an avid anatomist and dissector, combined his knowledge of cardiovascular anatomy with observations made during animal experiments to produce *De Motu Cordis*, the first accurate description of circulation. A thorough knowledge of normal structure and normal function would form the basis for an understanding of pathologic anatomy.

Autopsies would gradually become a standard part of academic clinical practice. With the notable exception of Thomas Sydenham (1624–1689) in England, the great clinicians of Europe were all enthusiastic practitioners of autopsy. The correlation of the patient's carefully documented clinical history with the anatomic changes seen at autopsy would serve as the basis for medical investigation and teaching. The first textbooks of pathology were compilations of instructive cases like Giovanni Battista Morgagni's (1682–1771) *De Sedibus et Causis Morborum per Anatomen Indagatis* (On the Seats and Causes of Disease Illustrated by Anatomy). Such series often included forensic autopsies.

Medicine and Law

The coroner system of death investigation in England dates back to 1194 and was established in the Articles of Eyre, which state, "In every county of the King's realm shall be elected three knights and one clerk, to keep the pleas of the Crown." The coroner represented the interests of the king in cases of suspicious death and deaths of prisoners in custody. The coroner's inquest had to be convened where the body was found and the coroner, in addition to examining the body, could call witnesses, detain suspects, and repossess the goods and properties of felons for the crown. An autopsy was not a routine part of such an investigation.

Perhaps the earliest known textbook dedicated to death investigation by a physician is the *Collected Cases of Injustices Rectified* (*Xi Yuan Ji Lu*) written in China in 1274 by Song Ci. In it, Song Ci stresses that

> A forensic medical doctor must be serious, conscientious, and highly responsible, and must also personally examine each dead body or that of a wounded person. The particulars of each case must be recorded in the doctor's own handwriting. No one else is allowed to write his autopsy report. A coroner must not avoid performing an autopsy because he detests the stench of corpses. A coroner must refrain from sitting comfortably behind a curtain of incense that masks the stench, let his subordinates do the autopsy unsupervised, or allow a petty official to write his autopsy report, leaving all the inaccuracies unchecked and uncorrected.

It is not clear exactly what was meant by an autopsy in this context.

The first recorded forensic autopsy took place in Cremona in 1286. In the midst of an epidemic that killed both chickens and townspeople, a physician autopsied the bodies of both human and avian victims and found similar anatomic changes in the hearts of both (Park 1995). As early as 1302, physicians in Bologna were consulted by the courts in cases of suspicious deaths (often to rule out poisoning) and in some cases asked to perform forensic autopsies. The first treatise on forensic medicine in Europe is thought to be *Medico-legal Questions* (*Quaestiones Medico-legales*) written by Paulus Zacchias (1584–1659), physician to Pope Innocent X. First published in 1621, it dealt with the role of the physician in decisions on a wide range of legal issues (determinations of virginity, establishing mental competence, rules of expert testimony, etc.) including the determination of live birth in cases of suspected infanticide. Zacchias also recognized the potential for fatal injury with head trauma, even in the absence of visible external injuries (Lynch 1985).

The relationship between medicine and law was very different during the middle ages. There were no dedicated medical examiners, but some municipalities did have an official physician referred to as a protomedicus. Such a physician was consulted in all matters of public health (such as management of epidemics) and was also asked for his opinion in legal matters including inquiries into homicide. To understand the role of the physician in legal inquiries, it is important to understand the legal system that existed in the Middle Ages. Medieval European criminal law strove for absolute certainty rather than certainty beyond a reasonable doubt in cases that called for the death penalty or severe corporal punishment (Langbein 1978). To meet the burden of certainty, only two forms of proof sufficed: a voluntary confession or the testimony of two reliable eyewitnesses to the crime.

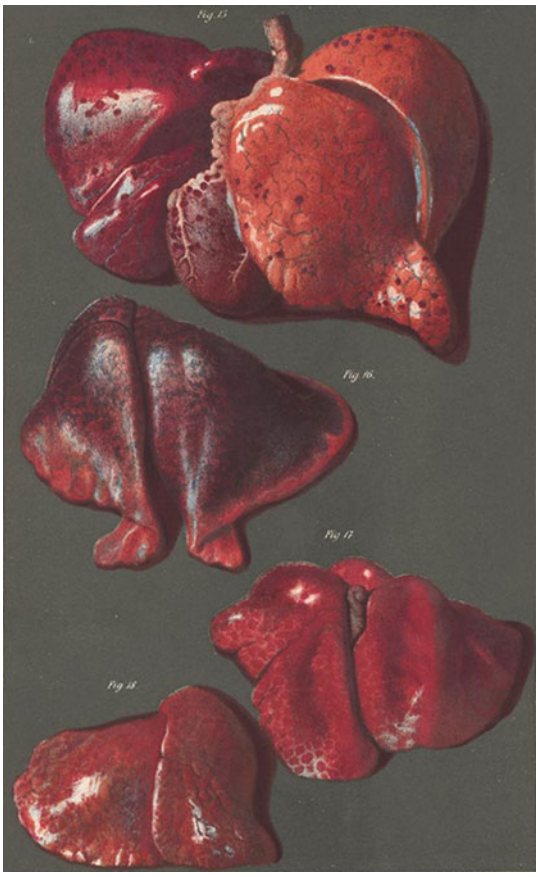

Fig. 1.1 Lungs of newborns (stillborn, live-born, and artificially inflated) (From Casper JL. *Atlas zum Handbuch der gerichtlichen Medicin* (Atlas for the Manual of Legal Medicine). Berlin: Winckelmann and Sons; 1864. Used with permission from Images and Archive Section of the National Library of Medicine)

If neither of these things could be obtained, a third path was available. If investigators could obtain sufficient circumstantial evidence (e.g., physical evidence or expert testimony) to implicate a suspect, then the suspect could be subjected to judicial torture in order to obtain a confession.

Infanticide cases presented some unusual challenges for investigators (Wessling 1994). The proceedings were usually initiated by the discovery of a dead newborn. Investigators had to locate the mother so she could be questioned about the incident, and they also had to determine that the newborn had indeed died as a result of violence and not of natural causes. Both of these steps involved the expert testimony of a physician. Women were examined for evidence of recent pregnancy and delivery such as vulvar swelling, cervical dilatation, uterine enlargement, lochia, darkened areolae, and lactation. The infant's body was examined to determine if it had been born alive. Determination of live birth was based largely on an examination of the lungs (Fig. 1.1). The lungs of a stillborn infant were said to be unexpanded by air and as a result did not fill the pleural cavities or cover the heart. In 1667, Jan Swammerdam (1637–1680) reported that the lungs of live-born

infants, expanded by inhaled air, float in water (the *Lungeprobe*), while those of stillborn infants sink (Hajdu 2006). The body was also examined for evidence of violent injuries.

The physician's opinion was crucial in these matters. The medical report was an essential element needed to obtain the half proof required before proceeding to judicial torture. Furthermore, women convicted of the intentional murder of a live-born infant were sentenced to death. If, on the other hand, the infant was stillborn, then the accused faced the less serious charges of concealment of pregnancy, fornication, or adultery which were punishable by a term in the workhouse.

The limitations of such an approach became apparent. Local physicians often had little firsthand experience with autopsies of any sort. Their ability to make reliable determinations of viability or cause of death based on the examination of a decomposed newborn was limited at best. It was also unlikely that they were sufficiently familiar with natural pediatric diseases or traumatic changes to distinguish between the two. Even something as apparently straightforward as floating the lungs on water was soon shown to be risky. Morgagni showed that under certain circumstances, the lungs of live-born infants could sink in water, and Wilhelm Gottfried Ploucquet (1744–1814) from the University of Tubingen described instances where postmortem gas formation in decomposing lungs could cause the lungs of stillborn infants to float. The English obstetrician William Hunter pointed out that there were well-known instances in which infants were born alive, drew breath, and died hours to days later of natural disease.

In what would become a recurring motif in pediatric forensic cases, there was great initial enthusiasm on the part of the courts for medical determinations that, with experience, proved not to be as simple or reliable as initially thought. In order to be effective, such determinations required a level of training and expertise that was vanishingly rare in most jurisdictions.

From the French Revolution to the Industrial Revolution

Society and Children

In 1803, the British Parliament passed a bill that made infanticide by unwed mothers a homicide like any other homicide, and in 1828 the law was expanded to include all episodes of infanticide. The law, like many others before it, was sporadically enforced. Those women who were charged under these statutes typically offered psychological defenses like lactational or puerperal mania and were usually acquitted (Oberman 1996).

With the industrial revolution, a significant fraction of the population in Western countries shifted to large cities. Some cities were further crowded by a large influx of immigrants. The crowded living spaces with limited sanitary facilities provided the ideal conditions for the spread of the usual infectious diseases. In addition, industrial work introduced new threats, direct and indirect, to child health. Urban women who became part of the huge unskilled labor force were often unable to

Fig. 1.2 "Street Arabs in sleeping quarters" New York City by Jacob Riis (1849–1914) (Used by permission from the Museum of the City of New York)

breast-feed or care for their young children, and bottle feeding at the turn of the century was a perilous proposition. There was little if any regulation of the sanitary conditions of city dairies and slaughterhouses (Holt 1913), and refrigeration was almost unheard of. Those fortunate enough to survive infancy began working before the age of 10 years for long hours under appalling conditions. These trends were reflected in the infant mortality rates. In 1860, there were 170 deaths per 1,000 registered live births in England and 223 in France (Holt 1913). Not all births were formally registered. The bodies of abandoned infants could be found floating in the Thames, the Tiber, the Seine, and waterways throughout Europe well into the nineteenth century. Conditions were no better in the United States (USA). In Philadelphia alone, the bodies of 483 abandoned infants were found on the streets between 1860 and 1890 (Oberman 1996).

The public took notice. Writers like Charles Dickens and Jacob Riis (Fig. 1.2) brought the plight of the working classes and their children to the attention of the public in newspaper articles and works of fiction. The industrial revolution also saw the beginning of modern social work. Religious organizations like the Salvation Army (founded in 1854) and similar secular organizations tried to address the problems that came with urban poverty, including the problems of urban children.

A Methodist missionary named Etta Wheeler discovered an especially shocking case of child abuse, that of Mary Ellen Wilson, in 1874 (Fig. 1.3). Mary Ellen had been a virtual prisoner inside her apartment and was beaten almost daily by her foster mother. Wheeler was exasperated to learn that the police had no authority to intervene under existing law. In desperation, she turned for help to Henry Bergh, founder of the American Society for the Prevention of Cruelty to Animals (ASPCA). With the legal assistance of the ASPCA, Mary Ellen was removed from her abusive foster parents, and her foster mother was sentenced to a year in prison. As a direct result of the trial, Bergh and other New York philanthropists founded the New York Society for the Prevention of Cruelty to Children

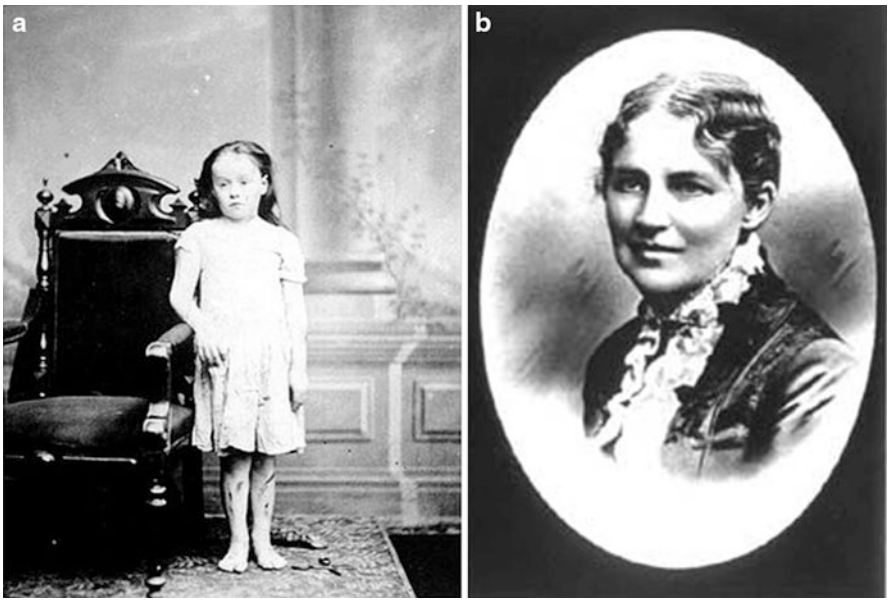

Fig. 1.3 Mary Ellen Wilson (**a**) and Etta Angell Wheeler (**b**) (Used by permission from the New York Society for the Prevention of Cruelty to Children)

(NYSPCC), the first dedicated child protection agency in the world (Myers 2008). Similar organizations were established throughout the Western world and began to effectively advocate for child-protective legislation.

Medicine

Late into the nineteenth century, 200 of every 1,000 children born alive in the USA died before the age of 1 year (Stanton and Behrman 2011). Most died of the same causes that had killed children since antiquity: infectious diseases and poor nutrition. The medical profession took notice. The 1800s saw the emergence of pediatrics as a separate medical specialty. Physicians like John Bunnell Davis lamented that the diseases of childhood had not received the attention, "which their obscure and fatal nature requires (Holt 1913)." He opened a public dispensary for children in London in 1816, which would go on in 1852 to become the Great Ormond Street Hospital, England's first children's hospital. The USA followed with children's hospitals in New York (New York Nursing and Child Hospital, 1854) and Philadelphia (Children's Hospital of Philadelphia, 1855). Abraham Jacobi (1830–1919), a German émigré to the USA, established the first department of pediatrics in the USA at New York Medical College in 1860. In 1888, Job Lewis Smith founded the American Pediatric Society with its journal, the *Archives of Pediatrics & Adolescent Medicine*. It should be noted that not all the additional medical interest was altruistic. Lederer describes disturbing instances of

medical research conducted on children from orphanages and foundling hospitals in the days before informed consent (Lederer 1995).

Early in the nineteenth century, some progress was made against one of the leading infectious causes of infant death, smallpox. Like many epidemic diseases, smallpox took the greatest toll on the very young and the very old. In a study on childhood mortality in England, John Bunnell Davis estimated that smallpox killed one fifth of all children younger than 10 years (Holt 1913). Variolation, the process of exposing healthy people to the dried scabs of smallpox patients, was introduced to England in 1721 from Turkey where it had been in use for some time before, and in 1796 Edward Jenner presented his landmark paper on smallpox vaccination. Groups opposed to variolation and vaccination appeared almost immediately (Best et al. 2004) (and persist to this day), and adoption of the procedure was slow. But the results on infant and child mortality were irrefutable.

The work of Louis Pasteur and Robert Koch established the germ theory as the scientific basis for the study of infectious diseases. Even before the advent of antibiotics, physicians, microbiologists, and hygienists isolated causative organisms, worked out the means of transmission, and instituted programs of disease prevention that translated into significant improvements in infant and child mortality. Diphtheria toxin was isolated in 1890, and antiserum was developed. The heating of milk had been practiced by some dairies since the late 1700s in order to extend shelf life. Pasteurization of milk was adopted as a food safety measure in France in 1890, in Chicago in 1908, and throughout much of the USA and Europe afterward.

This period also saw the rise of pathology as a separate medical specialty. After the French Revolution (1789–1799), medicine and medical education (like all institutions in France) were rethought and dramatically redesigned. The Hotel Dieu, the Salpetriere, the Charite, and the other great public hospitals of Paris became international centers of medical research and education that attracted students from all over Europe, the USA, and the world. This was due in part to the staggering number of patients seen and the variety of cases. The patients were attracted in turn by the opportunity to receive free medical care from one of the finest medical faculties in Europe. Of course, other European and American cities (London, Edinburgh, Glasgow, New York, Boston) had large hospitals with distinguished faculties. What Paris offered its faculty and students was incomparable access to human remains (Warner 1988). Service patients in the public assistance hospitals were admitted with the understanding that if they died (not an unusual event at the time), their bodies would be made available for anatomic dissection or autopsy. While medical students in the United Kingdom had to resort to grave robbery or trafficking with resurrection men, French medical students had simply to walk from lecture to rounds and to the morgue. Autopsies were no longer extraordinary events performed only in baffling cases. They had become part of the daily practice of academic medicine. In the process, the practice of pathology was gradually evolving from part of the practice of clinical medicine to a specialty in its own right. In 1836, Jean Cruveilhier, a student of Dupuytren, was appointed as the first chair of pathological anatomy.

The center of the medical world would eventually shift from Paris to Vienna and the General Hospital (Allgemeine Krankenhaus). The chair of pathology, Karl Rokitansky (1804–1878), was a dedicated, full-time pathologist who had never practiced clinical medicine. Rokitansky, who is said to have personally performed two autopsies a day every day of his 45-year career, made a life's work of the study of pathological anatomy, and his *Handbook of Pathology* became the standard textbook in the field. Rokitansky never fully took advantage of microscopy, but that defect was corrected by the work of his successor, Rudolph Virchow (1821–1902). Virchow would extend the reach of pathology from the gross to the microscopic level. He also made significant contributions to autopsy pathology, notably the insistence on complete autopsies performed with a standardized procedure.

Although there was no recognized subspecialty of pediatric pathology at the time, the enormous volume of autopsies done in Europe in the 1800s would lead to an improved understanding of childhood and congenital diseases. Rokitansky was well-acquainted with pediatric pathology as evidenced by his authoritative work on congenital cardiac malformations. Johann Friedrich Meckel, professor of pathology, anatomy, and surgery at the University of Halle and a student of comparative anatomy under Georges Cuvier, was one of the founding figures in the study of teratology. Etienne Fallot was professor of hygiene and forensic medicine in Marseilles when he described the cyanotic congenital defect that bears his name. Max Wilms (1867–1918), surgeon and pathologist at the University of Heidelberg, made an exhaustive study of renal tumors including the pediatric tumor still known as the Wilms tumor.

Medicine and Law

Meanwhile the coroner system in England was also undergoing gradual changes. The first medically trained coroner, Thomas Wakely, was appointed in 1839. A surgeon and founding editor of the Lancet, Wakely campaigned for a medical coronership. A select committee was convened in 1860 to review the duties of the coroner's office. Their report led to the Coroner's Act of 1887, which mandated the investigation of all suspicious deaths and empowered the coroner to call medical witnesses and order an autopsy (Sharma 2006). Similar legislation was passed in the USA by the State of Maryland in 1860 (Committee on Identifying the Needs of the Forensic Science Community 2009). The Commonwealth of Massachusetts took the next step in 1887 by abolishing the coroner system and replacing it with a medical examiner system which required all medical examiners to be physicians. The city of Baltimore followed suit in 1890 and New York City in 1918.

Perhaps the first pathologist to specifically address the issue of non accidental violent injuries in children was Auguste Ambroise Tardieu (1818–1879). Tardieu was a French forensic pathologist who captured the imagination of the public with his investigations and dramatic testimony in several high-profile murder cases. But more importantly for this discussion, nearly 100 years before the pediatricians became involved in the diagnosis and treatment of violence against children,

Tardieu wrote a series of three groundbreaking papers on the subject: *Etude medico-legale sur les attentats aux moeures* (A Forensic Study of Sexual Abuse, 1857), *Etude medico-legale sur les sevices et mauvais traitements exerces des enfants* (A Forensic Study on Child Abuse, 1860), and *Etude medico-legale sur l'infanticide* (A Forensic Study of Infanticide, 1868). His work was based on his own experience in examining hundreds of cases of abused and murdered children. He was the first to recognize that subpleural ecchymoses (Tardieu spots) can be associated with suffocation. He also recognized patterns of injury in children that had suffered non accidental trauma. He was unequivocal about the violent nature of these injuries and recognized that the assailants were most often parents and caretakers. He was also unrestrained in his condemnation of these acts and his call for more physician involvement. Despite the clarity of his papers and his stature as a forensic pathologist, the medical community at large did not appreciate the magnitude of the problem, and Tardieu's work on pediatric pathology went largely unnoticed.

The Twentieth Century

Society and Children

The child welfare movement in the USA continued into the early 1900s, largely in the hands of private agencies and state and municipal governments. A federal Children's Bureau was created in 1912, and the Sheppard-Towner Act of 1921 provided federal funding for maternal and child health programs, but that was the extent of federal involvement. By 1917, 47 of the 50 states had a juvenile court system empowered to take action in cases of child abuse. By 1922, an estimated 300 nongovernmental child protection agencies could be found scattered across the USA (Myers 2008).

The Great Depression would bring drastic changes. Many nongovernmental child protection agencies, which had been the backbone of protection services, lost their base of charitable contributors and were forced to merge with other organizations or close. In the USA, the void would be filled by the federal government. As part of the Social Security Act of 1935, Congress authorized the Children's Bureau to cooperate with state public welfare agencies in "establishing, extending, and strengthening" child welfare services for "the protection and care of homeless, dependent, and neglected children" (Myers 2008). It was the first step in the evolution of what would become the current federally funded system of child protection.

In an effort to offer more humane sentencing options to mothers accused of infanticide, the British Parliament passed the 1922 Infanticide Law (Oberman 1996). Under the terms of this law, a woman who killed her newborn before she had fully recovered from the mental effects of delivery was charged with manslaughter instead of murder. Most women convicted under the statute were given probation. In 1938, this law was extended to include not only newborns but also children up to the age of 12 months (Kellet 1992).

Medicine

Pediatrics would continue to grow as an academic discipline and as a career choice for graduating medical students. The American Academy of Pediatrics split off from the American Medical Association in 1930, and the American Board of Pediatrics was established in 1933. In the years after the end of the Second World War, antibiotics became widely available, and pediatricians now had powerful tools against bacterial infections. Polio vaccine became available a short time later. Effective vaccination programs against smallpox, diphtheria, and tetanus were in place. Deaths from natural disease would decrease dramatically.

Pediatric pathology began to emerge as a subspecialty of anatomic pathology. Since the late 1800s, women had gradually found their way in small numbers into established medical fields. What is remarkable about pediatric pathology is that it is a field that was founded in large part by women. Maude Abbott, a Canadian pathologist, established herself as a world authority on congenital cardiac malformations. She wrote a chapter on the subject in Osler's medical text and authored her own *Atlas of Congenital Heart Disease* in 1936. Edith Potter began her career in pediatric pathology at the Chicago Lying-in Hospital where she conducted thousands of autopsies in an effort to address the issue of infant mortality. In the process she became an expert in normal development and teratology and published *Pathology of the Fetus and Newborn* in 1952. The Paediatric Pathology Society was founded in Europe in 1955 and the Society for Pediatric Pathology in the USA in 1965.

All the pieces needed to create the field of pediatric forensic pathology were in place. Government-sponsored child-protective services and juvenile courts were prepared to investigate and prosecute abusers. Foster homes gradually replaced orphanages and provided an option for children who had to be removed from their homes. Professional pediatricians were trained to recognize and treat natural diseases of children. Pathologists with interest and expertise in the diseases of children were ready. All that remained was for the medical profession to become involved in the recognition and treatment of violence against children. The impetus would come from a new and somewhat unexpected source: radiology.

Radiology was a whole new field in medicine. Wilhelm Roentgen had first described x-rays in 1895, and within mere months, the first medical images were produced. With improvements in the speed and safety of equipment and the development of nonflammable radiographic film in the 1920s, diagnostic radiology was soon available even in the smallest hospitals. Radiologists quickly gained experience and expertise in interpreting images of adults. The first pediatric radiologist, John Caffey (1895–1978), began his training as a pediatrician. His interactions with radiologists convinced him that they lacked the clinical pediatric background to take full advantage of radiographic imaging. He took over the presentation of pediatric films, studied general radiology, and interacted closely with the pediatric staff. He would quickly become a national and international authority and write the standard textbook in the field. He made at least two major contributions to the study of pediatric forensic science. His first work was

instrumental in showing that "thymic hyperplasia" was not a cause of sudden infant death and thereby did away with unnecessary thymic surgery and irradiation.

More importantly, however, in 1946 he wrote a landmark paper in which he reported on six cases of children who presented subdural hemorrhages and long-bone fractures (Caffey 1946). His clinical summaries are precise and meticulous. He carefully documents each child's clinical, radiographic, laboratory, and even dietary data to show that none of them had evidence of underlying bone disease or coagulopathy. None of the parents gave any history of trauma when questioned. But all of the children came in with what appeared to be traumatic head injuries (recent work had shown that subdural hematomas are always the result of traumatic injury), and all had apparently traumatic long-bone fractures in various stages of healing. It is worth quoting his conclusions at some length:

> It is unlikely that trivial unrecognizable trauma caused the complete fractures in the femurs in cases I, II and V; in the humerus in Case IV; and in the radius in case I. Moreover in several cases ecchymoses were found near the sites of fractures. There was a striking similarity in the course of events in Case II and Case III. In each case unexplained fresh fractures appeared shortly after the patient had arrived home after discharge from the hospital. In one of these cases the infant was clearly unwanted by both parents and this raised the question of intentional ill-treatment of the infant; the evidence was inadequate to prove or disprove this point (Caffey 1946).

A similar report in 1953 attributed the long-bone fractures to "metaphyseal fragility" in infants despite the fact that children in this series also had bruises, retinal detachments, and black eyes (Astley 1953). It was not until 1953 that Silverman (1953) and two years later Woolley and Evans (1955) would take the next step and suggest that the observed fractures were the result of trauma whether the parents provided a history or not. (Recall that Tardieu had reached the same conclusion in1860).

The real watershed event was the 1962 publication by C. Henry Kempe (Fig. 1.4) and colleagues of their paper, the Battered-Child Syndrome. Kempe's coauthors included another pediatrician (Silver), a radiologist (Silverman), a psychiatrist (Steele), and an obstetrician gynecologist (Droegemueller), but no pathologist. The paper is concise and unequivocal. There is no attempt at diplomacy or gentility. In addition to cataloguing the characteristic physical and radiographic findings, the authors directly addressed two of the biggest obstacles to the diagnosis:

> In addition to the reluctance of the parents to give information regarding the attacks on their children, there is another factor that is of great importance and extreme interest as it relates to the difficulty of delving into the problem of parental neglect and abuse. This is the fact that physicians have great difficulty both in believing that parents could have attacked their children and in undertaking the essential questioning of parents on this subject. Many physicians find it hard to believe that such an attack could have occurred and they attempt to obliterate such suspicions from their minds, even in the face of obvious circumstantial evidence (Kempe et al. 1962).

Kempe's paper was a clear exposition of the problem and a call for increased physician participation in the solution. The influence of the paper extended beyond the medical community and received attention in the popular press. In a 1962 issue

Fig. 1.4 C. Henry Kempe (Image used by permission from the Kempe Center at the University of Colorado School of Medicine)

of *Newsweek*, Kempe was quoted as saying that "The battered-child syndrome isn't a reportable disease, but it damn well ought to be (Myers 2008)." Soon it would be.

The public and parent groups became vocal advocates for child health in the late 1960s. Parents of infants who had died unexpectedly were instrumental in bringing about a 1969 conference in Washington State to discuss what had been referred to as cot death, but which would afterward be known as the sudden infant death syndrome, or SIDS. The importance of parent groups in the progress of SIDS research is difficult to overstate. Abe Bergman, a prominent pediatrician and SIDS researcher, said of SIDS Foundation of Washington leader Mary Dore, "She was more important to SIDS than anyone in the world. Her doggedness helped people realize they did not kill their children. That's what triggered the whole research movement, not by doctors but by lay people like Mary (Gilmore 2007)." The continued advocacy of such groups was part of the impetus that led to the US congressional hearings on SIDS in 1973 that made millions of dollars available for SIDS research. Researchers proposed and tested theories that ranged from the mundane to the farfetched.

Similar congressional hearings resulted in the creation of the Child Abuse Prevention and Treatment Act (CAPTA) in 1974, which made federal money available to the states to improve research, investigation, and reporting of physical

and sexual abuse committed against children. A new agency, the National Center on Child Abuse and Neglect, was created to administer CAPTA funds. The research funding floodgates had opened, and the result was an explosion of research on the subjects of child abuse and unexpected death. In 1976, forensic pathologists AM Jones and JT Weston published a proposed standard procedure for use in the investigation and autopsy of suspected SIDS deaths.

In 1964, WJ German reported on his own subdural hematoma that he sustained, without any blow to the head, as a result of the violent acceleration and deceleration that accompanied an ill-advised amusement park ride. JT Weston had reported in 1968 on a series of cases of subdural hematoma in children, which included two children without evidence of external injuries (Gutkelch 1971). He speculated that shaking might have produced the injuries. In 1971, Guthkelch reported a series of infants with subdural hematomas without evidence of head trauma, including two cases (one fatal) in which a parent admitted to shaking the child. Guthkelch ends his paper by saying:

> One must keep in mind the possibility of assault in considering any case of infantile subdural hematoma, even when there are only trivial bruises or indeed no marks of injury at all, and inquire, however guardedly or tactfully, whether perhaps the baby's head could have been shaken (Guthkelch 1971).

Caffey is credited with actually coining the term "shaken infant syndrome" in his 1974 paper in the journal *Pediatrics* (Caffey 1974). Researchers would describe a triad of findings that would become the cornerstone of diagnosis for what became popularly known as the shaken baby syndrome: subdural hemorrhages, retinal hemorrhages, and cerebral edema. Like Kempe's battered-child paper before it, Caffey's paper goes beyond a description of the syndrome and calls for a "nationwide educational campaign" and an increased level of vigilance on the part of medical professionals.

In 1977, English pediatrician Roy Meadow reported two cases of mothers who intentionally and repeatedly lied about their children's health and adulterated their children's laboratory specimens in order to convince hospital staff to admit and evaluate them (Meadow 1977). In one case, a 6-year-old girl underwent 12 hospital admissions and an impressive list of diagnostic maneuvers (cystoscopy, cystogram, urethrogram, vaginogram, barium enema, gynecologic examination under anesthesia, 150 urine cultures, and 16 consultations) and prolonged antibiotic therapy for recurring but oddly transient urinary tract infections. Eventually suspicions were aroused. Closer investigation revealed that the mother had added her own urine and menstrual blood to her daughter's urine samples. Samples collected under close observation and transported directly to the laboratory were consistently normal. In the second case, a boy had multiple hospital admissions for vomiting, drowsiness, and hypernatremia starting at the age of 6 months. An extensive medical workup revealed no renal, endocrine, or other abnormalities, and his symptoms and laboratory abnormalities disappeared while he was in hospital without his mother and only recurred when the mother visited or at home a short time later. The staff became suspicious and contacted social services, but the boy

collapsed and died with hypernatremia at 14 months of age. Meadow referred to the mothers' behavior as the first example of Munchausen syndrome by proxy (MSBP). He wondered in his discussion if such behavior had never been reported, ". . .because that degree of falsification is very rare or because it is unrecognized?" (His subsequent activity as an expert witness in cases of suspicious child deaths suggests that he favored the latter possibility). David Southall, another English pediatrician, would provide stunning support for the diagnosis of MSBP in 1987 with a report of two cases of mothers captured by means of covert videotaping in the act of smothering their children (both who had proven to be diagnostic dilemmas) in the hospital (Southall et al. 1987).

By the 1970s, the medical community, government, and the public at large were focused on the issue of physical child abuse as never before. The issue of sexual abuse of children, however, had received comparatively little attention, and the medical literature was sparse. Despite laws that required medical professionals to report cases of suspected sexual abuse, physicians did not embrace the issue of sexual abuse with the same fervor as the issue of physical abuse. DeFrancis, who published a study of 250 sexually abused children in 1969, noted that the medical community had consistently failed to recognize the problem. That began to change in 1977 when C. Henry Kempe delivered his Anderson Aldrich Lecture titled "Sexual Abuse, Another Hidden Pediatric Problem" at a meeting of the American Academy of Pediatrics. Many physicians were uncomfortable with asking the appropriate questions and performing the necessary physical examination. One observer noted that "the genital exam has probably been 'deferred' more often than the neurological exam in routine pediatrics." Kempe urged physicians to overcome their reticence and become active participants in the investigation and reporting of sexual abuse. Research followed, which revealed the scope of the problem. In Finklehor's1979 survey of college students, 19.2 % of women and 8.6 % of men reported that they had been sexually abused as children. Russell in 1983 found that 16 % of 930 women surveyed had been sexually abused by a family member and 31 % by a non relative (Myers 2008). Kempe helped address the dearth of texts dealing with sexual abuse by publishing *The Common Secret: Sexual Abuse of Children and Adolescents* in 1984.

By the mid-1980s, for the first time in history, medicine was completely engaged in diagnosing, treating, and preventing child abuse. Physicians were an integral part of an elaborate, government-funded child protection apparatus. They had new tools to assist them in diagnosing abuse, responsive child protection agencies to report it to, unprecedented access to grant money to support child abuse research, and the expertise to participate as witnesses in the trials of accused abusers.

Medicine and Law

Much of the early work in pediatric forensics was of necessity based on the personal experience of individual physicians or single institutions. For obvious reasons, rigorous clinical studies of the type usually required to change medical practice were simply not possible. From a purely scientific standpoint, early data were exciting but still preliminary. Unfortunately, the criminal justice system could not wait for the field to mature.

In cases of suspicious infant deaths, expert testimony was often crucial in making the prosecution's case for child abuse. In the absence of the usual type of supporting experimental data for syndromes like the shaken baby syndrome or MSBP, the stature of high-profile medical experts could be a deciding factor for the jury. Pediatricians and pathologists presented findings like Tardieu spots and conjunctival hemorrhages as compelling evidence of suffocation. The triad of subdural hematoma, retinal hemorrhage, and cerebral edema was presented as strong evidence of violent shaking. The typical explanations offered by accused abusers (the infant fell from the crib or from my arms) were discounted by experienced physicians who assured juries that the triad of shaken baby syndrome could not be caused by a short fall or minor trauma. Repeated SIDS deaths in a single family were seen as particularly suspicious even with the lack of any evidence of abuse. Meadow popularized what became known as Meadow's Law: one SIDS death is a tragedy, two is suspicious, and three is murder until proven otherwise. In the USA and Europe, the number of cases of reported abuse increased dramatically as did the number of prosecutions and convictions.

Gradually, as more research was conducted, it became clear that some of the syndromes had been too broadly defined. Pathologists demonstrated that some of the findings of shaken baby syndrome could be seen with the trauma of delivery, with cardiopulmonary resuscitation, and in some cases in normal infants. John Plunkett, for example, combed the files of the US Consumer Product Safety Commission and found cases of fatal pediatric head trauma associated with independently verified short falls (between 0.6 and 3.0 m) from swings and playground equipment. Some of these cases had documented retinal hemorrhages, subdural hematomas, and cerebral edema (Plunkett 2001). The triad was consistent with, but not diagnostic for, fatal shaking.

It also became clear that multiple sudden infant deaths actually could occur in a single family. In the 1960s, researchers described the congenital long QT syndrome (LQTS) as a cause of sudden death, and in 1995 the gene was discovered. In the 1980s, researchers described inherited fatty acid oxidation deficiencies (such as medium chain acyl coenzyme A deficiency, or MCAD) that could present sudden unexplained infant death especially after viral infections and prolonged fasting. Authors warned of the dire consequences for children, accused parents, and the doctor-patient relationship that could result from the overdiagnosis of child abuse (Kaplan 1986). As early as 1987, Wigglesworth, Keeling, and colleagues, in a proposed protocol for the postmortem investigation of sudden infant death, suggested special studies for metabolic disorders and conduction anomalies in families with multiple infant deaths (Wigglesworth et al. 1987).

The so-called Meadow's Law would undergo a bruising challenge during the 1999 trial of Sally Clark. Ms. Clark, an attorney, was convicted of murder in the death of her sons Christopher and Harry. At the trial, which generated considerable media attention, Meadow testified that the odds of two SIDS deaths in a single affluent family were roughly 1 in 73 million. He obtained this figure by multiplying 1 in 8,543, the risk of a single SIDS death, by 1 in 8,543. Given the birth rate in Britain, he estimated that such an event would be expected to happen by chance

only once every 100 years. The same Home Office pathologist, Alan Williams, had performed the autopsies on both infants. He had originally concluded that the first infant had died of pneumonitis, but changed his conclusions after Clark's second son died. He said instead that the evidence suggested that the first infant had been smothered and the second had been fatally shaken. Unexpected support for the prosecution's case for murder came from David Southall who, after watching a televised interview of Ms. Clark's husband, contacted the child-protective authorities and suggested that Mr. Clark was the murderer. Sally Clark was convicted, an appeal failed, and she was sentenced to life in prison.

Undeterred, her family and friends continued to investigate the case. Careful review of the medical records showed that Dr. Williams' autopsy report included cultures from Harry Clark, which grew *Staphylococcus aureus*, a fact not mentioned during trial. The Royal Statistical Society weighed in and claimed in a public statement that Meadow's figure of 1 in 73 million was statistically invalid. The case was reopened, and the results were dramatic. Sally Clark was exonerated, but only after serving 3 years in prison. Drs. Meadow, Williams, and Southall were all subject to investigation by the General Medical Council. In 2003, Attorney General Lord Golding ordered a review of 258 cases in which parents had been convicted of murdering children less than 2 years old. Three other women convicted of multiple infant murders were exonerated. Dr. Meadow had testified at all three trials.

Around the same time, similar cases were coming to light in Canada. Charles Randal Smith, a board-certified pediatric pathologist, was made the director of a newly established pediatric forensic division at the Hospital for Sick Children in Toronto in 1992. Despite a lack of specialty training in forensic pathology, Smith was responsible for the postmortem investigation of all suspicious pediatric deaths in Ontario, and his testimony was crucial in obtaining convictions in several high-profile cases. By 2005, some of these convictions were being called into question. A death that Smith had deemed the result of shaken baby syndrome was found to be consistent with accidental trauma. Another case in which a mother was convicted of smothering her baby and fracturing his skull was dismissed after the exhumed body was found to be free of fractures. And in perhaps the most striking case, a woman was exonerated of the stabbing death of her 7-year-old daughter when a review of the case showed the child's injuries to be consistent with bite marks from the family's pit bull. A review of 44 of his cases was ordered by the Chief Coroner of Ontario. Serious problems were found in 20 of them. Ontario's Attorney General convened a panel under the direction of Judge Stephen Goudge to look into the state of pediatric forensic inquiry. The findings of the panel were released in 2007 and have become known as the Goudge Report (Goudge 2007).

The panel held Smith accountable for his own work and for his failure to seek outside help in difficult cases. But the report also found systemic problems with the training of pediatric forensic pathologists and with the process of pediatric death investigation in Canada. These same systemic problems are present to some extent in forensic pathology departments all over the world, and the solutions to them are not straightforward.

In order to distinguish violent injuries from the bewildering array of often rare natural diseases that can simulate them (nevi that look like bruises, hematologic disorders that lead to thrombocytopenia and easy bruising, bone disorders that result in suspicious fractures, subtle metabolic diseases, etc.), a pediatric forensic pathologist should first be well-trained in pediatric pathology (and in a perfect world, in pediatrics). But such training is clearly not sufficient. A successful pediatric forensic pathologist must also be well-versed in general forensic pathology and the physical sequelae of violence, abuse, and neglect. A familiarity with the legal process in his or her jurisdiction and its rules for expert testimony is essential. And like all physicians, pediatric forensic pathologists need help from their peers in the form of professional oversight, peer review, and consultation.

The difficulties in achieving the above-described ideals are succinctly addressed in a 2007 paper by Cordner et al. from the Victorian Institute of Forensic Medicine in Australia (Cordner et al. 2007). First of all, there are very few ideally trained pediatric forensic pathologists to serve as mentors, reviewers, or consultants. Of 2,500 fellows of the Royal College of Pathologists of Australasia, only 35 (1.4 %) were full-time forensic pathologists, and there were no full-time pediatric forensic pathologists. In 2007, there were only seven pathologists in the USA who were board-certified in both pediatric pathology and forensic pathology.

The problem of training more pathologists is daunting. There are some textbooks on the subject, and there is a specialty literature. However, expertise comes in great part from experience, and experience in pediatric forensic pathology is hard to come by. To illustrate, Cordner uses statistics from Victoria, Australia, with a population of over five million. In 2005, there were 32,606 deaths, 5,000 of which were reported to the coroner, 3,465 of which were referred for forensic autopsy. Of these autopsied cases, 105 were under the age of 18 and of those 7 were determined to be the result of interpersonal violence. In short, very few jurisdictions would be expected to have a sufficient volume of pediatric forensic cases to support a full-time pediatric pathologist or a fellowship in pediatric forensic pathology.

Conclusion

Clear summaries of the problems facing the field are now available to the general medical community, the law enforcement community, child protection services, forensic pathologists, and the general public. The pendulum has swung from complete neglect of the problem of violence against children to compensatory zeal for research, investigation, and prosecution (without a mature understanding of the forensic science to support it) and now toward correction of instances of overcompensation (and a reassessment of the field of pediatric forensic pathology). Much has been accomplished, but many problems remain. It is hoped that the light cast on these problems by recent experience in the United Kingdom and Canada will help focus governmental attention and funding on finding solutions.

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Pediatric Death Scene Investigation

2

Brad Randall

Contents

Abstract

A careful investigation of the scene where an infant or child dies (or becomes incapacitated) is critical to determining why infants and children die suddenly and unexpectedly away from the hospital. Despite the reliance on the autopsy to determine the causes of these sudden deaths, often the only explanation for a death can be found in a careful scene investigation. Not only must the scene be carefully documented and photographed, but those caring for the infant or child need to be carefully interviewed to understand exactly what happened prior to the death. Often the infants and children suddenly dying at a scene are no longer present at the scene at the time of the investigation. Therefore, it is necessary to accurately recreate the environment the infant or child was in at the time of death. This can be done best as part of a well-documented doll reenactment. Special attention must be given to the possibility of asphyxia as a cause of death since asphyxial deaths produce either no, or nonspecific, pathologic findings at autopsy.

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The scene investigation also is vital to corroborate positive autopsy findings such as evidence consistent with underlying natural diseases or potential mechanisms to explain documented trauma.

An Introduction to Infant and Child Death Scene Investigations

Pediatric Death Scene Investigation Versus Crime Scene Investigation

What is a pediatric death scene investigation? Why do we do pediatric death scene investigations? And, specifically, what do we gain from performing pediatric death scene investigations that helps us to determine the cause and manner of death for infants and children dying primarily (but not exclusively) outside of the hospital?

Although this handbook is devoted to "pediatric" (individuals $\leq$19 years of age) forensic pathology, the major emphasis of this chapter will be on infant (children less than 1 year of age) deaths. The majority of pediatric deaths beyond the toddler age (2–3 years) result in death scenes similar to those of adults. Although a death, for example, of a 5-year-old falling from a piece of playground equipment is relatively unique to the pediatric age-group, the processing of the body at the scene and the processing/recovery of evidence done at the scene would be performed identically had an adult been injured in similar circumstances. Thus, while children are often injured/killed in dangerous environments that adults would know to avoid (e.g., entangled in machinery, falling into wells, approaching dangerous animals, accidental electrocutions, becoming ensnared in cords and cables), in the majority of situations those death scenes would be processed identically for the child as they would if an adult had died in the same circumstances.

For the younger child death, however, a death investigator looking at a scene from an adult perspective may not recognize hazards the scene uniquely presents to much smaller people. As an investigator, lowering yourself to hands and knees may offer a better perspective of a death scene. At a lower perspective, you may be able to see exposed wiring, potentials for entrapment (e.g., cupboards and small spaces under furniture), and access to drugs/poisons that might not be visible to a standing adult.

The above represents a unique hazard to small toddler-age children. Adults may accidentally spill a couple of medication tablets on the floor and either forget to retrieve them or unknowingly incompletely retrieve them. A pediatrician friend once said that the easiest way to get a toddler to take a tablet of medication was to put it on the floor. Not only can prescribed or illicit drugs be potentially lethal to small children, over-the-counter vitamins, food supplements, and herbal remedies can also be toxic. Many household plants can also be extremely poisonous. Therefore, since small children are more likely to ingest toxic materials than older children or adults, death investigators at a small-child death scene, particularly where the cause of death is not obvious, should carefully search for potentially lethal hazards. This is even more important since many adult medications, herbal concoctions, and plant

poisons do not produce diagnostic changes at autopsy and may not be detected by common toxicology screening procedures. Local poison control agencies can be helpful in determining what is and what is not a pediatric hazard.

Lastly, in circumstances where the cause of a child's death is not immediately obvious, the death scene investigator should remember that even somewhat older children do not necessarily behave physiologically like small adults. Per kilogram, some drugs and toxins may be more dangerous in a pediatric population. Illnesses which may be relatively trivial in adults can rapidly progress to death in children with little warning. The death scene investigator should therefore carefully examine a scene (and interview the caregivers) for evidence of illness preceding a child death. There may be evidence of over-the-counter (or prescribed) medications commonly used to treat symptoms of colds, coughs, or diarrhea. Wet towels and empty ice cube trays may indicate efforts to reduce a fever (or the hyperthermia sometimes seen in cocaine overdoses). The discovery of medications commonly used to treat seizure disorders certainly should raise concerns that a death may be seizure-related (remembering that fevers can induce seizures in children without a known seizure history).

While the remainder of the chapter will emphasize the infant death scene, there is nothing magical about a child's first birthday. Children slightly more than a year old may still die in a fashion similar to their infant cousins. The death scene investigator will therefore have to determine whether a 12–14-month-old child's death, for example, is more representative of an infant death or not. This may become particularly important with children born significantly prematurely.

Several decades ago, it was often felt that many infants and young children dying at home died as a result of abuse until proven otherwise. This belief was fueled by the fact that indeed some infants were dying of abuse, but perhaps more importantly, it was difficult for most law enforcement officers to comprehend that what had been an apparently healthy infant the evening before could be found the next morning suddenly and inexplicably dead for no apparent reason – except as a consequence of abuse. Thus, law enforcement took the lead in investigating the scenes of these deaths. It was unusual 50 or 60 years ago for the public health death investigators charged with determining the cause and manner of these pediatric deaths – medical examiners and coroners – to even visit the scenes of the death. Whatever scene information the medical examiners or coroners used in their determination of cause and manner of deaths was derived from law enforcement officials.

While the "guilty of abuse until proven innocent" approach may have been effective in successfully determining when a child had been abused, the fact remained that the vast majority of these deaths had no evidence of abuse. The consequence of this approach for the families and caregivers of the dead children was that not only did they have to suffer the crushing grief of suddenly and unexpectedly losing their child, but they were at the same time being treated by law enforcement as if they had caused the death.

Over time public sentiment, and various medical examiner offices, began to pressure law enforcement agencies to accept the fact that the overwhelming majority of these deaths did not reflect parental or caregiver criminal abuse or neglect. As the pendulum swung, the prevailing belief of those responding to an infant death

became that the death most likely represented a natural disease process (such as the sudden infant death syndrome [SIDS]) and not abuse. The assumption upon arriving at a pediatric death scene then became that all parents and caregivers were innocent of any wrongdoing until proven otherwise.

This later approach was a boon to families and caregivers because it resulted in a compassionate and caring response to their loss while absolving them of any responsibility in the death. While a boon to families, the "innocent until obviously guilty" policy resulted in some true cases of abuse not being properly investigated and potential accidental causes of death not being recognized.

Over the last several years, the pendulum has begun to swing back toward a more realistic approach of avoiding "assumptions" when approaching a pediatric death scene. There no longer is an "assumption" of guilt but a realization that abuse might exist. Likewise, investigators now realize that the environment, particularly the sleeping environment, may play a role in many infant deaths. Increasingly, we are becoming aware that many infant deaths may no longer be the "acts of God" as they were once portrayed. The investigator's job now is to search out potential causative agents and factors which may be present at a death scene without bias of criminality or culpability.

The death scene investigation discussed in this chapter is an investigation conducted by a public health officer (coroner or medical examiner or their office investigators) for the purpose of determining why an infant died and the manner of death. Crime scene investigations are undertaken by law enforcement agencies, often aided by specialized crime scene investigation (CSI) teams. These two investigations usually occur simultaneously; they may cover the same or different aspects of the scene, but they are conducted by separate and distinct entities. The medical examiner/coroner and law enforcement are partners at the scene, sometimes equal partners, sometimes not.

When an infant death scene strongly suggests criminal abuse, then the law enforcement investigation usually takes primacy. The medical examiner/coroner may have to wait to enter this scene, for example, until the scene has been properly processed for trace evidence. Law enforcement personnel in this setting may be very reticent for any disturbance of the body before a formal autopsy examination. Yet it often is vital for the medical examiner/coroner to examine such a scene to more fully understand how the potential abuse relates to the scene (as will be discussed later in the chapter).

At the other end of the spectrum, a pediatric death scene may be highly suggestive of a natural death. For example, an infant may have a long medical history of a life-threatening condition and die in a hospice-like situation at home. Here, the medical examiner/coroner may take the lead by helping to identify medications and medical equipment at the scene that substantiate the infant's reported condition – findings that law enforcement personnel might be less familiar with. At this scene, perhaps while in a secondary role, law enforcement reminds the medical examiner/coroner that abuse must not be completely excluded. Likewise, the medical examiner/coroner plays a similar role at a suspicious scene by making sure law enforcement does not rule out the possibility of natural disease or accidental trauma.

The cause and manner of death in most infant death scenes, however, is usually not evident at the time of the death. In these scenes law enforcement and the medical examiner/coroner must work as equals. Without bias, law enforcement at these scenes will work to collect enough data and evidence so that should the death ultimately prove to be abusive, they can apprehend a suspect and proceed with a prosecution. While the medical examiner/coroner will in the course of his or her job inherently be collecting similar information at the death scene as law enforcement, their emphasis will be on discovering why the child died and not who may or may not be responsible for death.

In busy jurisdictions with several infant death scene investigations, law enforcement and medical examiners/coroners develop a natural relationship. A death scene is not the place to work out jurisdictional differences. An experienced medical examiner/coroner or law enforcement officer will know what expertise each agency brings to a death scene. Those less experienced, either as law enforcement or as medical examiners/coroners, would be wise to seek out the advice of their opposite partners at a scene. That being said, even novice investigators should know the basics of what needs to be done at a scene (to be discussed below for the medical examiner/coroner). New infant death scene investigators should be aware that occasionally more "experienced" law enforcement investigators may attempt to push you aside at a scene and keep you from doing your job. In most jurisdictions, statute clearly delineates the responsibilities that both law enforcement and medical examiners/coroners have at a death scene. It is strongly recommended that both parties discuss who does what at each kind of infant death scene well in advance of processing their first scene together.

Approach to Pediatric Death Scene Investigations

What Pediatric Deaths Need Scene Investigations?

The simple answer to the above of course would be "all of them." The obvious exception however would be the majority of pediatric deaths that occur in infants and children with well-documented natural disease processes who die under the care of a physician in a hospital.

If a death investigator is comfortable that a child has died at home (or at least out of the hospital) from a well-documented natural disease, there may be minimal need for a formal death scene investigation. That being said, it is incumbent upon the death investigator to document the medical condition of the infant and to have some level of comfort with the scene of the death (e.g., home or hospice setting). On one hand, there is the desire to avoid subjecting the dead infant's family to the intrusion of a formal investigation; on the other hand, rarely an infant with a limited expected life span may have their death "accelerated" by family or caregivers to shorten their period of "suffering." Common sense has to prevail to appropriately balance these two conflicting needs.

For almost every other pediatric death occurring outside of the hospital, a formal death scene investigation will be necessary. Some of these scenes will be

specialized, for example, transportation-related deaths, and will require a different type of scene investigation beyond the scope of this chapter. With the exceptions of the above however, essentially all infant and child deaths occurring either at home or elsewhere, where the death is sudden and unexpected, need a formal death scene investigation. While the emphasis of the chapter is on deaths occurring either at home or in a day-care setting, other settings such as playgrounds, stores, and even automobiles not involved in crashes deserve similar scene investigations.

What Is a Pediatric Death Scene?

The concept of what is a death scene often comes from watching television or reading crime novels. An unsuspecting pedestrian walking down a city street glances into an alley and sees a bloody body lying on the ground with a bloody knife nearby – a prototypical death scene, where the body is present where the individual died. This scenario however rarely happens in pediatric cases.

Imagine a typical infant death scenario. A parent or caregiver suddenly realizes that they have not heard their infant. They check the infant in the crib, or bed, or couch and find him or her unresponsive, cool, flaccid, and blue. Immediately, they pick the infant up, hysterically seek help, and perhaps begin to do CPR, most often not in the room where the infant was discovered. Emergency first responders arrive. Although they are aware that the infant is dead, they, either to appease themselves or the parents, may make an effort at resuscitation which may move from the floor to the ambulance and ultimately to a hospital emergency room. Thus, the body is no longer at the "scene" of death.

But sometimes the above scenario does not happen, and the body and scene are still together. Then it is incumbent upon the death investigator to assure that the infant is not moved from where discovered. There is a natural tendency for well-meaning family, first responders, and law enforcement to cover or move the body at the scene when the family may still be present. If at all possible, do not let that happen.

If the body is still at the scene, then the death investigator should view the body immediately before any potential disruption occurs. Assume that the body is not as originally found: Time has obviously passed since the infant was discovered and you arrived. The postmortem changes of algor, rigor, and livor mortis will all be underway.

Algor mortis refers to the cooling of a body after death. Although several algorithms have been constructed to use body temperature to determine time of death, none have been, given the complexities of variable bedding and initial scene temperatures, particularly accurate. The decision whether, and how, to record body temperatures at a death scene should be left to the death investigator officer in charge (coroner or medical examiner). At best, algor mortis can offer time of death determinations only in broad, general ways – a warm body has died recently, after a few hours a body will begin to feel cool, and ambient temperature bodies have been dead for several hours.

Livor mortis refers to the settling of blood after circulation stops at the time of death. It usually takes an hour or so to become visible on the dependent portions of the body, but this is variable. For a few hours after death, livor is "unfixed," meaning that if the body is moved during this time, the livor will likewise move to reflect new dependent points. When unfixed, livor can be blanched with pressure, which will not happen after a few hours when the livor becomes "fixed." A body discovered at a scene with livor in a non dependent area suggests that the body was moved at some point after death, but at a point after the livor had become fixed.

Rigor mortis refers to the stiffening of muscle tissue that occurs after death. This usually begins to occur a few hours after death and reaches its maximum 12–24 h after death. In infants with little muscle mass however, being able to appreciate early rigor can be difficult. First responders often notice early rigor when they report difficulty opening the mouth prior to performing CPR.

Most likely, at least some degree of bedding disruption must have occurred around the infant when he/she was discovered. If the infant has been moved, then the investigator needs to know exactly what happened from when the infant was picked up to when he/she was deposited as found. Was there one single pickup and move or was the body moved to multiple locations before being set down where found? What sort of resuscitation efforts were made, if any? The investigator should also be aware that at these so-called "intact" scenes, if the body is not actually in the house, it may be in the ambulance just outside.

Detailed examination of a body at the scene is not recommended since it may introduce confusing artifacts at the time of autopsy and may disturb evidentiary material usually collected at autopsy. However, careful documentation of postmortem changes and possible signs of trauma can be invaluable. Many of these changes, such as patterned livor, are ephemeral and may no longer be evident at the time of autopsy (Fig. 2.1).

More often than not however, the infant's body will not be present where the death occurred. "Where the death occurred" may also not be obvious to the new investigator. Frequently, a body is taken away by caregivers, emergency responders, neighbors trying to be helpful, etc., from where it was found to be "pronounced" dead upon arrival at a hospital. Usually however, this infant did not "die" at the hospital; it was just pronounced dead there. Occasionally however, the infant may indeed have had some signs of life at the scene and truly did "die" at the hospital. It is imperative that the investigator checks closely both with the emergency room physicians and the pathologist who is responsible for determining how the infant died to make sure exactly where the death occurred. Despite what might be on a "time of death" statement (either a death certificate or a hospital record), it usually is safest to assume that the child was found dead at the scene unless it is clear that that was not the case.

The good news about the exact site of death issue is that it really does not make any difference to how the investigation proceeds. Whether the infant or child did or did not die at the home (day-care center or mall), what started the process that ultimately led to the infant's death (wherever it occurred) usually started where the

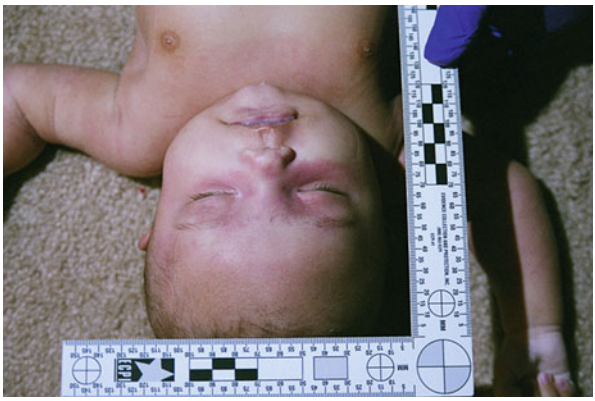

Fig. 2.1 Notice that the postmortem settling of blood (livor mortis) is blanched just on the cheeks and tip of the nose of this infant. The blanching was caused by the pressure of the head on the face, indicating that the face was down into the bedding at the time of death. Had the infant indeed died on the back, the livor would be present only on the posterior surfaces of the head and trunk and not, as seen, around the eyes. Only for the first few hours after death will livor be "blanchable" or unfixed. Therefore, if the infant seen in this figure had died only an hour or two earlier, and was then placed on the back, the blanching seen here would not be visible at the time of autopsy since it was unfixed at the scene and could still move posteriorly – thus requiring careful observation of livor patterns when the body is first observed

infant was discovered unresponsive. You, as an investigator, need to find out what factors were operative (if any) at the discovery scene, which initiated the process that led to the infant or child death.

Without the body at the scene however, those taking care of the infant must recreate what happened. However, even if the body is present, it is likely that it has been moved from where it was discovered, so the recreation process also depends upon the terminal caregivers. The mechanics of this recreation process are discussed below.

If the body has been removed from the home, then it is important that the investigator view the body at the hospital as soon as possible. Subtle death-related changes may come and go quickly and if not documented early on may not be evident at the time of the autopsy. Again, these should primarily be "observations" and not disruptions of the body. These initial observations (to include photographs) should only involve noninvasive determinations of temperature, rigor, and livor and perhaps a cursory examination for evidence of obvious trauma. Since some degree of medical intervention may have occurred, the investigator should be sure to recover any items that arrived with the infant or child (this usually includes, but is not limited to, diapers, clothing, and bedding).

Sometimes the child arrives at the hospital either alive or is resuscitated there. In these circumstances, the investigator must obviously give way to the medical personnel as they work to save the infant's or child's life. Nevertheless, the investigator should ask for an opportunity to view the child, recover materials brought in with the child, and document any injuries or abnormalities. Most lay investigators are intimidated by the activity and medical personnel that surround an

active resuscitation. There often are, however, breaks in the action when you, as the investigator can assess the child and take pictures. The opportunity to do this largely hinges on you simply asking.

Should the infant survive the emergency department, it usually will be taken to an intensive care area of the hospital. The role of an investigator is not finished. Both the medical examiner/coroner and law enforcement must coordinate with the health-care providers to assure that the proper procedures are undertaken should the infant die (in the vast majority of these cases, the child will die within a few days of admission).

Hospital Procedures to Follow a Sudden, Unexpected Infant Death

- Notify the appropriate law enforcement agency immediately.
- Notify the appropriate death investigation agency (coroner or ME office) immediately.
- Leave all medical equipment (IVs, endotracheal tubes, cerebral pressure monitors, etc.) in place.
- Allow handling of the body only as directed by the death investigator.
- Do not release the body to a funeral home.
- Make sure all biological specimens (particularly blood and urine – both at the bedside and in the laboratory) are not discarded.
- Make the medical record available to the death investigator.

Following the initial hospital admission however, it is important to view the child on at least a daily basis. While in the hospital, evidence of injury (usually bruises or contusions) may appear and disappear before the child dies. Photographic documentation of these changes can be invaluable to the pathologist as part of the autopsy examination. Sometimes an infant found unresponsive at home may arrive at the hospital and survive for weeks, months, or even years. Some of these infants completely recover, some are left with varying levels of impairment, and others remain in a vegetative state. As an investigator, there usually is little to be gained from viewing these infants beyond the first week or two.

If a death either occurred, or was initiated at, a day-care provider's location (or any other location away from the infant's home), then the investigator not only has to view where the death occurred or was initiated, and possibly the hospital, but also the home where the infant lived. A visit to the infant's home in these circumstances can offer information, for example, on the health status of the infant, what environmental challenges the infant was exposed to that may have manifested themselves elsewhere, and the possibility of trauma that might have occurred at home only to manifest itself elsewhere. The mechanics of this part of the investigation are exactly the same as if the child had died at home and are discussed below.

How to Do a Scene Investigation and Interview

Before addressing the mechanics of how to do a scene investigation, I have to emphasize the importance of safety – your safety. Your job, as an investigator, is

not to put yourself in harm's way. Do not enter a scene until it is safe to do so. Some scenes are structurally unsafe, for example, a condemned building. Other scenes can have dangerous people present, either from being emotionally overwhelmed or family members who are intoxicated or generally have little regard for "officials," no matter what governmental agency they represent. As a rule of thumb, do not enter scenes alone. If your instinct is telling you that a scene, or the people in it, poses a hazard, then proceed with caution. Usually law enforcement agencies are present at a scene and can provide the necessary security. Do not only inquire of the officers at the scene if it is safe to enter; make it clear that what is safe for an armed police person may not be safe for you. The medicolegal death investigator and law enforcement should clearly understand that law enforcement is responsible for the death investigator's safety. On the other side of that equation, the death investigator must listen and adhere to the safety concerns and recommendations of law enforcement.

As you approach a scene, remember that the people in these scenes are an integral part of your investigation. Interviewing those present, and those not necessarily present but knowledgeable about the infant, is a vital part of a pediatric scene investigation. Those to be interviewed obviously include all individuals who were caring for the infant prior to the infant being found either dead or unresponsive. Parents must additionally be interviewed if they were not the primary caregivers. Others to consider interviewing are family, friends, and neighbors who might have information regarding the health and safety of the infant prior to the event. Some of these people may be obvious; others you may have to actively search out.

The medical personnel who cared for the infant after he/she left the home should be sought for their opinions regarding their findings during their diagnosis and treatment of the infant. This should extend from the terminal admission to the infant's health-care providers prior to the death or event leading to hospitalization. One of the health-care providers often overlooked the first responders. The EMT/paramedics may be able to offer observations about what was going on early on in a scene before others arrived. The same may be true of the first-responding law enforcement officer.

The timing of the interviews, and also the physical scene investigation, may be problematic. Should those present at the scene be interviewed immediately as part of the initial scene investigation, or should this be delayed? In favor of an immediate interview and scene investigation is that all of the parties may be available. Caregivers often are either most truthful, or most obviously untruthful, if interviewed immediately before they have time to carefully think out, and perhaps modify, what their story/stories is/are. If there is a delay in viewing the scene, then it is likely that the exact condition of the scene will not exist at a later date. Often bedding (which frequently is taken by law enforcement officers) and other infant sleeping environments have either been significantly altered, dismantled, or even destroyed by parents and caregivers not wanting to retain such poignant reminders of the death. On occasion, there may be cultural reasons for destroying a dead family member's possessions.

Young families often escape to their own parental homes at times of severe emotional stress. Frequently, waiting a few days to allow a family or caregiver to deal with the immediate grief over an infant death means that the parents or caregivers may have left town with no immediate plans to return.

Regardless of whether or not a decision is made to immediately interview the caregivers of a deceased or critically ill infant, some interviews should take place immediately. There is no reason not to get statements from first responders and the medical personnel at the hospital emergency department. These individuals may be difficult to track down later if their statements are not immediately sought.

Again, if the decision is made to delay interviews, the scene still needs to be thoroughly examined. Careful photographic and diagrammatic documentation of the scene can assure that a delayed reconstruction of the events accurately encompasses the true condition of the scene at the time the first responders arrived.

The advantage of waiting a period of time before interviewing the caregivers is that with immediate interviews you are asking for statements and answers from individuals whose grief has rendered them uniquely unqualified to answer the specific types of questions being put to them. While waiting to interview does allow a caregiver time to construct a more benign version of what might have happened, experience has shown that deception is less of an issue than the faulty memory of someone unconsciously trying not to recall a very stressful event. However, the problem of a flawed memory subsequent to a delayed interview rarely is equally compensated by the advantage of more composure. If the interview is to be delayed however, the investigator should still immediately and carefully document the scene to assure that what the caregivers relate at a later date matches what was found at the scene initially.

Although some investigators do scene visits a few days after the death, I have found that immediate interviews and scene investigations work the best. Although caregivers and family members may be overwrought with emotion initially, a firm and caring persistence with the interview usually prevails. Caregivers most often can proceed with an interview if the interviewer makes it clear that they are just trying to impartially find out what happened. Empathetic persistence is the key. Scene investigators and interviewers unused to the emotional toil on both themselves and those they are interviewing are easily dissuaded from continuing an interview in the face of initial reticence on the part of the caregivers. The emphasis should be an acknowledgement that this is an unpleasant undertaking that needs to be completed in order to find out what happened to their infant or child.

One compromise approach would be to do the initial interviewing of "What happened?" along with the doll reenactment immediately to be followed up later with a more detailed interview when the caregivers are more composed. This can work well but requires the extra effort of two interviews which can be problematic due to staffing considerations or the inability to recontact the caregivers.

Occasionally, there are of course times when the interview and scene reconstruction need to be delayed. Most commonly, this occurs when the caregivers have left the scene en route to the hospital by the time you arrive. After assuring that the scene is being properly documented, it is then necessary for the investigator to visit

the caregivers/family at the hospital and set up a time to have them visit the scene with you for the reconstruction of what happened. The investigator should again be both empathetic and emphatic to set up the earliest appointment with the appropriate individuals to return to the scene for a recreation of events.

Ancillary interviews with non caregiver family, friends, the infant's medical personnel, etc. can be delayed for a few days for mutual convenience. Remember however that interviews delayed for more than a few days often do not happen.

What constitutes a pediatric death scene interview(s)? The interviews usually consist of "What happened?" addressed to the caregivers; "What did you see?" addressed to caregivers, first responders, and terminal-treating medical personnel; and "What do you know about this infant?" to be posed to just about everyone you would interview.

First and foremost, the medical examiner/coroner needs to know the condition of the infant/child when last seen alive and the conditions and environment surrounding the infant/child when found dead. Since these deaths often occur during sleep, the interview should specifically address how the infant was put down to sleep (with exquisite detail regarding body and face position, bedding, and the type and location of any object adjacent to the infant), and, in similar fashion, how the infant was found.

The next part of the interview addresses the condition of the infant/child in the few hours/days prior to death, in addition to medical conditions that may have existed in the past. This involves taking a detailed medical history not only of the infant but of everyone that might have been in contact with the infant. It is very important that any episodes of prior trauma be documented. Lastly, the interviews seek to document the environment in which the infant lived, both immediately prior to being found (hours to usually about 3 days) unresponsive/dead and in general (several days to months).

Satisfying these goals requires a skillful interviewer. Simplistically, the interviewer and scene investigator "just" have to paint a thorough and detailed picture of how an infant or child was found dead/unresponsive, the exact circumstances and scene/environment that surrounded that child/infant prior to death, and the background/condition of the infant/child.

Skills learned in medical interviewing can be invaluable. Too often, law enforcement personnel move too quickly to specific questions. Usually, sticking with the open-ended question – "Tell me what happened?" – for as long as possible before asking for specific details yields the best results. Nevertheless, there are specific details about each scene and infant that need to be recovered during the interview. A choir room in a large university contains the following quote: "Amateurs memorize, professionals write it down." The same is true for executing a good death scene interview. The good interviewer needs a complete checklist of what questions to ask. The checklist should be prepared well in advance of the interview and should adequately and consistently cover the needed information.

But how do I know what to ask? While several jurisdictions have put together their own interview checklists, most death investigators recommend the SUIDIRF form put together by the Centers for Disease Control [CDC] (www.cdc.gov/sids/PDF/SUIDI-Form2-1-2010.pdf [see Appendix 5]. For information about the form,

Indicate whether preliminary investigation suggests any of the following:

Yes No

- ☐ ☐ Asphyxia *(ex. overlying, wedging, choking, nose/mouth obstruction, re-breathing, neck compression, immersion in water)*
- ☐ ☐ Sharing of sleep surface with adults, children, or pets
- ☐ ☐ Change in sleep condition *(ex. unaccustomed stomach sleep position, location, or sleep surface)*
- ☐ ☐ Hyperthermia/Hypothermia *(ex. excessive wrapping, blankets, clothing, or hot or cold environments)*
- ☐ ☐ Environmental hazards *(ex. carbon monoxide, noxious gases, chemicals, drugs, devices)*
- ☐ ☐ Unsafe sleep condition *(ex. couch/sofa, waterbed, stuffed toys, pillows, soft bedding)*

- ☐ ☐ Diet *(e.g., solids introduced, etc.)*
- ☐ ☐ Recent hospitalization
- ☐ ☐ Previous medical diagnosis
- ☐ ☐ History of acute life-threatening events *(ex. apnea, seizures, difficulty breathing)*
- ☐ ☐ History of medical care without diagnosis
- ☐ ☐ Recent fall or other injury
- ☐ ☐ History of religious, cultural, or ethnic remedies
- ☐ ☐ Cause of death due to natural causes other than SIDS *(ex. birth defects, complications of preterm birth)*
- ☐ ☐ Prior sibling deaths
- ☐ ☐ Previous encounters with police or social service agencies
- ☐ ☐ Request for tissue or organ donation
- ☐ ☐ Objection to autopsy

- ☐ ☐ Pre-terminal resuscitative treatment
- ☐ ☐ Death due to trauma (injury), poisoning, or intoxication

- ☐ ☐ Suspicious circumstances
- ☐ ☐ Other alerts for pathologist's attention

Fig. 2.2 Page 8 of the CDC SUIDIRF form (2008) documenting the top 25 items a survey of forensic pathologists felt were most important for them to know so they could establish a cause and manner of death for an infant dying suddenly and unexpectedly

see www.cdc.gov/sids/SUIDAbout.htm. For information about using the form, see www.cdc.gov/sids/SUIDHowtoUseForm.htm.). The form appears intimidating, but novice scene investigators using the form for the first time usually do quite well. First-time investigators should review the "top 25" list found in the form (Fig. 2.2). These "top 25s" were the questions that a polling of several forensic pathologists believed were most important to know prior to their autopsy examinations. Of critical importance in the form is the section dealing with what happened immediately prior to and after the infant was found dead/unresponsive. The two most crucial questions are the following: Describe the conditions of how the infant was put down to sleep and describe the conditions of how the infant was found.

The SUIDIRF form is an invaluable aid to the interview process. Any potential investigator/interviewer should thoroughly review the form prior to using it for the first time. If an investigator does not frequently do death scene investigations, then they should review the form from time to time. As a final note to the first-time user, the form appears to be long and tedious. Actually, you will find that if you are familiar with the form, it flows logically and relatively quickly. The first-time interviewer often is apprehensive that emotionally distraught families will find it hard to process the questions and answers required. In reality, it often helps to focus and settle caregiver(s). It is important to keep reminding both the person(s) being

interviewed and yourself that you are proceeding with the interview (and scene investigation as a whole) with the sole purpose of finding out what happened to the infant. As much as possible, try to be empathetic (but not overly sympathetic) and use the infant's name during the interview.

How to Do the Scene Investigation

As the medical examiner/coroner investigator, you will in large measure be following the same procedure that law enforcement investigators use in a typical crime scene. The medical examiner/coroner investigator however brings additional expertise to the scene by focusing on those potential hazards at a scene that could explain a mechanism of death and/or evidence of underlying medical conditions.

The medical examiner/coroner investigator must document their scene investigation via notes and photographically (which may be augmented by diagrams as necessary). If you are not actually taking the photographs, then direct the law enforcement photographer to take the pictures you want (which may not be the same pictures the crime scene technician would have taken). If you plan on taking your own pictures, then please spend some time learning how to use the camera before your first scene to avoid common picture-taking errors (Fig. 2.3).

Scene documentation begins the moment the investigator arrives. The general principle is to start documenting the scene from far away and then move in, ultimately ending up at the location where the infant was discovered dead/unresponsive. Often investigators (crime scene technicians included) forget to document (photograph) the outside of the house/apartment building/day-care center where the death event started (Fig. 2.4a, b).

As the investigator moves into the scene, document the rooms that surround the discovery location. The investigator will be expected to answer questions about the general condition of the house/apartment, hazards that might be present (to include drugs/alcohol along with noxious fumes and vermin), and the general health status and sanitation of the dwelling and those who lived in it. Pay special attention to the nutritional status of the infant, those living at the scene, and what is nutritionally available at the scene. If the infant appears malnourished and/or neglected, find out whether a formula available at the scene simply was not being given to the infant. Does the scene appear well provisioned or is it largely devoid of food? If an infant is being breast fed, does the mother appear capable of providing adequate nutrition to the infant? To help address these questions, the investigator should confiscate both the formula/breast milk bottle(s) last known to have been fed to and/or prepared for the infant and samples of the formula mix containers which the caregivers used to prepare the infant's formula. If the formula was not being mixed with tested municipal water or bottled water, a sample of the water used to prepare the formula should also be secured. Formal testing of these samples should be left to the discretion of the pathologist.

An often overlooked finding at the scene is the temperature. While it is important to record the temperature at the scene, make sure to ask if this was representative of

Fig. 2.3 Examples of two common errors in scene photography. The *left* most frame illustrates a scene with adequate lighting while the *middle* frame illustrates the limited ability of a camera flash to adequately illuminate distant aspects of a scene at night. The furthest *right* frame documents the difficulty of capturing a room interior by shooting the picture through an open doorway

Fig. 2.4 (**a**) The *left* and *right* frames illustrate the progression of not only photographing, but processing, as seen from the outside to intermediate detail. (**b**) The conclusion of the "out to in" photographic documentation is the "close-up" scene, shown in this photograph

the temperature at the time the infant was discovered (the temperature, for example, may have been quite a bit warmer where the infant was found before doors were opened, and left open, by the first responders and subsequent investigators).

The documenting approach at the scene should continue to be overviews, intermediate views, and then close-up views. A review of law enforcement scene photos often reveals a preponderance of close-up views and not enough overviews. If an overview reveals a potential significant finding, then zoom in to document that observation followed by pulling back to an overview of a different location/room at the scene. The same approach is followed at the site where the infant was discovered.

The crime scene technicians at the scene should be helpful in directing where to look for those items that are not necessarily immediately visible. For example, occasionally it can be helpful to lower oneself to hands and knees to get a more revealing "child's" perspective of the scene. While searches of refrigerators and pantries might be obvious to assess the nutritional and alcoholic beverage status of the household, do not forget to look into medicine cabinets, trash containers

throughout the house, and other places where things might be stored that the occupants of the home might not want an investigator to see (in one scene, for example, the dishwasher was filled with liquor bottles).

The specifics of what to look for at a scene will become more obvious during the discussion of the possible mechanisms of infant deaths in the remainder of the chapter. Just as the SUIDIRF form addresses the scene interview, it also brings up many issues that will focus on the physical scene investigation/documentation. The SUIDIRF form not only allows to capture what was said at the scene, it also provides a format to record what was observed at the scene.

Death Scene "Don't Forget" Checklist

- Keep an open mind. Do not arrive with preconceived ideas.
- Make sure the scene is safe to enter.
- Have a SUIDI or comparable form to record observations.
  - Use open-ended, non leading questions before progressing to more specific questions.
  - Record the general condition of the scene (are there hazards to those living there?).
  - Health status of those living (or present) at the scene.
  - Look around (as allowed); look at drawers, medicine cabinets, trash, etc.
  - Record the air temperature where the infant was discovered along with the outdoor temperature.
- Bring a camera and know how to use it (or have someone else take pictures under your direction).
  - Start with distant general scene pictures (make sure to take a picture of the outside of the scene).
  - Take intermediate zone pictures (like the inside of a room).
  - Take close-up pictures.
- Bring a reenactment doll (use a stuffed toy if you forget).
  - Double-check to make sure the doll is placed in an environment exactly like what was there when the infant was discovered.
  - Reenact the position PLACED.
  - Reenact the position LAST KNOWN ALIVE.
  - Reenact the position FOUND.
  - Document layers of bedding/clothing above and below the doll.
  - Make sure all of these reenactments are photographed.
- Review pertinent medical/ambulance/police records.
- Remember, there may be more than one scene (e.g., a day-care center, home, hospital).

In the last several years, "doll reenactment" has revolutionized how infant death scenes are documented.

The theory is simple: using a doll to represent the infant, placing the doll in the position the infant was in at the time he/she was put down to sleep, and then recreating the conditions in which the infant was found. This simple concept has nuances that can spell the difference between a successful recreation and one that is not.

Fig. 2.5 An example of two different types of dolls that can be used in a doll reenactment. The doll on the *right* is a standard play doll that can be found at almost any toy store/department. While more realistic, the doll on the *right* is limited by a defined race and gender, a nonrealistic size and weight, and limited mobility of extremities and the neck. The larger doll on the *left* obviously is less realistic but is free of the other limitations listed above. The larger doll also is weighted (5.7 kg) to more closely approximate a real infant's weight

First, start with the doll. Controversy exists whether the doll should be "realistic" or more of a "Raggedy Ann" style. If the realistic approach is taken, should the doll be the same size, gender, and racially similar or dissimilar to the infant at the scene? While these are all worthy considerations, in practice, most investigators have not found that they significantly impact the doll reenactment process. A doll of the approximate size of the infant at the scene is helpful. Also helpful is a doll whose neck and arms articulate enough to replicate a real infant's sleeping positions. A suitable doll can be found at almost any toy store. The expensive recreation dolls to be found in law enforcement supply sites are good to work with, but are not necessary. All of the above being said however, it is better to do a doll reenactment with an imperfect doll than not to do it at all (Fig. 2.5). Should an investigator arrive at a scene without a doll, almost all infant death scenes have stuffed animal toys present which can be used (Fig. 2.6). Even stuffing a pillowcase with laundry can work.

Given the vital information that can come from a doll reenactment, any pediatric death scene investigator should have a doll as part of their scene investigation kit, as should law enforcement officers processing infant death scenes. At the scene the doll should be carried in its own carrying case. A simple duffle bag will work. The important part is to handle the doll with respect (Fig. 2.7). The investigator walks a thin line between handling the doll as a plaything and handling the doll as if it truly was the caregiver's infant. It is important to stress to those at the scene that the doll is only being used to recreate how the infant was put to sleep and found, solely for the purpose of helping the pathologist understand why your infant died.

Fig. 2.6 Most scenes of sudden and unexpected infant death have a stuffed animal toy that can be used in lieu of a more realistic doll in a doll reenactment

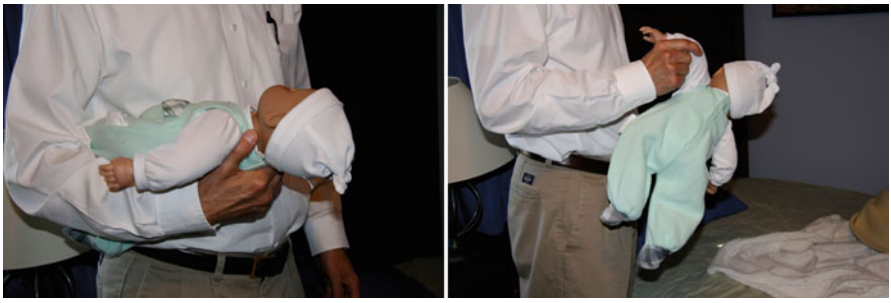

Fig. 2.7 During the doll reenactment the doll should be handled in a respectful manner (*left frame*). The doll should not be handled cavalierly (*right frame*) since to the caregivers present at the scene this might imply disrespect for the deceased infant

The timing of when to introduce the doll into the interview/scene investigation is a matter of personal choice. Some prefer to lead with the doll at the start of an investigation. Others prefer to wait until after the caregivers have been interviewed before introducing the doll. In either case, it is important to explain what is going to happen before taking the doll out of its carrying case. Some caregivers and family may object at this point; however, experience has shown that most caregivers will cooperate after explaining how important the reenactment is toward finding out what happened to the infant. The doll reenactment however requires the permission and cooperation of the caregivers and cannot proceed without it.

Once it is established exactly where the infant was found, ask the caregiver to place the doll "exactly" where the infant was discovered. At this point it is important to make sure that everything is exactly as it had been. This includes the condition of the bedding, sleeping surface, and, perhaps most importantly, others that might have been sleeping with the infant (Fig. 2.8). Does this mean that an

Fig. 2.8 The doll should be placed as exactly as possible in the positions placed and found

Fig. 2.9 In this photograph the caregiver has been asked to replicate the exact position he and the infant were in at the time the infant was put down for a nap. This bed-sharing scenario does not appear immediately life-threatening should it also represent the position found. Even in this scenario however bed-sharing should be considered a risk for sudden unexpected infant death since the veracity of the positioning always is an issue, along with possible undocumented relative adult-infant movement during sleep

investigator should expect other adults or children who might have been sleeping with the infant to get into bed with the doll? The simple answer is, "Yes" (Fig. 2.9).

If there are going to be caregiver/family objections to the doll reenactment, they are most likely to arise at this point. Assured that any photographs will be strictly confidential and that it is vital to exactly recreate the scene, most adults will comply with the request. If the adults refuse, then sometimes a surrogate (a police officer, for example) can be used. If that fails, then an inanimate object such as a pillow sometimes can be substituted for the adult bed-sharer, or the recreation can be done with a photograph. Another alternative, particularly if the caregivers were not at the scene

Fig. 2.10 The caregivers were not present during this death scene investigation. This infant was "found" where "placed" as marked by the caregivers on a photo taken at the scene

investigation, is to ask the caregivers to mark a photograph of the sleeping conditions with the "placed" and "found" positions of the infant (Fig. 2.10).

When everything is in place, then question the discoverer again to make sure that everything is indeed correct. It is best to couch these enquiries in the form that I, the investigator, am struggling to make sure that "I" correctly understand exactly what the correct position and conditions should be. Once everything is in place, the recreation should be carefully photographed in the same sequence used before – overview, intermediate, and then close-up. To properly understand the positioning of the recreation, it may be necessary to remove bedding or other objects in layers, photographing each sequence (Fig. 2.11).

Since proper documentation of how the infant was found is of paramount importance, many investigators prefer to proceed with the reenactment first (in case, for example, the caregivers develop concerns about the process and abandon the reenactment). Once the position found has been recreated, then repeat the process with the position placed (Fig. 2.12).

At the conclusion of the doll reenactment, the bedding under the infant should be documented. The layers of bedding should be removed in order, photographing and describing each layer as it is exposed. During this process it is important to document in the scene report exactly how soft and "breathable" each layer is (this usually is hard to accurately assess from a photograph alone).

After completing the photographic documentation, many law enforcement officers prefer to secure the bedding and possibly sleeping surface such as a crib or playpen as evidence. While sometimes this may seem to be a little too intrusive to a grieving family, it may be helpful at other times when the investigator is unable to adequately examine the bedding and sleeping surface at the scene (or no medical examiner/coroner scene investigation was done – which unfortunately happens more often than it should). If the bedding, and perhaps a crib or playpen, is taken from the scene, then the family/caregivers should be clearly told that the materials will be returned along with a general time frame in which to expect this.

Fig. 2.11 During the doll reenactment, the layers of bedding present on top of the infant (both as placed and found) should be carefully photographed as it is removed, layer by layer

Both the medical examiner/coroner investigator and the lead law enforcement investigator should leave their contact information with the caregivers (and family if not the caregivers) and encourage follow-up questions and statements.

Death Scenes that Explain the Cause of Death

Driving the necessity of pediatric death scene examinations is the perhaps underappreciated fact that there are a number of causes of infant death that either leave no pathologic changes at autopsy (a negative autopsy) or cause nonspecific autopsy findings.

A leading cause of death with a negative autopsy is asphyxia. Does this mean that an infant or child can asphyxiate with no abnormalities noted at the autopsy? The answer is clearly "yes."

Therefore, it is important to evaluate the pediatric death scene to determine whether the infant did asphyxiate, potentially could have asphyxiated, or had no

Fig. 2.12 Photographs should be taken during the doll reenactment, documenting the position placed (*left frame*) and the position found (*right frame*)

potential for asphyxiation. Pediatric asphyxiation can usually be subdivided into suffocation (e.g., face down on a plastic bag), mechanical asphyxia or wedging (e.g., caught between a mattress and a wall), smothering (e.g., being overlaid by an intoxicated adult), strangulation (e.g., an infant's neck becoming tangled in a window-shade draw cord), or rebreathing (e.g., face down on soft bedding that allows air to circulate only in a confined space such that carbon dioxide accumulates to lethal levels rather than being dispersed out into the atmosphere) (Fig. 2.13).

Only rarely does the first glance at an infant death scene reveal a definitive asphyxial death (Fig. 2.14).

Careful examination of the scene however may demonstrate items such as plastic bags that could potentially asphyxiate an infant. The investigator should carefully look at the scene to identify what "potentially" could have asphyxiated an infant. The asphyxial potential of a scene is often difficult to quantify. Frequently, an investigator has to simply trust their instincts. Many believe that the potential for asphyxia is something you subjectively recognize when you see it. Obvious potential asphyxial concerns are infants sleeping on soft bedding, infants sleeping on adult-sleeping surfaces (particularly adult beds and couches) (Fig. 2.15), and bed-sharing with adults. Although many cultures and parental support groups endorse adult–infant bed-sharing, an increasing number of infant death investigators believe that it represents a potentially asphyxial situation.

Fig. 2.13 The danger of "egg carton" foam is illustrated in this figure. It is clear that an infant face down on the overlying thin sheet could "breathe" but that the expired air is simply recycled in the interstices of the foam and "rebreathed"

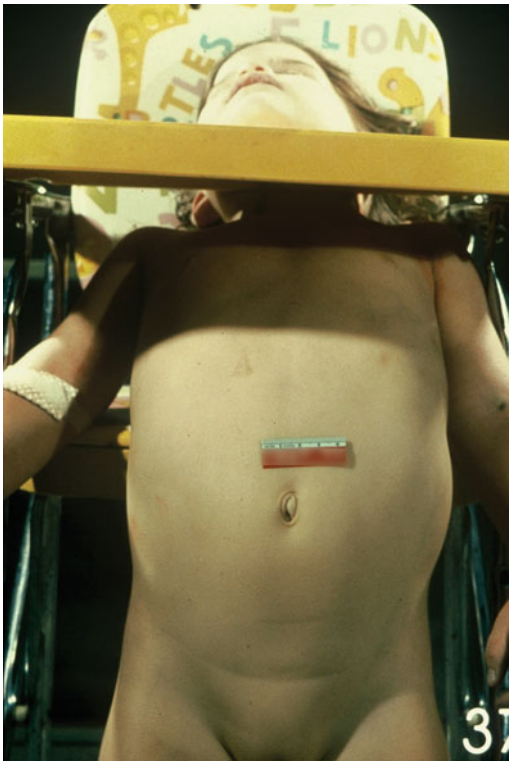

Fig. 2.14 This figure illustrates a hanging or strangulation type of asphyxia where, in this case, the infant's neck was compressed as she slid down from the seat of her high chair

The recent increasing use of the doll reenactment at infant death scenes has clearly illustrated a potential for infant asphyxia that had not been either realized or appreciated earlier. The doll reenactment can clearly show a potential for asphyxia by demonstrating how an infant was found face down in soft bedding (see Fig. 2.15), wedged into the corner of a crib (see Fig. 2.12), wedged between the mattress and crib slates, or covered up by an adult bed-sharer (Fig. 2.16).

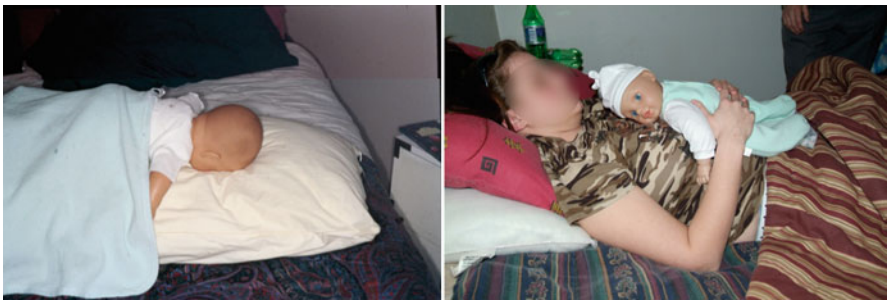

Fig. 2.15 This figure illustrates soft bedding surfaces that could all pose a potentially significant risk for asphyxia. We often do not appreciate that a mother's abdomen and chest (particularly a heavy woman with large breasts) poses a "soft bedding" hazard

Fig. 2.16 Here are two reenactments of overlaying asphyxia. In the *left* frame the mother accidentally rolled partially onto her infant. The *right* frame is a more commonly recognized scenario of a drunken individual collapsing onto a couch or chair unaware that they have collapsed onto an infant

Other more subtle asphyxial challenges can also exist at an infant death scene. Examination of the scene may reveal, for example, that the oxygen in the atmosphere surrounding the infant may have been partially replaced by another gas such as methane from a gas heater or carbon dioxide from an adjacent cooler filled with dry ice. Infants dying from this type of asphyxia have similarly negative autopsies as would a smothered infant.

Another external event that can cause an infant death yet be associated with a negative autopsy involves extremes of temperature since an infant can die of hyperthermia (overheating) or hypothermia (freezing to death) with few to no pathologic changes at autopsy. It is incumbent therefore for the scene investigator to document the temperature at the scene. As mentioned earlier, the temperature at the time an investigator arrives at the scene might not represent either the temperature at the time the infant was discovered or to which the infant was exposed immediately prior to death.

Fig. 2.17 Not only is this reenactment doll suggesting an unsafe bedding surface/position, the multiple layers of clothing and bedding suggests the possibility of hyperthermia given that the ambient temperature in the sleeping environment was 34 °C

Infant deaths have been documented where the temperature in the room where the infant was discovered was in the comfortable "room temperature" range, but when investigators came back later, the room's radiator was active and the room temperature had soared above 45 °C. Likewise, a room temperature may have been below 0 °C from an open window that was closed when the infant was initially discovered. Only careful interviewing and scene investigation can document what the temperature was at the time of his or her death.

The appropriateness of the infant's clothing also must be taken into account when assessing the potential for a temperature-related death. An infant can die of hyperthermia in a room temperature environment if overdressed (e.g., an infant wearing multiple flannel "onesies" and tucked under several thick blankets or quilts) (Fig. 2.17).

Likewise an infant only wearing a diaper can become hypothermic in an environment in the teens centigrade. Therefore, the investigator must document what the infant was wearing while sleeping, along with what bedding may have been over the infant at the time. Both of these items should be addressed while doing the doll reenactment.

Carbon monoxide can kill infants preferentially while leaving the adults present with few (perhaps a headache), if any, other symptoms. While carbon monoxide can clearly be identified at autopsy, infants can die with levels of carboxyhemoglobin that might not produce the characteristic cherry red color in blood and tissues. This type of infant carbon monoxide poisoning therefore might only be detected if the scene investigator found the potential for carbon monoxide poisoning (most commonly seen with indoor heaters, confined open indoor fires/barbeque grills, and faulty furnace flues) (Fig. 2.18). If carbon monoxide poisoning is suspected at the scene, an air sample can be collected in an empty red-top vacutainer or an empty mason jar. Preferably however, the carbon monoxide level should be tested immediately at the scene. Small, portable carbon monoxide detectors are often readily available, particularly if the fire department is part of the emergency response team. The investigator can also check to see if a previously installed, working carbon monoxide detector might already be present at the scene.

Fig. 2.18 Carbon monoxide can be lethal for infants without producing serious symptoms in adults. A sudden unexpected infant death associated with other caregivers complaining of headaches or confusion should warrant a search for possible sources of carbon monoxide, such as this faulty furnace flue

Although electrocution may leave characteristic burns on the body, low voltage (110–220 V household current) can be lethal with no external or internal autopsy findings. The investigator therefore must search out the potential for an infant to have been in contact with any electrical device or power cord. In addition to the obvious, such as power cords lying across a crib or an electric blanket, the investigator should also determine if electrical devices might have come in contact with a sleeping surface (e.g., an electric heater leaning against a metal crib). If an electrical device is suspected to have caused a death, then it should be confiscated and tested by a competent electrical technician to assess its potential to have produced an electrocution death.

Occasionally, a scene will suggest an obvious toxicology-related cause of death, for example, a young child found dead on the floor with an open bottle of methadone syrup adjacent to the body. Other adjacent adult medications, prescription or not, would raise similar concerns. Even if an infant or child does not have obvious access to a drug, drugs potentially available to an infant or child should be documented as potential causes of the death. Particular concern is warranted when obvious drugs of abuse (Fig. 2.19) are found at a scene. Intoxicated adults at such a scene can potentially either deliberately give children drugs of abuse or drugs may be inadvertently left where infants and children can find them while their caregivers are unable to provide adequate supervision. One "drug of abuse" that should never be overlooked is ethanol. An older infant potentially could drink from an unattended glass of distilled spirits, and caregivers may have given an infant alcohol as a sedative. Over-the-counter cough medications are often used for infant sedation and can also result in drug-related infant deaths.

While toxicology testing done from samples collected at autopsy may detect drugs and toxins either causing or contributing to an infant death, not all drugs and toxins will be found in routine toxicology testing. Sometimes toxicology testing is confined to "drugs of abuse." Despite the fact that the more comprehensive testing done by many forensic pathologists will be able to detect a large array of drugs,

Fig. 2.19 Infants and children can come into contact with a variety of toxic substances and medications/drugs that can be lethal. In the *left* frame, we see a variety of dangerous chemicals associated with a methamphetamine laboratory. The infant in this scene died after ingesting volatile hydrocarbons. In the *right* frame, we see the more common scenario where both alcohol and prescription medications are present. In this case the infant died of asphyxia perhaps in part contributed to by low blood levels of both alcohol and benzodiazepines which most likely came from maternal use and were transferred to the infant via breast-feeding

there remain other drugs and toxins that will not be detected by even comprehensive "routine" toxicology. Examples include poisons such as strychnine and cyanide, household toxins such as pesticides and herbicides, volatile hydrocarbons, and many medications such as methotrexate. Almost any drug or toxin can be detected and quantified by a toxicology laboratory if they know how to look for it. Therefore, it falls to the scene investigator to identify those drugs and toxins present at the scene, not just those near where the infant was found, but particularly with older children, present anywhere throughout the home.

Deaths Explained by Autopsy

Even when an autopsy produces a cause of death, the scene remains a valuable part of determining the cause of death. Sometimes, the scene is helpful in corroborating what was found at autopsy. In other circumstances, a cause of death established at autopsy might have been found only because the scene investigation suggested a more directed autopsy examination (e.g., the presence of an unusual toxin as mentioned above).

Deaths of infants and children occurring outside the hospital have been arbitrarily divided into two categories: Where the scene provides the clues for the cause of death and where death is established at autopsy; the caveat in this latter group is that at the time the death investigator is at the scene, he or she will not know the autopsy results. Therefore, the scene investigator must proceed both from the standpoint that their investigation will provide the potential cause of death should the autopsy be negative or that their findings at the scene will either corroborate or direct subsequent positive autopsy findings.

Medical/congenital conditions remain the most common cause of death in infants, although less so than in those infants dying suddenly outside hospital. Nevertheless, medical and congenital diseases can cause sudden unexpected deaths. Careful interviewing may reveal that an infant's death actually was not as sudden or unexpected as initially believed. Once the initial attempts at resuscitation are over, caregivers may be able to give a more thorough medical history. Sometimes those caring for an infant may not be aware of significant medical problems which come to light only after more immediate family members are interviewed.

Just because the family of an infant states that an infant has an underlying significant medical history, for example, a severe congenital defect or a large tumor, the investigator should confirm this history with a medical provider. Even then, infants and children with severe underlying diseases can still die of accidental suffocation or inflicted trauma.

In other cases of infants dying of natural diseases, the time course may be more acute. The SUIDIRF form allows the investigator to ask those questions which might point to a more acute illness. Questions about changes in feeding, fever, coughs, vomiting and diarrhea, and rapid breathing can point to the development of diseases such as pneumonia. Unlike adults where natural diseases causing death often develop over many hours to days, infants and children can progress from apparently healthy to dead in only a few hours. Only careful interviewing can tease out the signs and symptoms (which can be relatively inapparent to nonmedical observers) that might suggest a rapidly evolving underlying medical condition. Consultation with a pediatrician may be helpful in interpreting subtle signs and symptoms unique to infants.

The physical scene can also suggest underlying disease. Any pediatric medications present should be examined to include what the medication is for, whether it appears to have been used appropriately, and the prescribing physician who might be able to provide additional medical information. Over-the-counter medications present at the scene also may suggest an acutely ill infant. Likewise, other equipment found near where the infant was found, e.g., vaporizers, monitors, and fever thermometers, may also suggest an ill infant (Fig. 2.20).

Careful interviewing of the caregivers/family may not only suggest a possible underlying illness in a dead infant but should also reveal if others in the family or those in contact with the infant (e.g., in a day-care setting) have been ill. As an example, a caregiver recovering from influenza may be significant, since viral illnesses can cause rapid deaths in infants, but may be difficult to detect at autopsy without special diagnostic testing.

In addition to natural diseases however, trauma also can cause sudden infant and child deaths. In many cases the traumatic nature of the death is obvious, most notably motor vehicle crashes and documented falls. Accidental trauma in the home may be obvious. A toddler may have fallen from a window, or heavy furniture such as a television stand or dresser may have fallen on an infant or child. Are there stairs a toddler could fall down or a window to fall out of? (Fig. 2.21) Is the apartment cluttered with objects that could cause a fall or does it appear that the caregivers have made an effort to "childproof" the scene? The investigator at such a scene

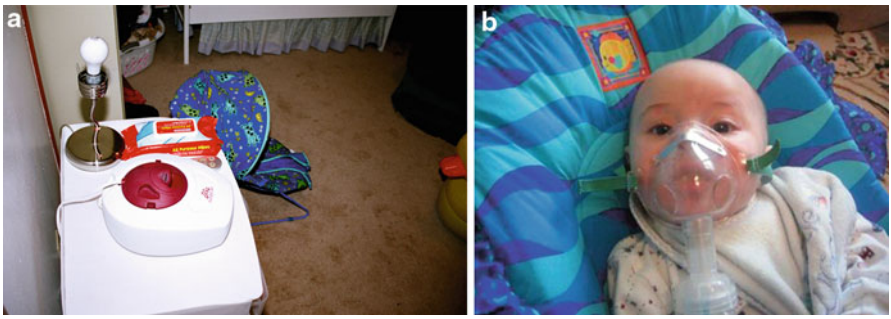

Fig. 2.20 The presence of a vaporizer near where an infant was found dead may be unrelated to death but could also suggest that the infant may have had some respiratory symptoms (**a**). The supplemental oxygen mask is suggestive of a more severe underlying illness, often respiratory damage associated with prematurity (**b**)

Fig. 2.21 The steep staircase represents a significant potential for a hazardous fall. In this case however, the pattern of skeletal injuries and abdominal trauma was not consistent with a fall, even from an unsafe staircase such as this

should both carefully document the circumstances of the trauma and also investigate the potential for the trauma to have occurred. For example, is it possible that the dresser could have fallen onto a toddler simply by the toddler climbing onto a drawer, or would more force have been necessary for the dresser to fall? Was an

infant physically capable of accessing the open window whence he reportedly fell? Is the tap hot water sufficiently hot to scald (which obviously would require a measurement of the tap water temperature at the scene)? Could an infant or toddler have drowned (requiring careful descriptions, photographs, and measurements of the purported drowning environment)? These questions reflect the necessity of assuring that "accidental" trauma is indeed accidental.

A negative interview for trauma however does not eliminate a traumatic death. Those being interviewed may be deliberately denying a traumatic event or more benignly may have simply forgotten what at the time appeared to be a relatively trivial episode. In other cases the traumatic event may not have been witnessed, such as a fall or trauma inflicted by other young children.

To be discussed elsewhere in this book, a major concern with traumatic deaths is the differentiation of inflicted from non inflicted injuries. A careful scene investigation will be invaluable in determining the plausibility of trauma occurring in an accidental fashion or not. To help rule inflicted trauma in or out, the scene should be carefully canvased to detect subtle signs of trauma that might not be immediately evident. Much of this effort will fall upon the crime scene technicians to discover trace evidence such as blood and hairs and fibers adherent to objects that could have been used as weapons.

Other indications of inflicted trauma might include unexplained minor injuries to a caregiver (e.g., a caregiver's bruised hand from inflicting a slap). A child thrown against a wall might produce subtle indentations in wallboards. Evidence of objects being violently thrown around and/or broken furniture in a nursery (when the remainder of the home is neat and clean) could suggest an adult caregiver's rage reaction to a fussy infant.

Since inflicted trauma to infants and young children often is not apparent when the infant is discovered unresponsive or dead, the investigator's job is complicated by the need to adequately document the scene should trauma become evident later at the autopsy while not at the same time creating unwarranted suspicion that the caregivers are responsible for potential unrecognized trauma.

Conclusion

While we would like to believe that autopsy is the ultimate procedure for determining why infants and children die suddenly and unexpectedly, for these young victims it often fails to determine a definitive cause of death. Over the years we have increasingly found that information gathered at the scene of these deaths can be invaluable in determining why these infants and children die.

At the crux of the matter is the fact that many external conditions can kill a child or infant without being detected at the autopsy. Extremes of temperature and other environmental hazards fall into this group, but the two leading potential causes of death with a negative autopsy are asphyxia and SIDS. Often only a thorough scene investigation can differentiate between those two.

Identifying potential causes of, or contributors to, a sudden unexpected pediatric death requires a detailed and exacting death scene investigation. As an aid to both the experienced and novice death investigator alike, the CDC SUIDIRF form (www.cdc.gov/sids/PDF/SUIDI-Form2-1-2010.pdf) offers easy-to-follow directions on the proper procedure to process a pediatric death scene. Coupled with detailed photographs of the scene, the SUIDIRF form offers the pathologist charged with determining the cause of an infant or child death the detailed information needed to fill in the gaps that might remain after a complete autopsy examination.

An integral part of the scene investigation is the doll reenactment of how the infant/child was put down to sleep and/or last seen and how the body was subsequently discovered. All too often this doll reenactment reveals asphyxial or other hazards that were not immediately obvious from the verbal descriptions of the scene elicited from the caregivers.

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The Pediatric Autopsy

3

Richard M. Conran and J. Thomas Stocker

Contents

Abstract

The forensic autopsy plays a key role in the determination of the cause and manner of death. Many protocols exist for the performance of a hospital-based autopsy. Standardization allows for a comprehensive and systematic approach. The forensic autopsy, however, provides its own unique issues. The individuality of the case

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as representing the views of the Uniformed Services University or the Department of Defense.

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may dictate deviation from standard protocols. This chapter focuses on the standard format for the infant autopsy that can be modified as needed, based on the decedent's age and the circumstances surrounding the decedent's death.

Introduction

Inherent in the investigation of death is the identification of the decedent and the determination of the cause and manner of death. The autopsy is critical in this process. In contrast to the typical hospital-based autopsy, the forensic autopsy has its own unique considerations. Protocols for performing an autopsy (Bohm 1988; Busuttil and Keeling 2009; Collins 2010; Finkbeiner et al. 2009b; Gilbert-Barness and Debich-Spicer 2005; Hutchins 1994; Macpherson 1994; Ophoven 2007; Seibert 2007; Stocker 2011; Valdes-Dapena and Huff 1983; Valdes-Dapena et al. 1993) including forensic considerations (Busuttil and Keeling 2009; Ophoven 2007; Corey and Collins 2011) and the pathology that may be observed at autopsy have been published (Bohm 1988; Gilbert-Barness and Debich-Spicer 2005; Husain and Stocker 2011).

The forensic autopsy may present challenges, however, requiring deviation from the standard protocol. "The individuality of the case must often determine the plan of examination" (Virchow 1896). Legal considerations also play a role (Carpenter et al. 2009). The standard approach to infant autopsy is the focus of this chapter and is based on the experience of the authors incorporating many techniques from these references and our colleagues' experience and is further illustrated in our prior publication (Stocker 2011). The following autopsy protocol can be modified in older children where the prosection is similar to adult autopsy. Specific forms useful in documenting autopsy findings are included in the appendices. Subsequent chapters discuss special techniques and dissections that deviate from the standard protocol in the forensic setting.

Authorization (Autopsy Permit)

In the hospital setting, permission for the standard non forensic autopsy is ordinarily granted by the legal next of kin in accordance with standards set by the legal jurisdiction through an autopsy permit. Restrictions on the extent of dissection and the use of tissue for research and education are specified. In contrast, the forensic autopsy is authorized by the legal jurisdiction where the injury or death occurred (Nath and Conran 2010; Carpenter et al. 2009). Discussion of specific rules for each jurisdiction is beyond the scope of this chapter; however, it is imperative that the pathologist performing the autopsy be familiar with the laws governing the practice in their respective jurisdictions. For most forensic cases, the legal jurisdiction authorizes the pathologist to perform whatever dissection is needed to determine the cause and manner of death. Retention of tissue for research and education is usually not authorized. Hospital-based pathologists need to know the criteria for medical examiner/coroner, jurisdiction in their respective communities.

Medical Records

After validating the authority to perform the autopsy, the pathologist needs to review the decedent's medical records (including birth records) and reports from death investigators and other personnel who have background information pertaining to the autopsy. Photographs from the death scene or location where the child was before transportation to a medical facility may be useful. Any social records, feeding records, pharmacy records, next-of-kin information, and witness statements are also helpful.

Photography

Photography is an integral and highly important part of any autopsy. Upon receipt of the body, the decedent is removed from the bag used to transport the body to the autopsy suite. Photographs of the entire body as received to include clothes, medical devices, and artifacts are initially taken. Specific photographs of injuries or other evidentiary material are obtained next. Prior to external examination of the decedent by the pathologist, whole-body photographs and images of specific injuries or anomalies need to be obtained. Basic images should include the external surface of the body (front and back) and anterior and lateral views of the face. After removal of the decedent's clothing, it may be saved as evidence with proper chain of custody. Areas of suspected trauma along with nontraumatic areas should be photographed for comparison. Use of draping is recommended to minimize the "shock effect" of certain injuries and to eliminate distractions, such as chest tubes or IV lines, from the injuries. Draping is also effective in forensic cases to focus on the site of injury and to exclude extraneous features a jury may find offensive, therefore minimizing their exclusion as evidence in a legal proceeding. Case and/or autopsy number (case identification) and a standard ruler should be included in all photographs. A ruler placed at the edge of the picture helps define the dimensions of a lesion. Throughout the prosection, images of internal organs are taken as needed to document anatomic abnormalities or specific pathologic features (e.g., necrosis, hemorrhage, exudate, anomalies). Incisions of the back, buttocks, and extremities should be photographed particularly in cases of suspected non accidental trauma.

The availability of digital technology allows many photographs to be taken with the "excess or unnecessary" images easily removed at no cost (Belanger et al. 2000) although this is not permitted in some jurisdictions. While fixed photography equipment is useful (Finkbeiner et al. 2009a), a handheld SLR camera is more easily utilized and encourages the taking of images throughout the performance of the autopsy. Furthermore, the images can easily be transferred electronically to law enforcement officers.

Imaging

Imaging via X-rays, magnetic resonance imaging (MRI), or computed tomography (CT) is important in diagnosing and documenting skeletal abnormalities, central

nervous system (CNS) pathology, tumor metastases, and congenital or developmental anomalies (Patriquin et al. 2001). Imaging may also be helpful in recording the presence of pneumothorax, pneumopericardium, and pneumoperitoneum; air in the lungs; and air in the gastrointestinal system. The role of imaging is further discussed in ▶ Chaps. 15, "Evaluation of Pediatric Fractures at Autopsy," and ▶ 20, "Neuroimaging of Pediatric Inflicted Injury".

Autopsy

Instrumentation

The instruments used in performing the pediatric autopsy are different from those used in adult autopsies, both in type and size. Pediatric autopsies, particularly those done on fetuses and neonates, require smaller and more delicate instruments than the "full-sized" instruments used on larger children or adults (Table 3.1).

External Examination

The external examination of the body is one of the most important aspects of the pediatric autopsy. Examination is critical for identification of the decedent through fingerprints, dental records, and other identifying marks. The external examination also offers information about the general health of the child, evidence of therapy, and signs of trauma and portends what might be expected when the body is opened. The external examination is a good indicator of chronic disease, malnutrition, child neglect, or abuse. Regardless of age, general measurements at autopsy include body weight and body length (crown-heel length and crown-rump length). Additional measurements include foot length, arm span from the tip of the fingers of one hand to the tip of the fingers of the other hand (which in most cases approximates the crown-heel length), head circumference (occiput to frontal), chest circumference (at level of nipples), and abdominal circumference (at level of umbilicus) (Fig. 3.1). This information can be recorded in the external description and/or on drawings included in the final autopsy report. External markings such as needle marks, IV tubes, chest tubes, incisions, and abrasions also need to be measured, photographed, and recorded.

In the forensic setting, documentation of livor mortis and rigor mortis are indicated (Corey and Collins 2011; Ophoven 2007).

Face, Eyes, Ears, and Mouth (External and Internal)

Examination of the face begins with an overall view to determine symmetry and gross abnormalities. Special attention should be paid to midfacial development (hyper/hypotelorism, nasal bridge deformities) and hair patterns. The hair growth pattern usually consists of one or two whorls in the upper occipital/parietal area. More than two whorls or actual defects in the scalp are associated with underlying CNS abnormalities. The anterior and posterior fontanelles are examined for their

Table 3.1 Instruments used in performing the pediatric autopsy

Scissors
a. Thin, small, with tapered points, and curved tip, used more for dissection than cutting. Limit their use to soft tissues and organs, not for bone, cartilage, or dense tissues
b. Medium sized, straight, or curved for opening bowel
c. Large or heavier ones for opening calvarium and vertebral column
Forceps
a. Small and medium sized, but WITHOUT teeth (which only tears tissue)
Hemostats
a. Small and medium sized
b. Straight and curved
Scalpels
a. #10 size curved for most routine work
b. #1 size with pointed tip for delicate cutting
c. Double edged, rectangular for sectioning organs such as spleen, lung, liver, and kidneys
Knifes
a. Straight, of various sizes for sectioning larger organs such as liver, brain, or organs of larger children
Balances for weighing
a. Standard hanging balance for weighing neonates, infants, or small children
b. Electronic balance (accurate to 0.1 g) for weighing organs
Probes of various diameters to establish patency of various openings including nares, ears, ureters, urethra, biliary tract, and heart valves

From Stocker (2011)

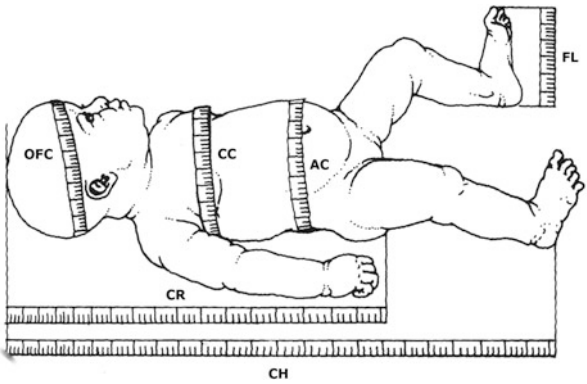

Fig. 3.1 External measurements. Routine measurements taken as part of the infant autopsy are illustrated. (*OFC* occipital-frontal circumference, *CC* chest circumference, *AC* abdominal circumference, *FL* foot length, *CR* crown-rump length, *CH* crown-heel length) (Reproduced from Macpherson (1994))

size (maximum length and width), shape, and "fullness" (i.e., bulging, depressed). The neck should be flexed and extended as far as possible to determine its range of motion.

The eyes are examined for both size and location. The measurement of each palpebral fissure should, in a normal infant, equal the intercanthal distance effectively dividing the face at the level of the eyes into three equal expanses (Fig. 3.2).

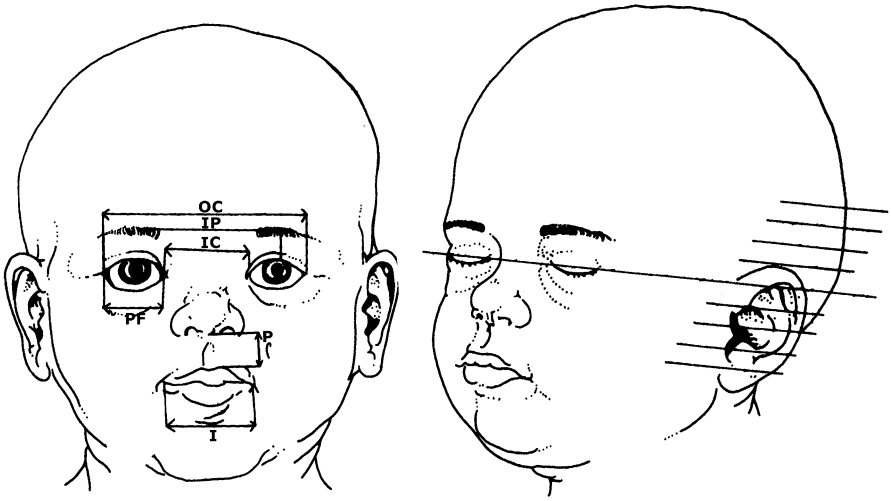

Fig. 3.2 Facial measurements. The length of the palpebral fissure is compared with the intercanthal distance in evaluating the infant for hypertelorism. The height of the superior helix of the external ear is measured in comparison to the palpebral fissure. (*I* intercommissural distance, *IC* intercanthal distance, *IP* interpupillary distance, *OC* outer canthal distance, *P* philtrum length, *PF* palpebral fissure) (Reproduced from Macpherson (1994))

If the fissure length exceeds the intercanthal distance, the eyes are closer together than normal (hypotelorism), and conversely, if the intercanthal distance exceeds the palpebral fissure length, the eyes are too far apart (hypertelorism).

Examination of the eye itself includes the diameter of each globe and comparison with each other to determine if the eyes are of equal size. If one is smaller than the other, microphthalmia may be present. The pupils are examined for their size and symmetry and the irides for color and completeness (which may be difficult to determine in a premature infant).

The nose examination includes its position and shape (e.g., upturned, flat) with evaluation of cartilage development. A curved probe is used to determine the patency of the choanae (posterior nasal apertures). The lip beneath the nose (the prolabium) should be observed and determined if it is longer than usual. Examination of the ears begins with determining their position on the side of the head relative to the level of the palpebral fissures. In near-term and term infants, the superior helix of the ears should be above the level of the palpebral fissures or they are considered to be "low set" (Fig. 3.2). The ears are also examined for patency of the external auditory canal (via small caliber probe) by pulling down on the earlobe as the probe is inserted. The external ear is evaluated for its shape, completeness, and the presence of cartilage.

The mouth is inspected both externally and internally looking for signs of injury, for example, laceration of the frenulum. A finger is inserted into the mouth to

examine the alveolar ridges of the jaw for the presence (or absence) of teeth and for determination of the shape and completeness of the palate. The tongue can be palpated as well, but may also be removed intact after the thoracic organs have been removed (see below).

Arms, Hands, and Fingers

The upper extremities are examined for symmetry, mobility, and the presence of skin lesions. The axillae are palpated for the presence of lymph nodes or other masses. The positioning and mobility of the fingers should be noted along with their length. Some chromosomal syndromes (e.g., trisomies 13 and 18) may produce an overlapping of the little finger over the fourth finger and the index finger over the third finger. Children with Down syndrome (trisomy 21) often display short metacarpals and phalanges and hypoplasia of the midphalanx of the fifth finger. Nails are examined for the presence of hypoplasia, dysplasia, or trauma. The palms of the hands are examined for aberrant patterning, most notably for the presence of a Simian crease or a malpositioned axial triradius, common findings in Down syndrome but also seen in a wide variety of other syndromes (see ▶ Chap. 35, "The Disabled Child").

Chest: Front and Back

Examination of the chest begins with the determination of its symmetry, position of the nipples, and length and positioning of the sternum (e.g., pectus excavatum or carinatum). The junction of the neck with the chest is assessed to note the shape and length of the neck (short neck or webbed skin). The clavicles are palpated for degree of development (e.g., hypoplasia) and the presence of fractures. Breast development is determined using a system such as the Tanner Stage I to V system (Marshall and Tanner 1969).

Turning the body over or rolling it onto its side allows for examination of the back for symmetry (e.g., scoliosis, lordosis) and/or the presence of scars, irregular pigmentation, or lesions. Particularly important in infants is the presence of spinal and vertebral column defects indicative of meningomyelocele and spina bifida, remembering that one form, spinal bifida occulta, may not be visible as a skin defect.

At this point, prior to the opening of the chest and abdomen, aspiration of the thorax for air, blood, and/or fluid can be performed. In young children in particular, the presence of air or fluid in each hemithorax can be determined as well as its amount. With the body in the supine position, a 12–14 gauge needle on a 5–25 cc syringe (depending on the size of the child) can be inserted parallel to the autopsy table at the rib–sternal junction between the 4th and 5th or 5th and 6th ribs, being careful to avoid the heart. When inserted through the parietal pleura, aspiration of air or fluid within the free space of the hemithorax can be attempted. If nothing is present as the syringe plunger is pulled back, the plunger when released will move back toward the needle. If air or fluid is present, it will be withdrawn as the plunger is pulled back until it can no longer be done. At this point, the amount of fluid/air in the syringe can be measured and, if a sterile draw has been performed, the fluid may be sent for culture. If the plunger is pulled back to its maximum length, the needle and/or syringe can be removed and the amount of air/fluid measured and expelled

from the syringe and then reinserted into the same needle hole for aspiration of as much air/fluid as is left (repeating as many times as needed). The same procedure can then be performed on the other hemithorax. This allows for an accurate measurement of the amount of pneumothorax, hemothorax, or transudate/exudate present on each side.

Abdomen: Front and Back Including Anogenital Area and Urethra

The shape of the abdomen is evaluated for distension (e.g., ascites or abdominal air), depression (e.g., secondary to malnutrition/dehydration), and wall thickness (edema, muscular atrophy, etc.). Sterile aspiration of abdominal fluid may be performed for culture prior to incising the abdominal wall. Signs of premortem medical intervention such as needle marks or incisions should be recorded. In neonates, the umbilicus is examined for evidence of inflammation or necrosis. The umbilical stump is examined for the presence of two umbilical arteries and one umbilical vein. Discoloration of the abdominal wall may indicate underlying hemorrhage, infection, or gastrointestinal necrosis as in neonatal necrotizing enterocolitis. The external genitalia are examined for anatomic development. In boys, the presence or absence of testes in the scrotum is noted along with the size and development of the penis. A staging system can be used to describe pubic hair growth in males and females. In females, the patency of the vaginal opening is determined visually. The anus is probed for patency in neonates, recognizing that anal atresia may be higher than the anal opening. The presence of meconium is a clear sign of anal patency.

Legs, Feet, and Toes

The lower extremities should be examined for symmetry and length (i.e., in proportion to trunk and arm length). The hips can be rotated to determine laxity. Feet are examined for the presence of an arch to the sole versus a "rocker-bottom" configuration as may be seen with certain trisomies. Five toes should be present on each foot, and the spaces between toes should be of equal depth.

Internal Examination

Chest and Abdomen

The opening of the body is most commonly done via a "Y"-shaped incision or some variation (e.g., "U"-shaped over chest with extension to the symphysis pubis). In either configuration, the incision begins in the anterior axillary line at the level of the clavicle, extends to the xiphoid area just below the sternum, and then continues to the opposite anterior axillary line. In a neonate or infant, the chest incision can be positioned through or adjacent to the nipples to allow sampling of breast tissue while obtaining a section of skin. Subcutaneous tissue may also be measured (thickness) and observed to determine the state of nutrition or hydration. Edema can often be noted in the subcutaneous tissue of the chest. From a point below the xiphoid process, the incision is extended toward the symphysis pubis lateral to the umbilicus or encircling the umbilicus.

The skin of the chest and abdomen is reflected to either side after dissecting it free from the sternum and thoracic cage. The abdominal skin is freed along the lower rib margin. The following measurements may be made prior to removing the chest plate in the infant. The size of the liver is judged by measuring the distance that it extends below the costal margin (assuming no diaphragmatic hernia is present). Measurements are made in the anterior axillary lines, the midclavicular line, and the midline. If the liver does not extend to the left anterior axillary line, the distance from the midline to where it disappears beneath the costal margin is measured. Other measurements include:

1. The distance the spleen tip extends below (or above) the costal margin.
2. The distance the gallbladder extends above or below the margin of the liver – done primarily to see that a gallbladder is present.
3. The distance the urinary bladder extends above the symphysis pubis.
4. The root and radius of the mesentery. The root is determined by moving the bowel toward the upper right quadrant and measuring the length of its attachment to the vertebral column. The radius is determined by placing one end of a ruler on the vertebral column where the mesentery attaches and pulling up a segment of the small bowel and measuring the distance from the vertebral column to where it attaches at the mesenteric border of the bowel.
5. The amount the diaphragm leaflets is pushed up into the thorax by the abdominal organs. This is assessed by placing a finger beneath the rib margin in the right and left midclavicular line and feeling how high the leaflets extend. This is determined by noting where one can feel one's finger in relationship to a rib or intercostal space (e.g., fifth intercostal space or sixth rib). This measurement is significant for determining whether the diaphragm leaflets are intact and whether air or fluid (e.g., blood, pus) in the thorax has forced the leaflets down.

Thymus

The thymus in infants is often quite large and may obstruct the view of the pericardium and great vessels of the heart. It is helpful to dissect the thymus free from the other chest organs and weigh it before proceeding to the examination of the heart and lungs. Care must be taken to include the portion of the thymus that extends "outside" of the chest into the cervical tissues of the neck.

Cardiac/Thoracic Ratio

Prior to removal of the organs of the chest, the width of the heart at its widest point should be measured and compared to the width of the thorax at the same point. The ratio is helpful in detecting/predicting cardiac anomalies since a ratio of >0.5 is often associated with many of these anomalies. With this initial suspicion, a "nonstandard" approach to the heart's dissection may be employed as previously illustrated in a prior publication (Stocker 2011).

Removing the Organs

Two methods of organ removal, each with its own advantages and disadvantages, have evolved. With the Rokitansky method, the prosector removes all organs en

bloc preserving their associations with other organs. The Virchow method allows for in situ removal of organs one at a time. The Rokitansky method is best performed by beginning in the area of the neck and working caudally. The neck organs are dissected by working around the larynx, esophagus, and descending aorta, freeing them with blunt dissection from the soft tissues laterally and behind. Anteriorly, the left brachial artery, the left carotid artery, and the right brachiocephalic artery may be tied off and transected to allow later access by the mortician. Once dissection has extended behind and laterally above the larynx, the region above the epiglottis can be transected allowing the complete larynx with attached esophagus to be pulled inferiorly. Alternatively, in cases where tracheoesophageal malformations are absent, the trachea and esophagus can be transected after examination of the soft tissues of the neck, with the trachea and attached esophagus pulled inferiorly (Fig. 3.3). The larynx with the attached thyroid gland and the remaining trachea can then be removed after the thoracic and abdominal blocks are removed (Fig. 3.4). In cases with suspected trauma to the neck, this approach is preferred. Following this, the left lung can be pulled aside to allow an incision to be made along the spinal column just behind the esophagus and aorta. When this procedure is repeated on the right side, the neck organs along with the heart/lung/esophagus can be pulled forward. The abdominal organs are mobilized by cutting the diaphragm (a good time to take a diaphragm section for microscopic examination) along the contour of the body wall and dissecting inferiorly along the spinal canal, freeing up the spleen and kidney on the left and the liver and kidney on the right. Care must be taken to avoid cutting across the ureters as they pass along the sides of the spinal column before entering the bladder. At this point, the urethra and rectum (and vagina in a female) can be transected and freed from the pelvic soft tissue, allowing the entire neck/chest/abdominal block to be removed en bloc.

Testes/Ovaries

In neonates and infants, it is often easier to remove the ovaries (and testes if undescended) shortly after opening the abdomen. The small size of an infant's ovaries may cause locating them difficult. By finding the uterus and fallopian tubes behind the urinary bladder, one can locate the ovaries adjacent to the tubes. They can then be removed, weighed, and often submitted in toto for microscopic examination. Larger ovaries from older infants and young girls may be hemisected. These often contain small fluid-filled cysts.

Testes that are present in the scrotum may be removed by putting pressure on the scrotum in the direction of the inguinal canal, then inserting a forceps into the canal from the open abdomen, pulling on the vas deferens and extracting both the vas deferens and testis. Before dissecting the testis free from the vas deferens and attached soft tissue, the bloc is examined for the presence of a vascular malformation or a hydrocele. The testis can then be weighed and submitted for microscopic examination.

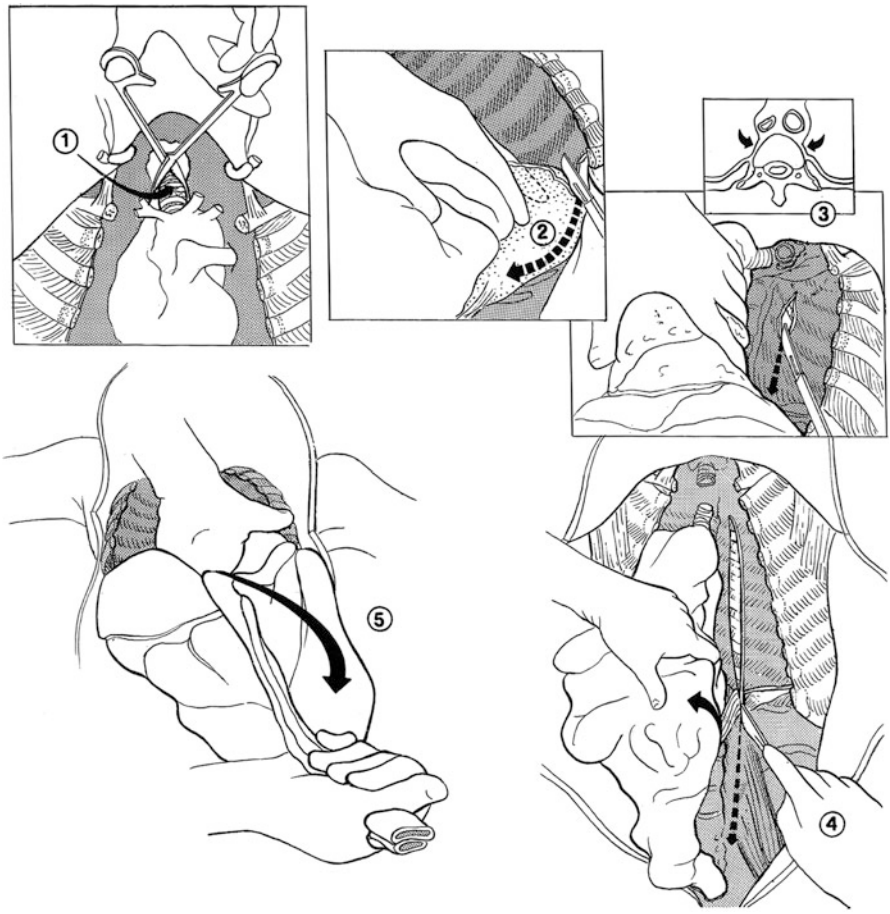

Fig. 3.3 Organ block removal. After removal of the thoracic plate and opening of the abdominal cavity, grasp the trachea and esophagus and with a scissors or scalpel transect them (Step 1). Clamping the trachea with a hemostat or forceps, retract the thoracic and abdominal organs cutting the diaphragmatic attachments (Step 2). As the trachea is pulled inferiorly, cut the pleura along the vertebral bodies with a scalpel (Step 3). While retracting the thoracic and abdominal blocks inferiorly, continue the pleural incision through the crus of the diaphragm and then along the lateral aspects of the lumbar vertebrae above the psoas muscle (Step 4). After the thoracic and abdominal blocks have been freed from the vertebral column, deliver the organs en bloc by detaching any remaining connections (Step 5) (Reproduced with permission from Collins KA, Hutchins GM. (2005) *An Introduction to Autopsy Technique: Step-by-Step Diagrams*. 2nd ed. Northfield, IL: College of American Pathologists (Collins and Hutchins 2005))

Examination of the Body Cavity

Following removal of the chest and abdominal organs, the body cavity is examined for abnormalities of the ribs and spinal column. Special attention should be given to the costovertebral area in which the ribs abut the spinal column as this is a region in

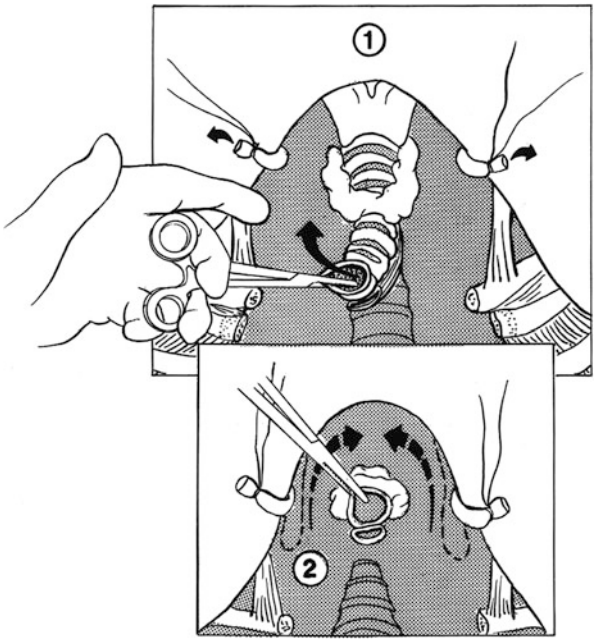

Fig. 3.4 Removal of the neck organs. Clamp the end of the trachea as shown and free the larynx with attached thyroid and parathyroid glands and unresected trachea with blunt dissection (Step 1). With a scissors or knife, detach the neck organs from the mandible by cutting anteriorly and medially along the inner aspect of the mandible (Step 2) (Reproduced with permission from Collins KA, Hutchins GM. (2005) *An Introduction to Autopsy Technique: Step-by-Step Diagrams*. 2nd ed. Northfield, IL: College of American Pathologists (Collins and Hutchins 2005))

which rib fractures, both old and recent, may be detected. A section of rib including the costochondral junction can be taken for microscopic examination and assessment of bone and bone marrow.

Psoas Muscles

The psoas muscles provide an easily accessible source of skeletal muscle and often include ganglion cells from the paraspinal ganglia.

Vertebral Column/Spinal Cord

Cerebrospinal fluid (CSF) Aspiration: Prior to removing the vertebral column, CSF can be aspirated by passing a sterile needle through the intervertebral disc after the tissue covering the lumbar vertebrae has been seared with a hot spatula.

Removing the Vertebral Column: While older children may require spinal cord removal similar to that of an adult, neonates and infants have vertebral columns easily removed from an abdominal approach to provide ready access to the spinal cord. This is accomplished by an incision through two of the lowest intervertebral discs, bending the pelvis backwards to allow a round/blunt-end scissor into the vertebral canal and transecting the pedicles on both sides of the vertebral column. As one moves cephalically, the vertebral column can be lifted to allow the thoracic and cervical vertebrae to be freed by cutting their pedicles. To remove the vertebral column completely, the highest cervical intervertebral disc accessible can be transected. Upon removal of the vertebral column, vertebral body anomalies can

be identified and a vertebral body taken for fixation, decalcification, and microscopic examination.

Removing the Spinal Cord: With the vertebral column removed, the spinal cord in its dura is dissected free by cutting across the spinal nerves exiting through the dura. The spinal cord is dissected at this time with cross sections taken from the upper, middle, and lower levels or may be placed in fixative with the brain for dissection after fixation.

Separation and Examination of Heart/Lung

Prior to separating the heart–lung block from the abdominal organs, assuming the Rokitansky technique was used to remove the organs, an examination of the esophagus is performed. By placing the block so its posterior surface is exposed, the esophageal entrance behind the larynx can be probed with scissors. An incision is made from the opening to the point where the esophagus passes through the diaphragm. This posterior exposure allows examination of the internal surface of the esophagus with particular attention paid to the anterior wall of the esophagus adjacent to the trachea. Esophageal atresia can be easily discovered, and the presence of a tracheoesophageal fistula can be established prior to the esophagus being separated from the trachea. Following this examination, the upper portion of the esophagus is separated from the larynx and the mediastinal tissue. The esophagus is left intact with the remainder of the gastrointestinal tract.

Section Thoracic/Abdominal Aorta and Inferior Vena Cava. With the esophagus separated from the thoracic organs, the descending aorta is examined for abnormalities. If none are present, the aorta is transected beyond the arch and freed from the mediastinal tissues and left with the abdominal organs. This leaves the chest and abdominal organs attached by only the inferior vena cava. Transecting the inferior vena cava as near to the diaphragm/liver as possible will separate the two blocks.

Standard Examination of the Heart. Following identification and transection of the pulmonary arteries and veins, noting their anatomic relationships (i.e., origin and position), the heart is separated from the lungs. The heart is weighed and examined by opening the chambers along the line of blood flow. This is most easily accomplished by opening the right atrium between the inferior vena cava and the atrial appendage. The incision leaves intact the sinoatrial node, which is located in the anterior wall of the right atrium just below the entrance of the superior vena cava. Scissors are used to cut through the lateral wall of the right atrium, through the tricuspid valve and along the lateral portion of the right ventricular wall. With the right side of the heart opened, the atrium is examined for completeness of the foramen ovale, entrance of the coronary sinus, tricuspid valve leaflets and circumference, and right ventricular free wall thickness.

The next incision, most easily accomplished with blunt-nosed scissors, extends along the anterior wall of the right ventricle adjacent to the septum, along the outflow tract, into and through the pulmonary valve. This allows examination of the ventricular septum for septal defects, assessment of the three pulmonary valve cusps, and measurement of the pulmonary valve circumference. With the

pulmonary valve opened, the right and left pulmonary artery branches are identified and the ductus arteriosus evaluated (for patency, circumference, and length).

The left side of the heart is examined by cutting between the openings of the pulmonary veins, down the lateral left atrial wall, through the mitral valve, and along the left ventricular wall. The mitral valve circumference is measured and the leaflets observed for orientation and completeness. The left ventricular wall thickness is measured, and the septum is examined for defects. The systemic outflow tract is then opened with an incision through the anterior wall of the left ventricle adjacent to the septum, behind the mitral leaflet into the aorta. When opening the aorta, care must be taken to move the opened pulmonary trunk aside and incise through the aortic valve. The aortic valve circumference is measured and the three cusps examined, noting the position of the origin of the coronary arteries above and behind two of the cusps (the right and left coronary sinuses). Finally, the arch of the aorta is examined for anomalies (e.g., coarctation, patent ductus). If myocardial infarction is suspected, the right and left ventricles may be "bread-loafed" remembering that the papillary muscles usually show the first signs of myocardial damage.

Examination of the Thymus: The thymus is weighed and described, and a representative section is submitted for microscopic examination.

Examination/Removal of Thyroid and Parathyroid Glands: The thyroid is usually readily visible adjacent to the lower larynx and should be dissected free and intact. The thyroid is weighed, and a representative section is submitted for microscopic examination. The parathyroid glands may only rarely be visible in a neonate or infant. To ensure that they are available for microscopic examination (if clinical history warrants), the entire thyroid gland and adjacent soft tissue are submitted.

Removal/Examination of the Tongue: Removal of the tongue not only allows more extensive examination of the mouth and nasopharynx but provides another specimen of skeletal muscle for microscopic examination. Once the larynx has been removed (or in continuity with the removal of the chest organs), the tongue is freed from the mandible by cutting with a scalpel (or preferably a pair of scissors) along the inner edge of the mandible. Care must be taken to not cut the lips or outside of the mouth. A good technique is to use scissors (rather than a scalpel) and open the blades only after inserting the scissors inside the mouth.

Examination of the Respiratory System

Following removal of the heart from the heart/lung block as described above, the respiratory system can be examined. The pulmonary arteries and veins are identified and examined for the presence of thromboemboli. If present, the arteries or veins should be opened along their length into the lung to determine if there is vascular obstruction.

The *larynx* (with thyroid and parathyroid glands removed) is separated from the trachea and examined for patency from above and below. It may be hemisected from anterior to posterior allowing a view of the vocal cords and laryngeal mucosa.

The *trachea* is probed for patency and for the size of the entire extent of the lumen. The cartilage plates along the tracheal circumference are examined for the

presence of complete rings. The trachea is resected at the carina leaving as much as possible of the right and left main stem bronchi.

Lung examination begins by weighing the right and left lungs separately, noting the lobation of the lobes (two on the left and three on the right) and documenting their color and consistency. At this point, it is often helpful to inflate one of the lungs with formalin by inserting a syringe in the mainstem bronchus and slowly injecting 10–50 ml of formalin depending on the size of the lungs. A hemostat is used to close off the bronchus. The lung is placed in formalin for an hour or two (or overnight if possible) before dissecting. The other lung is examined by gently probing the bronchi and vessels and then sectioning the lung perpendicular to the hilum. This allows examination of the parenchyma for lesions (cysts, abscesses, areas of consolidation, hemorrhage). Sections are taken from obvious areas of pathology as well as from normal, pleural, and hilar regions.

Examination of the Abdominal Organs

In females, separate the uterus, fallopian tubes, and ovaries if not previously removed from the abdominal block.

The spleen may have been removed earlier (see above) but, if not, should be dissected from the abdominal block with special attention paid to the areas adjacent the spleen and liver for smaller "accessory" spleens. If none are present, the spleen can be weighed and sectioned, and a sample is taken for microscopic examination. From the anterior portion of the abdominal block, the diaphragm can be removed and the liver examined. The biliary tract is difficult to dissect in a neonate or infant, but its patency can be demonstrated by making an incision in the duodenum in the region of the ampulla of Vater. The gallbladder is compressed against the liver and, if the biliary tree is patent, bile can be expressed through the ampulla. Following this, the liver can be removed from the block, weighed, and sectioned at 1.0 cm intervals with representative tissue taken for microscopic examination.

Adrenals and Kidneys: From the posterior abdominal block, the aorta is opened and the origin and patency of the celiac axis, mesenteric arteries, renal/adrenal arteries, and iliac arteries assessed. The renal veins can be observed entering the inferior vena cava and their patency observed. The adrenals are dissected from the kidneys, weighed, and sectioned with a cross section from each submitted for microscopic examination.

The kidneys, ureters, and bladder can be dissected en bloc either with or without the renal arteries and section of the aorta. After identifying the origin, course, and entrance into the bladder of each ureter, each kidney can be removed, weighed, and examined by clearing off the soft tissue from the capsule (without stripping the capsule) and bisecting the kidney. The cortex and medullary thicknesses are measured and both examined for lesions before sections are taken for microscopic examination. The renal pelvis should be opened, the entrance to the ureters examined, and the entire length of the ureters opened into the bladder. The bladder is opened, the mucosa examined, and a section is taken for microscopic examination

if indicated. The urethra can be probed for patency. When opened in a male, the prostate can be examined and a section submitted for microscopic examination.

Removing, Measuring, and Sectioning the Bowel: The bowel is removed prior to removing the chest/abdomen block or when dissecting the abdominal organs. In either event, the bowel is best separated from the other organs by beginning in the area of the sigmoid/rectum and working toward the stomach, using curved scissors to cut along the mesenteric attachment as close to the bowel wall as possible. Identify, and do not cut across the appendix when working near the cecum. In a small neonate or infant, the bowel may be wrapped around one's fingers, progressing from the sigmoid to the duodenum. At the duodenum, it is transected at the point where it passes beneath the inferior duodenal fold. The entire bowel can then be spread on a cutting board for measuring the length and width of the small intestine, colon, and appendix. If lesions are identified along the length of the bowel, they may be cross-sectioned and examined; or the entire length of the bowel may be opened for inspection before sectioning. The most proximal part of the gastrointestinal tract (esophagus, stomach, and upper duodenum) along with the pancreas is then (if not previously done) separated from the diaphragm and liver. The incision in the previously opened esophagus (see above under section "Separation and Examination of Heart/Lung") can be extended through the gastro-esophageal junction, along the edge of the stomach, and through the pylorus into the duodenum. Gastric contents can be examined and a portion saved for further analysis if indicated. Beyond the pylorus, the ampulla of Vater is again identified and its relationship to the pancreas observed. The pancreas is dissected from its attachment to the duodenum and weighed, and sections are taken from the head and tail for microscopic examination. With the entire gastrointestinal tract now opened, sections along its length may be taken.

Central Nervous System

Examination of the External Scalp: The scalp should be examined for abnormalities in the pattern of the growth of the hair, looking for two or more swirls of growth; the more swirls or defects in hair growth, the more likely there will be abnormalities in the structure of the brain. The anterior and posterior fontanelles should be palpated in infants to check for fullness or depression.

Opening the Scalp: An intermastoidal, suboccipital incision allows reflection of the scalp anteriorly to the level of the eyebrows and posteriorly to below the posterior fontanelle. In young neonates and infants, pushing a finger between the scalp and calvarium and rolling the skin forward may accomplish this. In older children, dissection of the tissue between the scalp and calvarium may require scissors or scalpel.

Measuring the Calvarium: With the fontanelles exposed, they may again be palpated and measured (length and width). The calvarium is examined for developmental defects, fractures, or hemorrhage.

Opening the Calvarium: In neonates and infants whose calvarium has not completely ossified, the calvarium may be opened with a scalpel and scissors along the unfused sutures. Removal of the fetal brain is illustrated in ▶ Chap. 37, "Ancillary Studies and Dissection Techniques in the Pediatric Autopsy". Examination of the sagittal sinus is conducted by cutting with scissors through the parietal bone from the anterior fontanelle to the posterior fontanelle about 1 cm to each side of the sagittal suture. Lifting the edge of the middle strip allows a view of the intact sinus.

Extending the incisions parallel to the sagittal suture to the anterior and posterior portions of the calvarium and then laterally from both ends of the incision into the parietal bone (on both the right and left sides) until they are 1–4 cm apart (depending on the size of the head) allows both parietal and frontal bones to be reflected laterally. By cutting across the anterior extension of the sagittal suture and reflecting it posteriorly, the brain is exposed. The calvarium of older infants and children is removed as one would for an adult.

Removing the Brain: The brain of a neonate or infant is removed from anterior to posterior by placing one's hand behind the head with the reflected sagittal suture between the middle and ring fingers and tilting the head backward. As the brain falls away from the base of the skull, the cranial nerves, pituitary stalk, and tentorium are cut across as they come into view. Eventually, one can see into the spinal canal and insert a scissor to cut across the spinal cord well below the brainstem. At this point, the brain is easily "delivered" into the hand held beneath the head.

Examination of the External Brain: Following removal, the brain is weighed and the external features examined for the basic development of the cerebral cortex related to the neonate's/infant's gestational age. The vessels at the base of the brain are examined, but further manipulation of the brain should be put off until it can be made firm by formalin fixation. Different jurisdictions have specific rules regarding retention of the brain for diagnostic purposes, and pathologists need to be familiar with these.

Sectioning the Brain and Spinal Cord: The spinal cord, if removed via the abdominal approach, can be fixed along with the brain. Examination consists of opening the dura along its length and sectioning the cord at 0.5–1.0 cm intervals, submitting two or more sections for microscopic examination.

The *brain after fixation* is examined for gross abnormalities (e.g., area of hemorrhage or necrosis, developmental anomalies such as holoprosencephaly) and a unique approach to dissection determined by any abnormalities. In most instances, however, major anomalies are not seen and a more "standard" approach is taken. This consists first in examining the vessels at the base of the brain after gently removing the meninges. The circle of Willis is identified and any variations recorded. The cerebellum and brainstem are removed from the cerebrum by making a transverse section in the region of the cerebral peduncles. In a neonate's or infant's brain, this cerebellar/brainstem block may be cut transversely at 0.5–1.0 cm intervals to view the cerebellar folia and dentate nucleus along with the lower brainstem. In larger brains, the brainstem might be separated from the cerebellum prior to sectioning.

If significant hemorrhage is present in the cerebral hemispheres, the meningeal arteries may be followed into the cerebrum to search for a site of an aneurysm or rupture. After the exterior of the cerebral hemispheres have been examined, the brain is placed "base up" and transverse (coronal) sections made at 1.0–1.5 cm intervals (depending on the size of the brain) from the anterior lobe to the occipital lobe. If possible, these sections (often only 5 or 6 in infants, but as many as 12–15 in older children) should include ones through the stalk of the pituitary, the mammillary bodies, the apex of the interpeduncular fossa, and the top of the cerebral peduncles (Fig. 3.5). This allows close examination of the numerous deep gray-matter nuclei.

Examination of the Inside of the Cranium

Removal of the Pituitary: The pituitary can easily be removed from the hypophyseal fossa of the sella turcica after the brain has been removed. The gland is usually quite soft and delicate, and the best approach is to use small curved scissors to dissect around and beneath the gland.

Opening of Middle Ear: The middle ear can be visualized by removing the petrous portion of the temporal bone with a heavy (bone) scissor or with saw cuts on either side of the petrous protrusion. A more detailed en bloc excision is illustrated in ► Chap. 37, "Ancillary Studies and Dissection Techniques in the Pediatric Autopsy". With removal of the bone, the middle ear is examined for infection (pus or cloudy fluid) and a culture performed if indicated.

Removal of Eye(s): Removal of the eye(s) is accomplished through an anterior or posterior approach. The posterior approach minimizes damage to the face and is illustrated in ► Chap. 37, "Ancillary Studies and Dissection Techniques in the Pediatric Autopsy".

Access to the eye is made by cutting a square opening in the superior surface of the orbital plate of the frontal bone. In a newborn or young infant, this is accomplished with a scalpel and scissors but may require a saw in older patients. When the opening is large enough to accommodate the size of the eyeball, the optic nerve and orbital muscles are visualized, dissected, and transected. As the eye is moved posteriorly, the ligaments holding the eye to the orbit are cut across (with special care taken to avoid cutting the eyelid) and the eye pulled through the opening in the orbital plate.

Special Techniques and Studies

As an adjunct to the standard autopsy dissection, special studies and dissections may be indicated to determine cause of death. Procedures for postmortem chemistry, microbiological examination, cytogenetics, and molecular studies as well as special dissections are outlined in ► Chap. 37, "Ancillary Studies and Dissection Techniques in the Pediatric Autopsy". Toxicological analysis of tissue and body fluids is discussed in ► Chap. 29, "Pediatric Toxicology".

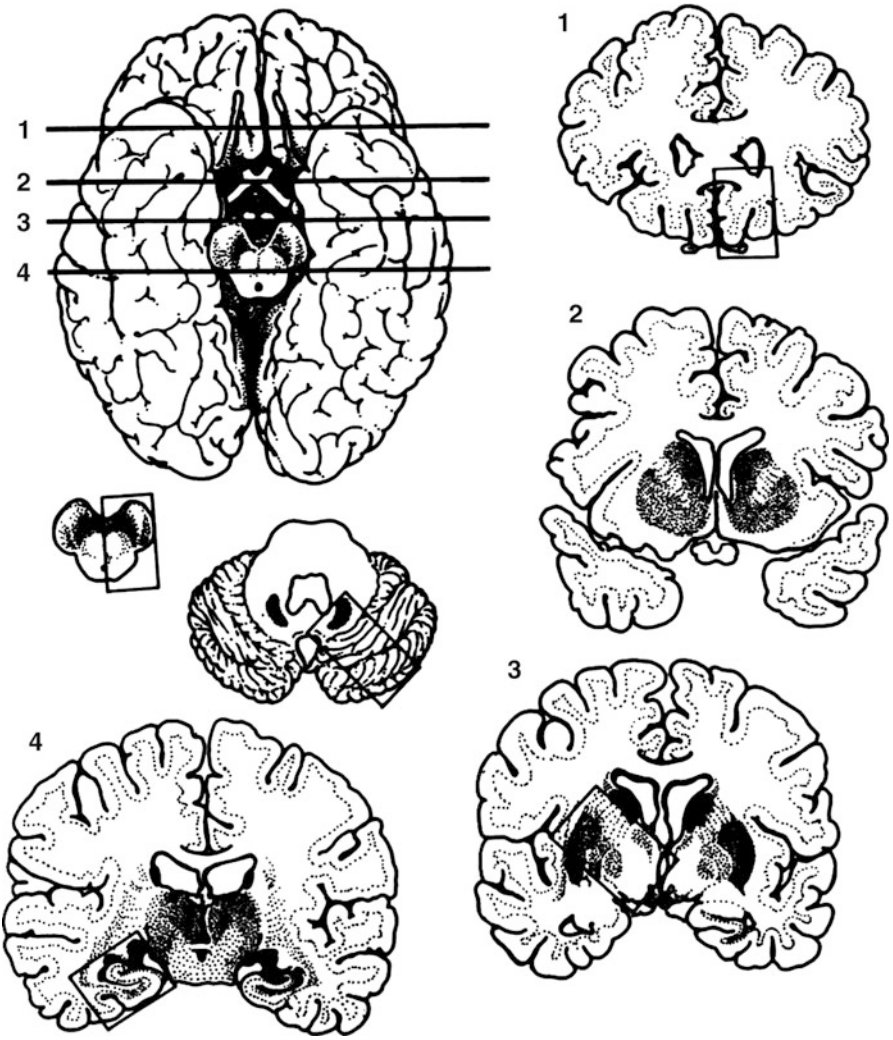

Fig. 3.5 Gross examination of the brain. The brain is viewed from its base after the brainstem and cerebellum are removed. Standard coronal sections of the cerebrum with their appearance on cross section are illustrated. Rectangular boxes outline the standard histological sections of the cerebrum, cerebellum, and brainstem that should be obtained (From Stocker JT, Dehner LP (eds.), *Pediatric Pathology*, 2nd ed., Appendix 15, Philadelphia: Lippincott, Williams & Wilkins. Used with the permission of Dr. Trevor Macpherson, Magee Woman's Hospital, Pittsburgh, PA and Dr. Hannah Kinney, Children's Hospital, Boston, MA (Stocker and Dehner 2001))

Histological Examination

In addition to the external and internal examination of the decedent, representative sections need to be submitted for histological examination. Table 3.2 outlines the

Table 3.2 Recommended sections for histological examination

Thorax, abdomen and pelvis
Strongly recommended
Heart (left and right ventricle, interventricular septum)
Lungs (each lobe)
Trachea
Larynx
Kidneys (right and left)
Pancreas
Adrenal glands
Spleen
Thymus
Mesenteric lymph nodes
Liver
Brain (see below)
Recommended
Esophagus
Gastroesophageal junction
Stomach
Small intestine
Colon
Anus
Psoas muscle
Rib
Vertebral body
Tongue
Diaphragm
Recommended when indicated
Submaxillary gland
Urinary bladder
Breast
Umbilicus
Uterus-cervix-vagina
Skin
Peripheral nerve
Fallopian tube and ovary
Testis
Prostate
CNS
Brainstem – pons
Cerebellum including dentate nucleus
Frontal (or occipital) cortex and white matter
Hippocampus
Internal capsule/posterior limb/thalamus
Cervical, thoracic, and lumbar spinal cord

From Valdes-Dapena et al. (1993), Stocker (2011)

routine sections recommended for histological examination as part of the standard protocol. Additional tissue sections required for submission are based on findings at autopsy. A cassette or block summary of sections submitted for processing to blocks and/or slides is included in the autopsy report.

Preparing the Remains for Disposition

Upon completion of the autopsy dissection, tissues NOT submitted for histological examination or special studies should be returned to the body in a plastic bag of appropriate size. This includes the chest plate and vertebral column. The body's "Y" incision and scalp over the calvarium may be sewn closed, as determined by local custom or funeral home requests. The outside of the body should be appropriately tagged for identification, washed, dried, and wrapped in appropriate material for transfer to the funeral home.

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Fetal, Intrapartum, and Neonatal Deaths

4

Kim A. Collins

Contents

Abstract

Due to differences and inconsistencies in the interpretation of definitions, different classification systems, various international registration systems, and an overall dispute over epidemiological metrics, it is a challenge if not an impossibility to fully understand fetal, intrapartum, and neonatal mortality data. However, as medical practitioners, we can take the science and evidence-based research and attempt to categorize the current knowledge for a methodical assessment of these entities. This chapter will examine these three divisions of child death with a focus on risk factors, causes, autopsy findings, and ancillary studies.

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Introduction

Fetal, intrapartum, and neonatal deaths are particularly challenging because of the numerous variables involved: from a sterile, intrauterine environment "feeding and breathing" by way of a complex maternal–placental–fetal circulation; to the process of labor and delivery with a sudden change to respiration and digestion; to the vulnerable neonatal period when a child's systems must function independently in constantly changing, often hostile, surroundings. During these few weeks, numerous fetal, maternal, and placental factors are involved in every aspect of a child's pathophysiology.

Definitions

Embryonic period: Time from fertilization to the end of the 8th week of gestation.

Fetal death: Death after 20 weeks gestational age. Some areas in the world use 22 weeks gestational age (Reddy et al. 2009; The Stillbirth Collaborative Research Network Writing Group 2011a).

Late fetal death: Death after 28 weeks gestation.

Neonate: A child from birth to 1 month, or 28 days, of age (Lawn et al. 2005, 2006; Bryce et al. 2005).

Neonatal death: Death during the first month, or 28 days, of life (Lawn et al. 2005, 2006; Bryce et al. 2005).

Early neonatal period: The first week of life (Lawn et al. 2005, 2006; Bateman and Seed 2010).

Infant: A child from 1 month to 1 year of age (Coté 2010).

Very low birth weight infant = <1,500 g.

Extremely low birth weight infant = <1,000 grams.

Small for gestational age (SGA) = <10th percentile (McCowan and Horgan 2009).

Intrapartum death: Death which occurs during labor and delivery (Reddy et al. 2009).

Premature: Born less than 37 weeks gestational age (Reddy et al. 2009).

Stillbirth: Fetus born with no signs of life after 28 weeks gestational age (Varli et al. 2008; Ishaque et al. 2011).

Full term: Child born between 37 and 42 weeks gestation (Reddy et al. 2009; Rutherford 2001).

Viability: The ability of a neonate to survive outside the mother.

Fetal Death

Fetal death is defined as intrauterine death after 20 weeks gestation. Some countries use 22 weeks gestation. Late fetal death is death after 28 weeks gestation.

Table 4.1 Risk factors for fetal death

Maternal age over 35 years
Maternal hypertension
Maternal thyroid disease (hypo- or hyperthyroidism)
Maternal cholestasis, fatty liver
Maternal diabetes mellitus (especially late fetal death)
Maternal malnutrition, obesity
Maternal tobacco use (especially 3 months prior to and during pregnancy)
Maternal alcohol and drug use
Maternal third trimester radiation (over 100 rads)
Maternal thrombophilias
Maternal AB blood type
Previous stillbirth or preterm birth
Preeclampsia/eclampsia
Maternal periodontal disease
Maternal iron-deficiency anemia
Maternal folate deficiency
Small for gestational age fetus
Intrauterine growth restriction
Congenital malformations/deformations
Chromosomal/genetic abnormalities
Multiple gestations

Approximately half of fetal deaths occur prior to 28 weeks gestation, and about 20 % are at or near term (The Stillbirth Collaborative Research Network Writing Group 2011b; Pardi et al. 2002; Reddy et al. 2010; Silver 2007).

The sterile fetus has no bacterial flora. It grows and develops in sterile amniotic fluid contained within the amniotic membranes. The fetus' development is determined by its genetic makeup, blood supply (maternal-placental-fetal circulation), and the composition/volume of amniotic fluid (Pardi et al. 2002). Any disease of the mother or abnormality of the placenta/umbilical cord can impact the development and survival of the fetus.

Intrauterine fetal death (IUFD) has many causes and associated risk factors. Many fetal deaths cannot be predicted or prevented, but risk factors are known and can be assessed for early intervention (Table 4.1) (Varli et al. 2008; McCowan and Horgan 2009; Ishaque et al. 2011; The Stillbirth Collaborative Research Network Writing Group 2011b; Reddy et al. 2010; Silver 2007; Silver et al. 2007; Huang et al. 2000; Saugstad 2011; Yakoob et al. 2010; Fretts et al. 1995; Zera et al. 2011).

Often, the causes and risks overlap as a risk factor for death can sometimes be the proximate cause of death. At other times, a risk factor may be present but is not the cause of death. The risk factors and causes of fetal death can be divided into fetal, maternal, and placental.

Fetal Factors

Approximately one fifth of fetal deaths are due to inherent fetal anomalies (Pauli 2010). These include malformations, deformations, genetic/chromosomal abnormalities, nonimmune hydrops, metabolic disorders, and malignancies (Pauli 2010; Sebire and Jauniaux 2009; Michels and Tiu 2007). Genetic/chromosomal abnormalities are present in up to 13 % of fetal deaths (Korteweg et al. 2012). Common chromosomal anomalies are similar to those seen in live births: monosomy X, trisomy 21, trisomy 18, and trisomy 13 (Varli et al. 2008; Silver 2007; Michels and Tiu 2007; Wapner and Lewis 2002). Approximately 10 % of fetal deaths result from multiple gestations (Silver 2007). Multiple gestations may cause growth restriction, preterm labor, preterm rupture of membranes, preeclampsia, twin-to-twin transfusion syndrome, and fetal death (Varli et al. 2008; Huang et al. 2000; Fretts et al. 1995). Tumors can cause fetal death due to their location or potential for malignancy. These include neuroblastoma (the most common fetal malignancy, accounting for 30 % of all fetal tumors), hepatoblastoma, leukemia (especially in Down syndrome and usually acute myeloblastic leukemia – AML), lipoma, lymphangioma, teratoma (especially sacrococcygeal), hemangioma, cardiac fibroma, and rhabdomyoma (especially cardiac and associated with tuberous sclerosis) (Sebire and Jauniaux 2009; Woodward et al. 2005).

Maternal Factors

Knowing the mother's past medical and prenatal/obstetric history is important in the death investigation and certification of the cause of death. Maternal risks or causes of fetal death are trauma, malnourishment, advanced age, obesity, drug/alcohol and tobacco use, infections, diabetes mellitus, hypo-/hyperthyroidism, hypertension, and thrombophilias (Table 4.1) (Reddy et al. 2009; Ishaque et al. 2011; Reddy et al. 2010; Huang et al. 2000; Yakoob et al. 2010; Zera et al. 2011). Malnourishments that adversely affect the fetus are maternal deficiencies of folate, iron, lysine, protein, and omega-3 fatty acids (Ishaque et al. 2011). At the other end of the spectrum, maternal obesity is also associated with complications of hypertension, preeclampsia, diabetes, macrosomia, and fetal death. Numerous drugs are known teratogens; however, drugs (prescription and drugs of abuse) can also compromise the uteroplacental circulation or cross the placenta to result in toxic fetal levels and death.

Maternal thrombophilias can result in placental damage (necrosis, infarction, vascular thrombi) and uteroplacental insufficiency. These include antiphospholipid syndrome, prothrombin gene promoter G20210A mutation, factor V Leiden mutation, protein C deficiency, protein S deficiency, and antithrombin III deficiency (Varli et al. 2008; Silver 2007; Battinelli and Bauer 2011). Objective evidence of uteroplacental insufficiency includes intrauterine growth restriction, delay in central nervous system (CNS) maturation, thrombosis, and placental infarction. Resultant fetal death is highest during the second and third trimester.

Placental Factors

In one third to three fourths of fetal deaths, the cause can be determined by examination of the placenta and umbilical cord, especially after 24 weeks gestation (Horn et al. 2004). Therefore a complete autopsy with placental examination is critical (The Stillbirth Collaborative Research Network Writing Group 2011a, b) (See ▶ Chap. 5, "Placental and Maternal Conditions in Perinatal Deaths"). Placental causes of fetal death include structural developmental abnormalities, chorioamnionitis, abruption, villitis, placental infarction, atherosis, maternal floor "infarction"/perivillous fibrin deposition, fetal thrombotic vasculopathy, uteroplacental insufficiency, confined placental mosaicism, and amnion rupture sequence (Fig. 4.1) (Varli et al. 2008; Pardi et al. 2002). Primary placental neoplasms can also occur (Sebire and Jauniaux 2009). Umbilical cord abnormalities include funisitis, true knots, prolapse, abnormal insertions, hemorrhage/hematoma, thrombosis, torsion, and nuchal cords (Silver et al. 2007; Huang et al. 2000). Of note, nuchal cords are reported in up to one third of uncomplicated pregnancies (Reddy et al. 2009; The Stillbirth Collaborative Research Network Writing Group 2011a; Silver 2007; Silver et al. 2007; Carey and Rayburn 2000).

Infections

Infections have been reported to account for 10–25 % of fetal deaths in developed countries (Reddy et al. 2009, 2010; Ishaque et al. 2011; Silver et al. 2007; McClure et al. 2012; Tita and Andrews 2010; Lamont et al. 2011) (Table 4.2). The proportion is higher in developing countries (Ishaque et al. 2011; Silver 2007; Yakoob et al. 2010). Infections can cause fetal death by direct infection of the fetus, placental damage, or severe maternal illness (Varli et al. 2008; Silver 2007; McClure et al. 2012; Lamont et al. 2011). Infections can lead to congenital deformity and damage to a vital organ such as the brain or heart. Placental infection can prevent oxygen and nutrients from reaching the fetus. Infections can also precipitate preterm labor and fetal death (Fig. 4.2) (Reddy et al. 2009). Infections can be divided into hematologic/transplacental and ascending infections. The TORCH infections (Toxoplasmosis, "other," rubella, cytomegalovirus, and herpes) are causes of fetal abnormalities and may cause death (Ishaque et al. 2011). The "other" category is expanding to include not only syphilis but also parvovirus and human immunodeficiency virus – HIV (Ishaque et al. 2011; Yakoob et al. 2010; Lamont et al. 2011). Cytomegalovirus is the most common fetal and neonatal viral infection, but it rarely results in fetal death. Likewise, herpes rarely causes fetal death (Ishaque et al. 2011). The virus most commonly associated with fetal death is parvovirus B19 (Lamont et al. 2011). Ascending infections are usually bacterial, especially Group B streptococcus and Listeria (Tita and Andrews 2010). Cultures, nucleic acid tests, polymerase chain reaction, serology, as well as immunohistochemistry and immunofluorescence can positively identify these infectious agents.

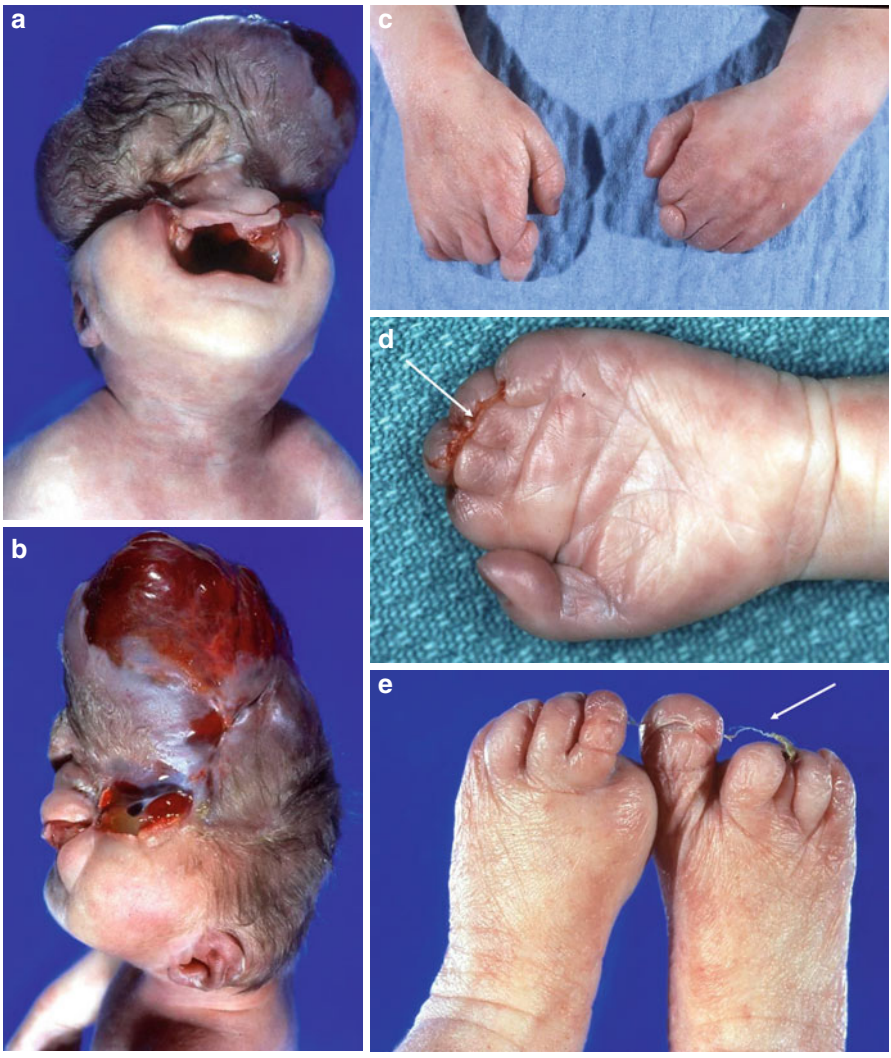

Fig. 4.1 (**a**–**e**). Fibrous bands of amnion cause entrapment of the fetus, constricting body parts as the fetus grows. (**a** and **b**) Frontal and left side view of the cranial distortion. Fetal hands: (**c**) (dorsal) and (**d**) (ventral): Deformation and amputation of the fingers. See amniotic band at *arrow*. (**e**) Deformation and amputation of the toes. Note the amniotic band still intact (*arrow*) (Courtesy of Patrick E. Lantz, MD)

Fetomaternal Hemorrhage

Fetomaternal hemorrhage is defined as the transplacental passage of fetal blood and cells into the maternal circulation before or during delivery (Samadi et al. 1999; Ahmed and Abdullatif 2011). It has been attributed as the cause of 5–14 % of all

Table 4.2 Infectious causes of fetal death

Escherichia coli
Group B streptococcus
Ureaplasma urealyticum and *Mycoplasma hominis*
Toxoplasma gondii
Listeria monocytogenes
Leptospirosis
Parvovirus (B-19)
Enteroviruses (Coxsackie A and B)
Cytomegalovirus
Herpes
Syphilis, malaria, HIV, rubella, measles, mumps

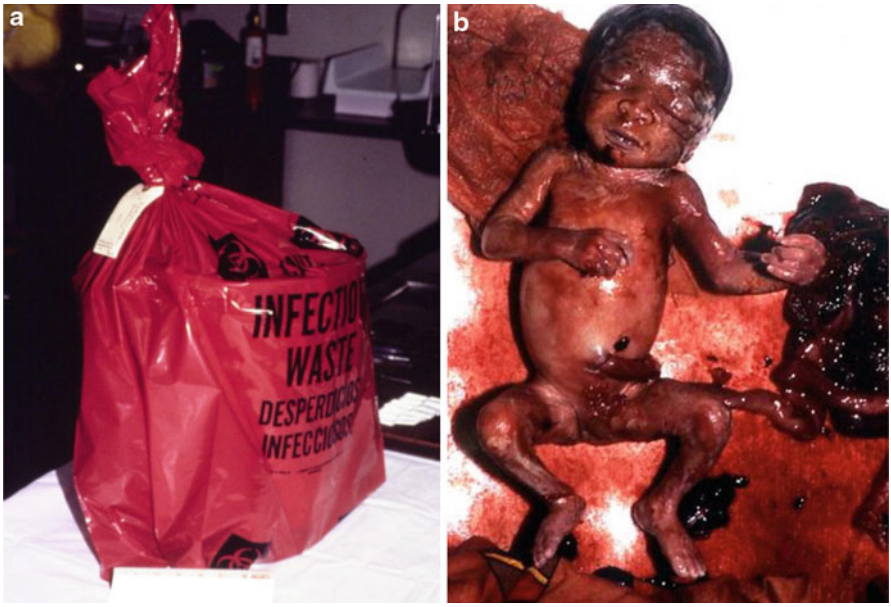

Fig. 4.2 (**a**) 14-year-old mother prematurely delivered a stillborn fetus and placed it in a bucket. She had concealed both the pregnancy and the home delivery. Later, she hemorrhaged and confessed to the delivery. (**b**) The fetus was well-developed and without trauma. The autopsy confirmed that the fetus was a stillbirth. Toxicology was negative. The placenta, membranes, and umbilical cord showed marked acute inflammation. The cause of death was acute chorioamnionitis and funisitis. The manner of death was classified as natural

fetal deaths and can cause intrapartum and early neonatal death (Reddy et al. 2009; Varli et al. 2008; Silver et al. 2007; Carey and Rayburn 2000; Samadi et al. 1999; Ahmed and Abdullatif 2011). The cause of the fetomaternal hemorrhage is a breach of the integrity of the placental circulation. This breach can be secondary to trauma, abruption, chorionic villus sampling, amniocentesis, choriocarcinoma, vasa previa, or external cephalic version (Ahmed and Abdullatif 2011). Transplacental passage

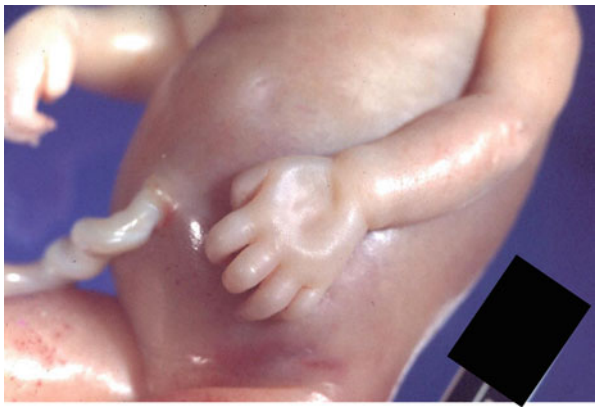

Fig. 4.3 Hydrops fetalis secondary to heart failure. Marked anasarca. Note the pitting edema when the left hand is pressed by the pathologist

Table 4.3 Histopathology of chronic fetal stress

Loss of thymic cortical lymphocytes, decreased thymic weight
Macrophage infiltration of thymic cortex and Hassall bodies
Adrenal gland cortical pseudofollicular change (cortical cytolysis)
Nucleated red blood cells in fetal vessels
Foci of hemorrhagic necrosis in liver, adrenals, kidney, spleen
Intrathoracic serosal petechiae[a]
Intrauterine growth retardation

[a]Intrathoracic serosal petechiae may resolve several days after insult and not be present at the time of autopsy

of fetal cells into the maternal circulation occurs. The threshold for fetomaternal hemorrhage severe enough to cause stillbirth is unknown and is affected by the rate (acute or chronic) of the bleed and the gestational age. The volume of fetal blood that has passed into the maternal circulation can be estimated by various tests such as the Kleihauer-Betke test. A small leak is <0.1 mL up to 2 mL of fetal blood loss (Ahmed and Abdullatif 2011). A massive fetomaternal hemorrhage is >150 mL, or some use 20 mL/kg, of fetal blood loss (Ahmed and Abdullatif 2011). The mechanism of death is severe anemia, neurological injury, nonimmune hydrops fetalis with heart failure, or massive acute exsanguination (Fig. 4.3).

Histological Indicators of Chronic Fetal Stress

If a fetus has been stressed for several days to weeks prior to death and delivery, certain histopathological changes may be seen at autopsy. These could indicate such entities as poor oxygenation, infection, anemia, or cardiovascular stress (Ahmed and Abdullatif 2011) (Table 4.3).

Fig. 4.4 Maceration with epidermal sloughing and a red underlying dermis

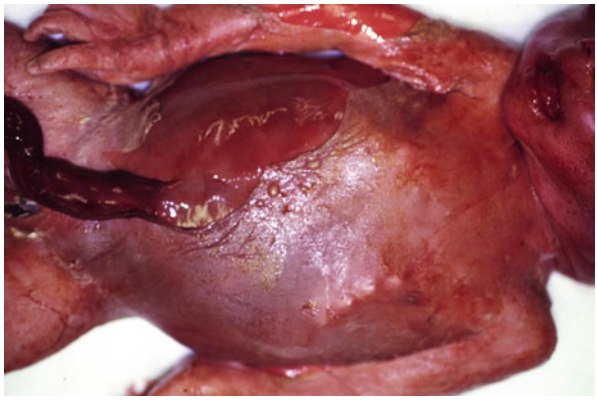

Fig. 4.5 Maceration with blister formation, skin sloughing, red discoloration of the dermis, and red-brown discoloration of the umbilical cord

Autopsy Findings of IUFD

At autopsy, the appearance of the fetus depends largely upon the postmortem interval or the death-to-delivery interval. Maceration is the degeneration of fetal tissues after death. Autolysis (due to endogenous proteolytic enzymes) and putrefaction (due to the action of bacteria) may both be involved, depending on the sterility of the fetus and the postmortem environment. The umbilical stump will change color to a red–brown within 6 h (Genest and Singer 1992; Wainwright 2006). The epidermis will separate from the dermis and slough with a loss of 1 cm $\geq$ 6 h (Genest and Singer 1992; Wainwright 2006). The underlying dermis will be moist and red (Fig. 4.4). Desquamation of the face, back, or abdomen will occur by 12 h (Genest and Singer 1992; Wainwright 2006). Fluid will accumulate beneath the epidermis resulting in bullae formation (Fig. 4.5). Generalized desquamation

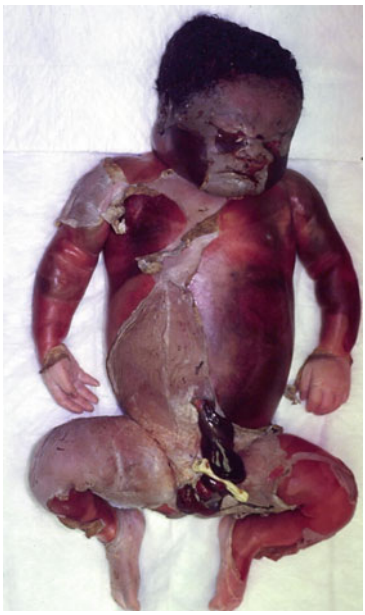

Fig. 4.6 Maceration. Skin sloughing is over the entire body. Note the brown discoloration of the umbilical cord

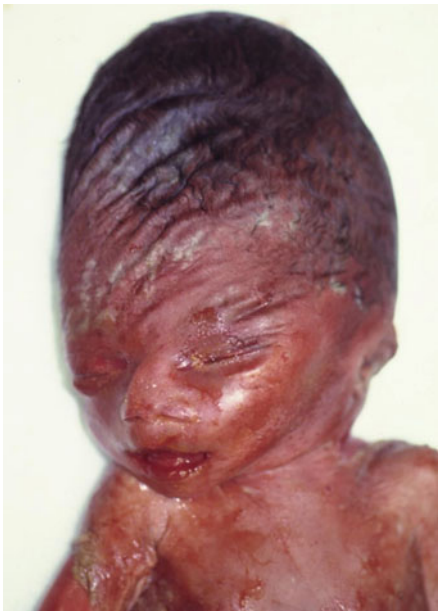

Fig. 4.7 Intrauterine fetal demise with maceration demonstrating the boggy scalp and misshapen head due to brain liquefaction and overriding skull plates

with discoloration of the underlying dermis will occur by 24 h (Fig. 4.6) (Genest and Singer 1992). The scalp will become boggy (Fig. 4.7). By 4–5 days, the skull plates separate from the dura and periosteum and will override resulting in a dysmorphic cranium (Figs. 4.7 and 4.8). Joints become hypermobile with

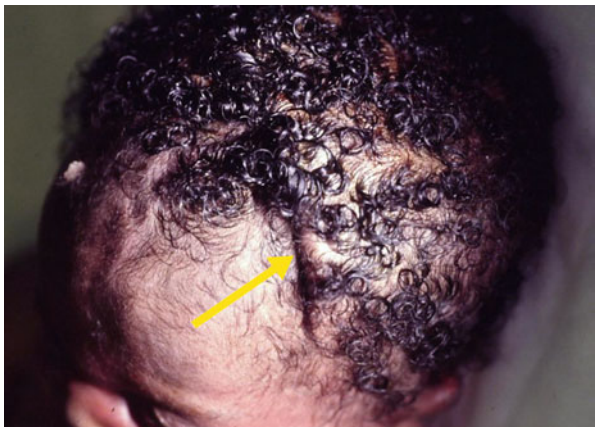

Fig. 4.8 Intrauterine fetal demise with overriding skull plates (*arrow*). This distortion has been mistaken for neonatal skull fractures

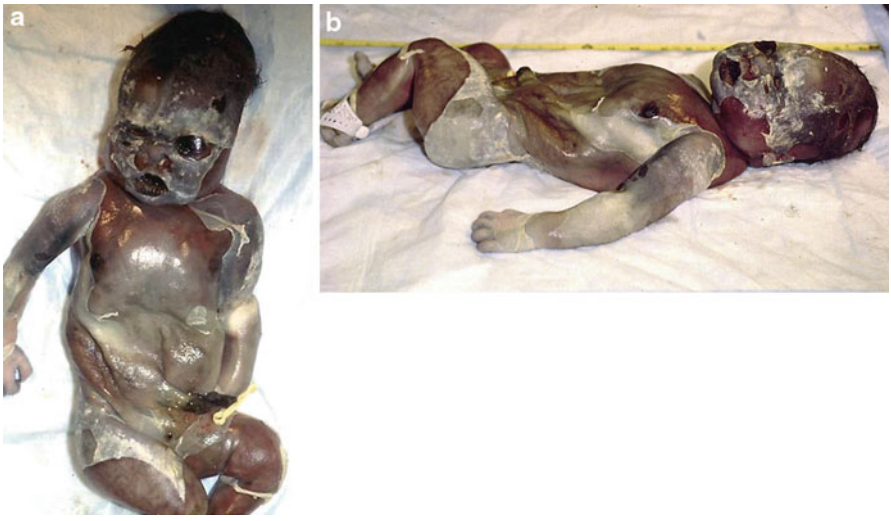

Fig. 4.9 (**a** and **b**) A 40-year-old mother reported that she did not know she was pregnant. Family members complained of an odor. With medical intervention, she delivered a partially decomposed, full-term fetus. The skin was sloughing, and the underlying dermis was green-brown. The skin of the abdomen had started to mummify (**b**)

autolysis of connective tissues. Before 48 h, little change has occurred to the internal organs aside from softening of the brain and liver. After 48 h, the internal organs turn dark red-purple due to red blood cell breakdown. Abdominal organs may become dark green-gray due to leakage of bile. By 2–7 days, serosanguinous fluid collects in serosal cavities and organs begin to liquefy. Mummification will occur 2 weeks after death (Genest and Singer 1992; Wainwright 2006) (Fig. 4.9a and b). A fetus papyraceus is a mummified fetus that died in

Table 4.4 Histological changes consisting of cellular nuclear basophilia loss in certain organs can also be used to estimate postmortem interval (Genest et al. 1992; Wainwright 2006)

Loss of nuclear basophilia, individual cells	**Death-to-delivery interval**
Renal cortical tubules	4 h
Liver	24 h
Inner half of myocardium	24 h
Outer half of myocardium	48 h
Bronchial epithelium	96 h
Tracheal cartilage	1 week
Loss of nuclear basophilia, all cells	**Death-to-delivery interval**
Liver	96 h
Gastrointestinal tract	1 week
Adrenal	1 week
Kidney	4 weeks

utero, usually during the second trimester. Fetus compressus is a mummified, flattened fetus of a multiple gestation that remains compressed between the uterus and the vital sibling's amniotic sac until delivery (usually when the term is completed). Often these two terms are used interchangeably.

Of note, fetal foot length is the most reliable body measurement for gestational assessment of the macerated fetus (Wainwright 2006).

Besides gross changes of maceration, histological changes in certain fetal organs have also been researched to assist in the estimation of the postmortem interval (Table 4.4).

Diagnostic Work-Up of a Fetal Death

The diagnostic work up for fetal deaths involves thorough analyses of the fetus, mother, and placenta (Table 4.5). The most valuable tests are the fetal autopsy with ancillary studies, placental examination, cytogenetic analysis, and analysis for fetomaternal hemorrhage (Varli et al. 2008; Silver 2007; Pauli 2010; Korteweg et al. 2012).

Intrapartum Death

Intrapartum death is the death of a child that occurs during labor and delivery. These are most often secondary to birth trauma or birth asphyxia. Birth trauma is covered in ▶ Chap. 6, "Birth Trauma". Birth asphyxia is an insult to the fetus or newborn due to lack of proper gas exchange or lack of perfusion to various organs during delivery resulting in hypoxia, hypercapnia, and acidosis (Lawn et al. 2005, 2006, 2010; Simunek 2008; Herrera-Marchitz et al. 2011; Majeed et al. 2007). The mother may have medical conditions that lower her oxygen levels; a placental

Table 4.5 Diagnostic work-up for fetal death

Placental examination with histology of placenta, membranes, and umbilical cord
Fetal karyotype (fascia lata, tendon, skin)
Fetal autopsy with toxicology
Fetal microbiology/viral cultures and nucleic acid tests
Fetal analysis for inborn errors of metabolism
Full-body radiographs
Maternal toxicology
Maternal glucose and hemoglobin A1c
Kleihauer-Betke test or flow cytometry to identify fetal red blood cells in maternal circulation
Indirect Coombs
Maternal viral, syphilis, and protozoan serology
Maternal lupus anticoagulant
Maternal anticardiolipin antibodies
Maternal screen for protein C, protein S, antithrombin III deficiency; thrombophilia testing

abnormality may prevent adequate circulation to and from the fetus; or the neonate may be unable to breathe at birth (Majeed et al. 2007). Immediately after delivery, mother-dependent respiration is replaced by autonomous breathing (Herrera-Marchitz et al. 2011). If delivery is delayed or prolonged, intrapartum asphyxia with a multisystem metabolic cascade can result (Herrera-Marchitz et al. 2011). The most severe consequences are neonatal encephalopathy, multiorgan failure, and death (Simunek 2008).

As with fetal death, risk factors for intrapartum death can be divided into fetal, maternal, and placental categories. Fetal factors include macrosomia, malpresentation, dystocias, post-term, congenital heart disease, diaphragmatic hernia, spina bifida, intrauterine growth restriction, and multiple gestations (Dudenhausen and Maier 2010; Milsom et al. 2002). Maternal factors are diabetes mellitus, heart disease, renal disease, hypertension, anemia, preeclampsia/eclampsia, excessive uterine contractions, maternal fever during labor >38 °C, uterine rupture, drugs, and prolonged labor, especially second stage. A prolonged labor with intrapartum metabolic acidosis can lead to multiorgan failure and encephalopathy in the neonate (Simunek 2008). Investigation into the labor and delivery records as well as the mother's past medical history is very important. Placental factors include nuchal cord, cord compression, rupture of membranes over 24 h, chorioamnionitis, abnormal vessel integrity, acute retroplacental hemorrhage, abruption, fetomaternal hemorrhage, and placenta previa.

When investigating a possible birth asphyxia death, signs of fetal intrapartum stress due to asphyxia should be evaluated (Majeed et al. 2007; Milsom et al. 2002; Singh and Archana 2008; Nishijima et al. 2005) (Table 4.6). One of these signs is the aspiration of squamous cells and elements of vernix caseosa. Vernix caseosa is a proteolipid biofilm produced by the fetus during the last trimester. It has several in utero and postnatal functions such as a thermal regulator, antimicrobial, antioxidant, moisturizer, and enhancer of wound healing (Singh and Archana 2008).

Table 4.6 Indicators of intrapartum asphyxia

Non-reassuring fetal heart tones
Passage of meconium
Low Apgar scores (<7 at 5 min)
Acidosis (cord blood pH < 7)
Seizures
Intrathoracic serosal petechiae at autopsy (pleura, epicardium, thymic cortex)
Pulmonary hemorrhage
Hepatic subcapsular hemorrhage
Squamous cells and elements of vernix caseosa in the distal airways at autopsy

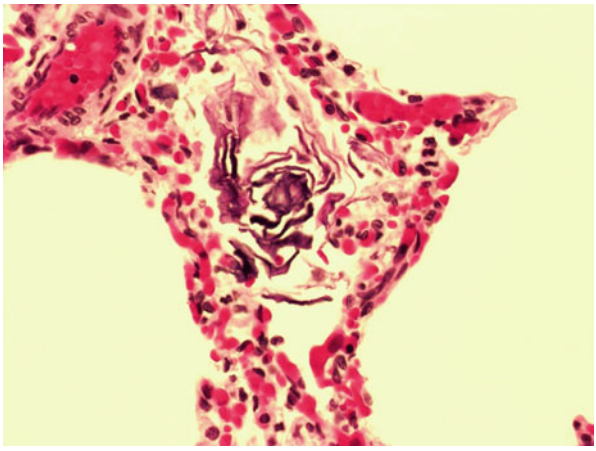

Fig. 4.10 Squamous cells and debris from vernix caseosa are in the alveolar spaces of an infant who experienced birth asphyxia (Hematoxylin and Eosin, H&E × 40)

Vernix caseosa is composed of water, lipid, and protein, in particular water-containing corneocytes embedded in a lipid matrix. Fetal distress leads to reflex gasping efforts by the fetus. Histologically, numerous stacks of flattened, desquamated squamous cells and vernix components such as mucin and lipid can be seen in the distal airways (Figs. 4.10–4.16). Such aspiration can be so massive as to lead to vernix aspiration syndrome and/or airway obstruction (Nishijima et al. 2005).

Another sign of fetal distress is the early passage of meconium (Milsom et al. 2002). Meconium is the first fecal matter passed by a neonate, a highly complex matrix composed of water, mucopolysaccharides, bile salts and acids, bile pigment, epithelial cells, intestinal enzymes, cholesterol and other lipids, as well as a residue of swallowed amniotic fluid (Gallardo and Queiroz 2008). It is generally accepted that meconium begins to form at approximately 12 weeks gestation (Gallardo and Queiroz 2008). It is excreted by the neonate several times a day for the first 1–5 days postpartum (Gallardo and Queiroz 2008). If passed in utero or during delivery, meconium is an indicator of fetal stress and asphyxia as neural stimulation

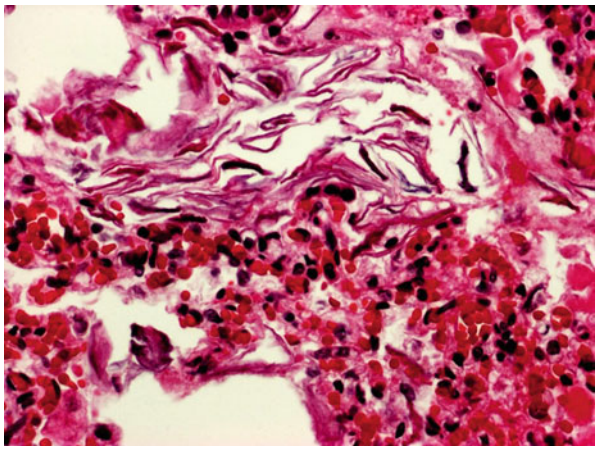

Fig. 4.11 Aspirated stacks of anucleated squamous cells from the fetal skin secondary to birth asphyxia (Hematoxylin and Eosin, H&E × 40)

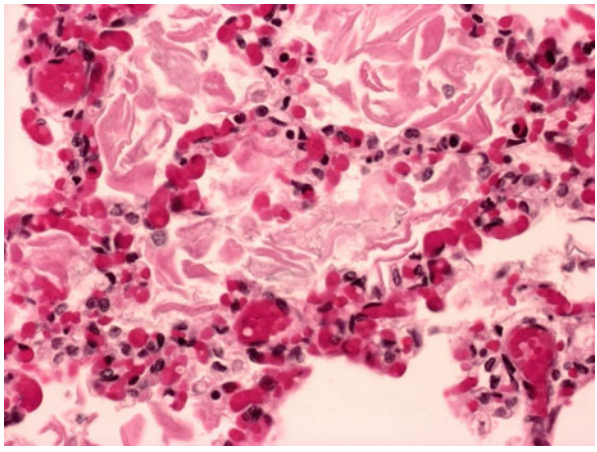

Fig. 4.12 Eosinophilic debris and squamous cells fill alveolar spaces (Hematoxylin and Eosin, H&E × 40)

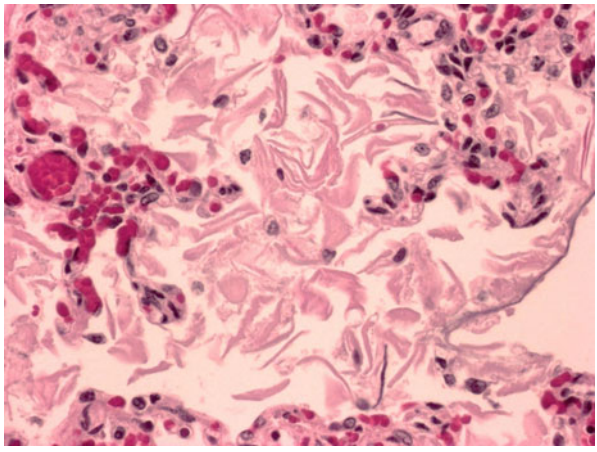

Fig. 4.13 Numerous aspirated squamous cells and debris of vernix caseosa (Hematoxylin and Eosin, H&E × 40)

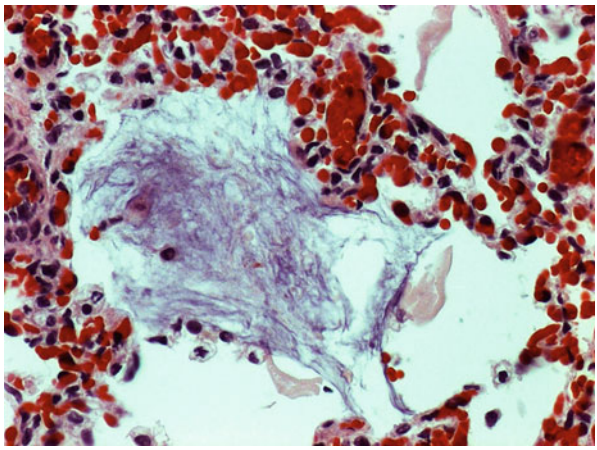

Fig. 4.14 Blue-gray mucin, proteinaceous debris, and squamous cells in the alveolar spaces (Hematoxylin and Eosin, H&E × 40)

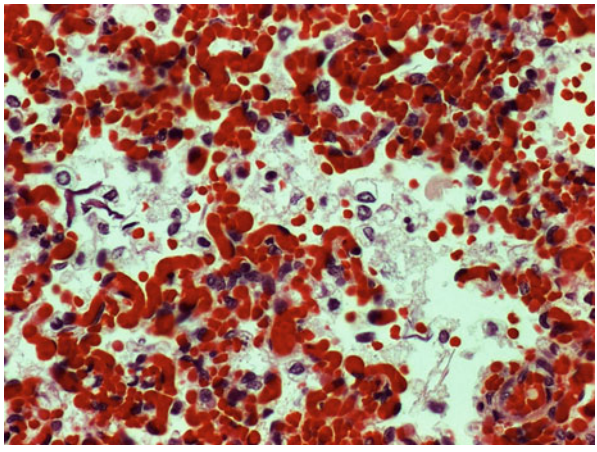

Fig. 4.15 4-day-old neonate: Numerous foamy macrophages and squamous cells in the air spaces (Hematoxylin and Eosin, H&E × 40)

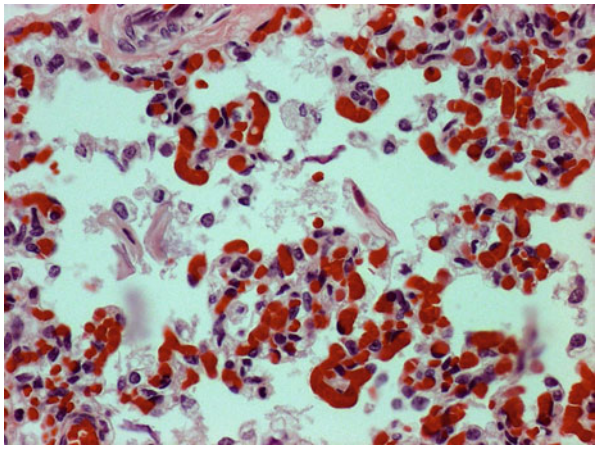

Fig. 4.16 4-day-old neonate who survived after birth asphyxia died of hypoxic ischemic encephalopathy. The air spaces contain foamy macrophages, squamous cells, and eosinophilic proteinaceous material (Hematoxylin and Eosin, H&E × 40)

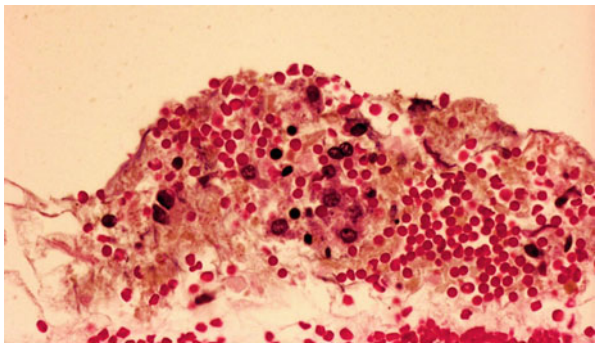

Fig. 4.17 Meconium-stained (bile pigment) placenta of a term neonate who experienced birth asphyxia and passed meconium (Hematoxylin and Eosin, H&E × 40)

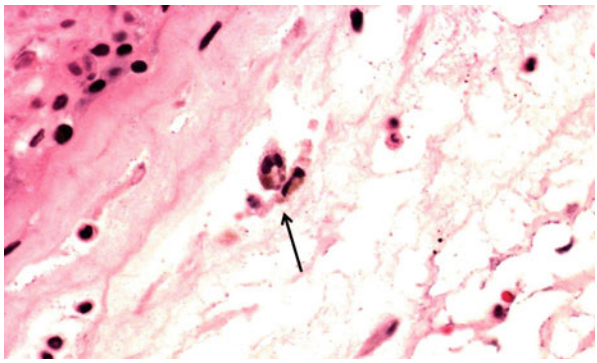

Fig. 4.18 Amniotic membrane meconium/bile pigment in macrophages (*arrow*) (Hematoxylin and Eosin, H&E × 40)

of the rectal sphincter causes relaxation and allows excretion (Milsom et al. 2002). This is evident as meconium-stained amniotic fluid, meconium-stained placenta/membranes/cord, and meconium on the fetus/neonate's skin, nails, and behind the ears (Fig. 4.17). Meconium can be identified in chorionic macrophages after 3 h (Fig. 4.18). Meconium may be aspirated (Fig. 4.19) or swallowed; meconium aspiration syndrome is described under neonatal death.

The central nervous system (CNS) is the most sensitive to intrapartum asphyxia, and the major organ injured is the brain. If the asphyxial episode is acute, resulting in rapid death, generalized edema, pale cerebral cortex, and congested white matter may be identified. Other specific areas of the brain damaged during intrapartum asphyxia are the basal ganglia, thalami, hippocampi, and corticospinal tracts around the central fissure (Rutherford 2001; Herrera-Marchitz et al. 2011). The ischemic lesions are infarctions with or without hemorrhage. In 82 % of cases, more than one organ system besides the brain are involved (Rutherford 2001; Herrera-Marchitz et al. 2011). These organs include kidney, lungs, liver, heart, and intestines. If intrapartum asphyxia does not cause death during delivery, death may occur days later during the neonatal period. Subsequent reperfusion and generation of free

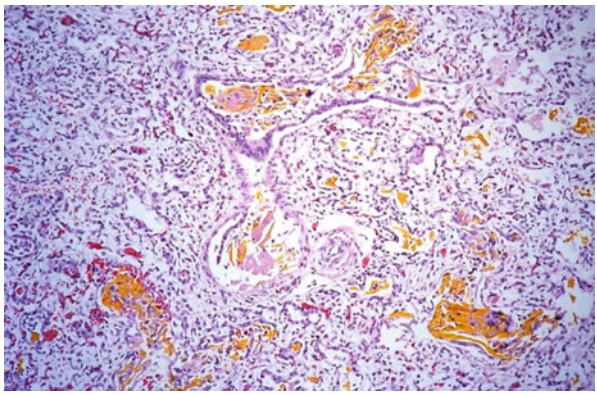

Fig. 4.19 Neonatal lung with meconium aspiration: Yellow-green bile pigment and squamous cells in distal airways and alveolar spaces (Courtesy of Patrick E. Lantz, MD) (Hematoxylin and Eosin, H&E × 40)

radicals contribute to ongoing injury. The CNS lesions will be most visible radiographically and pathologically if the child survives into the neonatal period.

Neonatal Death

A neonate is a child from birth to 1 month of age. It is estimated that each year four million children die during the neonatal period, a global average of 30 deaths per 1,000 live births (Lawn et al. 2005, 2006, 2010). Throughout the world, up to 80 % of neonatal deaths are due to infection (sepsis, pneumonia, diarrhea, tetanus), complications of birth asphyxia, and prematurity (Saugstad 2011; Lawn et al. 2010). Neonaticide is discussed in ▶ Chap. 7, "Neonaticide".

A. Infections are the single largest cause of neonatal deaths globally (Tita and Andrews 2010). Infections are usually secondary to chorioamnionitis that manifest as sepsis, pneumonia, and myocarditis both congenital and neonatal (Berardi et al. 2011; Kristof et al. 2009; Berman and Moss 2011) (Figs. 4.20–4.22). In many areas of the world, deaths are due to malaria, syphilis, and HIV. Neonates are at particularly high risk for infection because of their reduced immunity and the immature biochemical and mechanical properties of their mucosal surfaces, in either function or quantity (Bateman and Seed 2010). Early onset sepsis, which occurs from birth to 6 days, is commonly due to *Escherichia coli* and Group B streptococcus (Bateman and Seed 2010). These pathogens are generally acquired from vaginal passage during birth (Bateman and Seed 2010). Herpes simplex virus, also transmitted during vaginal delivery, is another cause of neonatal infection leading to long-term disabilities or death (Gallardo and Queiroz 2008) (Fig. 4.23a–c). Late onset sepsis, from day 7–30, is most often due to organisms acquired from the environment and/or the caregiver (Bateman and Seed 2010). The major pathogen is coagulase-negative staphylococcus comprising almost 40 % of cases (Bateman and Seed 2010). Others organisms include *Escherichia coli*, *S. aureus*, *Enterococcus* sp., *Klebsiella*, *Enterobacter* sp., *Serratia marcescens*,

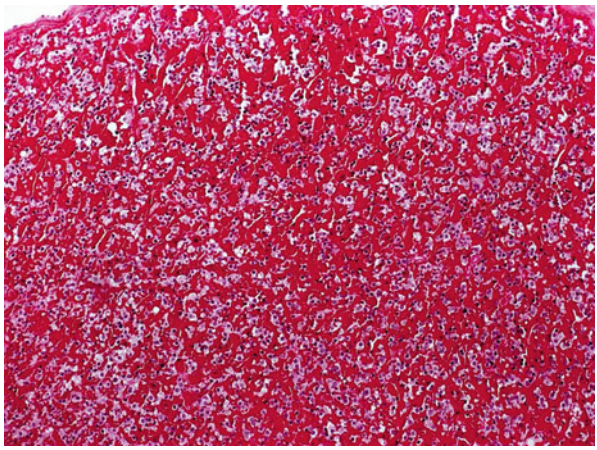

Fig. 4.20 Adrenal gland hemorrhage in a child with sepsis. Waterhouse–Friderichsen syndrome (Hematoxylin and Eosin, H&E × 40)

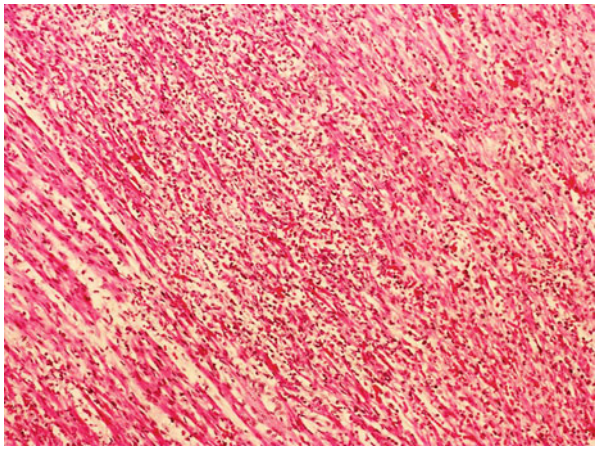

Fig. 4.21 Heart of a neonate with bacterial sepsis and acute bacterial myocarditis shows an infiltration of segmented neutrophils, edema, and myocyte necrosis (Hematoxylin and Eosin, H&E × 40)

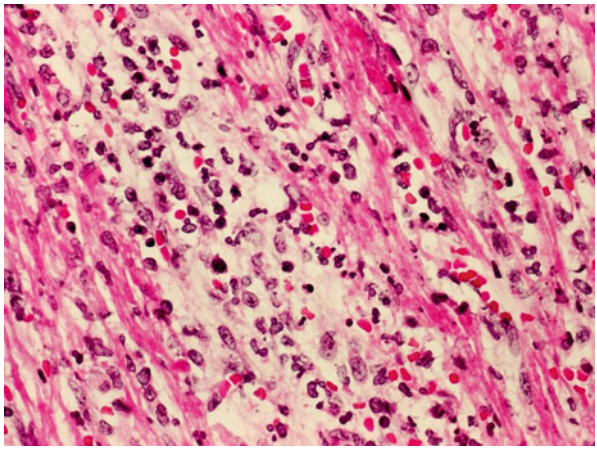

Fig. 4.22 Acute bacterial myocarditis secondary to bacterial sepsis shows segmented neutrophils, myocyte necrosis, and karyorrhexis (Hematoxylin and Eosin, H&E × 40)

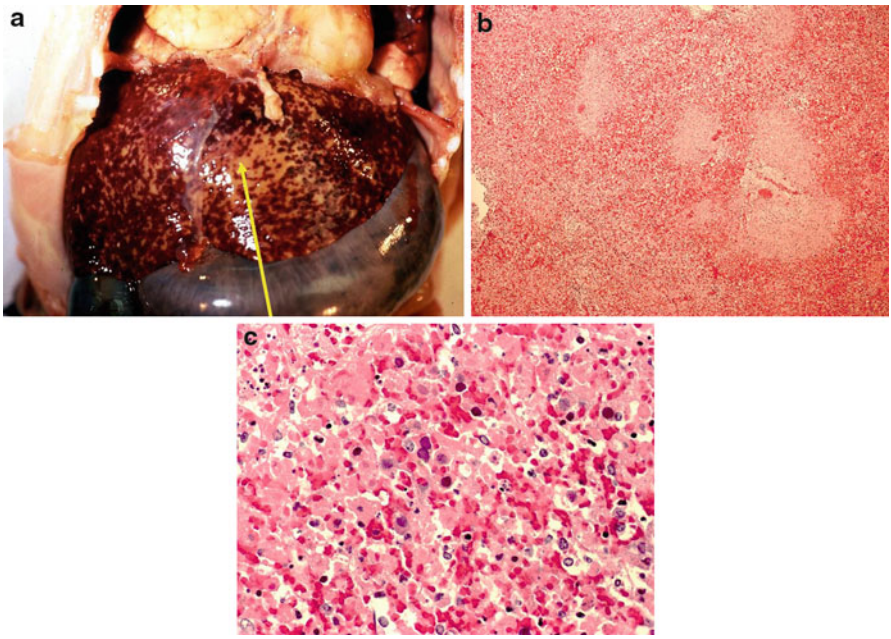

Fig. 4.23 (**a**) Gross liver in situ at autopsy with numerous yellow-tan necrotic areas (*arrow*) throughout the parenchyma. The child has herpes. (**b**) The yellow-tan areas seen grossly correspond to the focal hepatic necrosis (Hematoxylin and Eosin, H&E ×10). (**c**) Many hepatocytes have "ground-glass" nuclear inclusions. The background is hepatocellular necrosis and karyorrhectic debris (Hematoxylin and Eosin, H&E × 40)

Pseudomonas aeruginosa, and Group B *Streptococcus* (Bateman and Seed 2010). Not surprisingly, sepsis is more prevalent in premature neonates especially by Gram-negative organisms and Candida (Tita and Andrews 2010; Kristof et al. 2009).

B. Complications of birth asphyxia that can lead to death in the neonatal period include hypoxic ischemic encephalopathy, intracranial hemorrhage, cardiac papillary muscle necrosis, and meconium aspiration syndrome (Rutherford 2001; Simunek 2008). Cerebral white matter necrosis and cystic degeneration may be seen if a neonate survives 18–24 h. Cerebral infarcts may be identified in the basal ganglia, thalami, hippocampi, and corticospinal tracts around the central fissure (Rutherford 2001). Histopathological brain findings in a neonate who dies from birth asphyxia complications consist of gliosis, neuronal karyorrhexis, lipid and hemosiderin-laden macrophages, and eosinophilic neurons (Fig. 4.24a–g). Other systemic changes seen in neonatal deaths secondary to intrapartum asphyxia include renal acute tubular necrosis (Fig. 4.25a–d), renal corticomedullary hemorrhage, stress involution of the thymus, (Fig. 4.26a–c) hepatic centrilobular necrosis, hepatic microvesicular steatosis, and massive aspiration of squamous cells (Figs. 4.10–4.16).

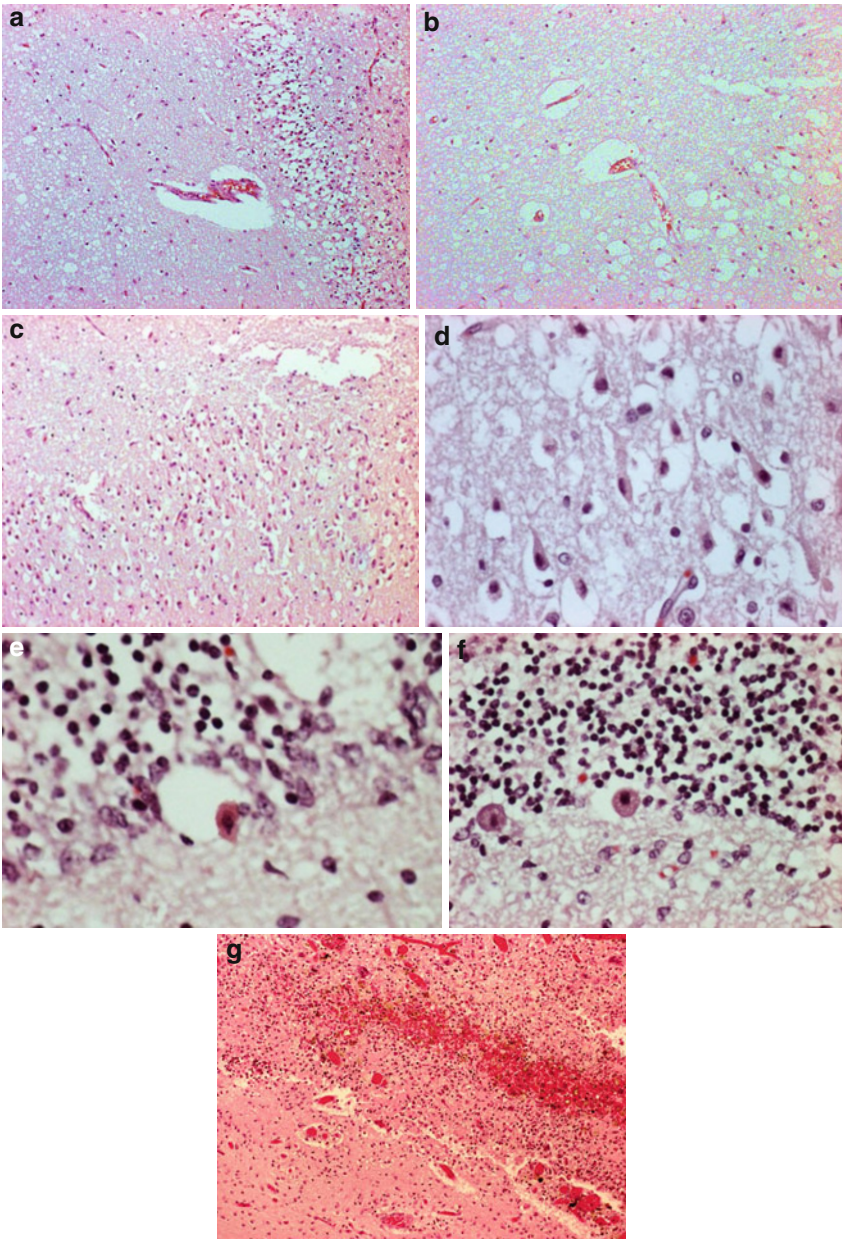

Fig. 4.24 (**a**–**f**) A four-day-old neonate suffered birth asphyxia with hypoxic ischemic encephalopathy and multiorgan failure. Sections of brain show edema, prominence of perivascular spaces, and shrunken, pyknotic neurons. (**e** and **f**) The cerebellar Purkinje cells have eosinophilic cytoplasm with dark, pyknotic nuclei. (**g**) A recent cerebral infarct showing hemorrhage, hemosiderin, edema, and karyorrhexis (Hematoxylin and Eosin, H&E; a,b,c,g × 10; d,e,f × 40)

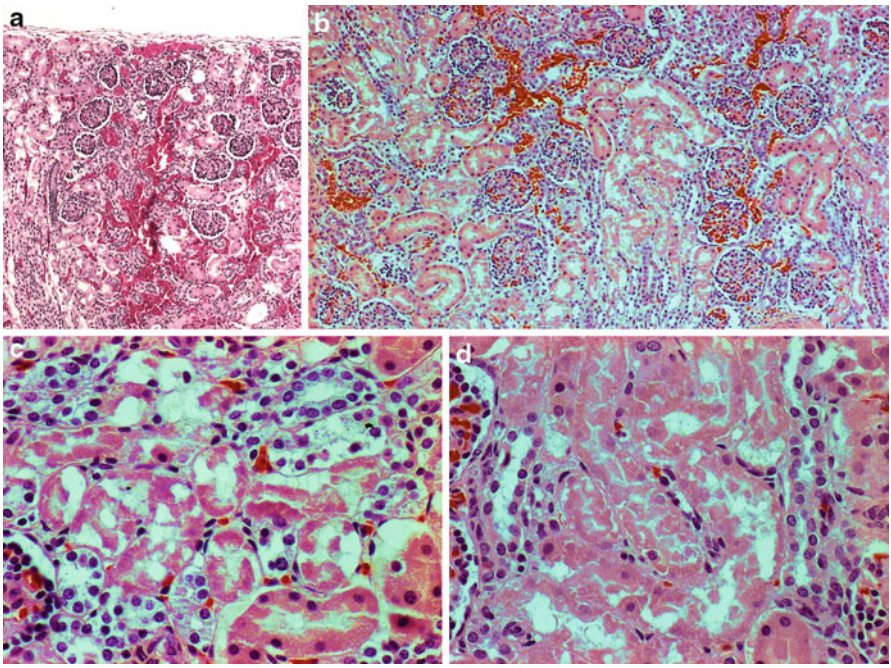

Fig. 4.25 (**a**–**d**) Acute tubular necrosis of the kidney and cortical hemorrhage in a neonate following birth asphyxia (Hematoxylin and Eosin, H&E a × 4; b × 10; c × 40; d × 40)

Meconium aspiration syndrome consists of chemical pneumonitis with hyaline membrane formation, surfactant dysfunction, mismatched ventilation–perfusion, possible airway obstruction, and possible pulmonary hypertension (Fig. 4.19). The mortality rate is as high as 20 %. Bile pigments can be absorbed by the lungs and excreted in the urine (green urine) within 24 h. Meconium may also be seen in the esophagus and stomach.

C. The worldwide prematurity rate is 9.6 %, highest in Africa (11.9 %) and North America (10.6 %). Besides sepsis, other complications of prematurity that can cause neonatal death are respiratory insufficiency and hyaline membrane disease, pneumonia, intracranial hemorrhages (especially germinal matrix and intraventricular), and in the second week of life, necrotizing enterocolitis (Dudenhausen and Maier 2010; Kristof et al. 2009; Nissen 2007; Gupta et al. 2009) (Figs. 4.27, 4.28a, and b). The greatest risk of death from pneumonia in childhood is in the neonatal period (Nissen 2007).

D. During the neonatal period, one may also see deaths from congenital malformations (most commonly congenital heart disease), metabolic disorders, and cardiac channelopathies such as prolonged QT interval (Coté 2010; Sadowski 2009) (Figs. 4.29 and 4.30). Malnutrition and diarrhea cause many

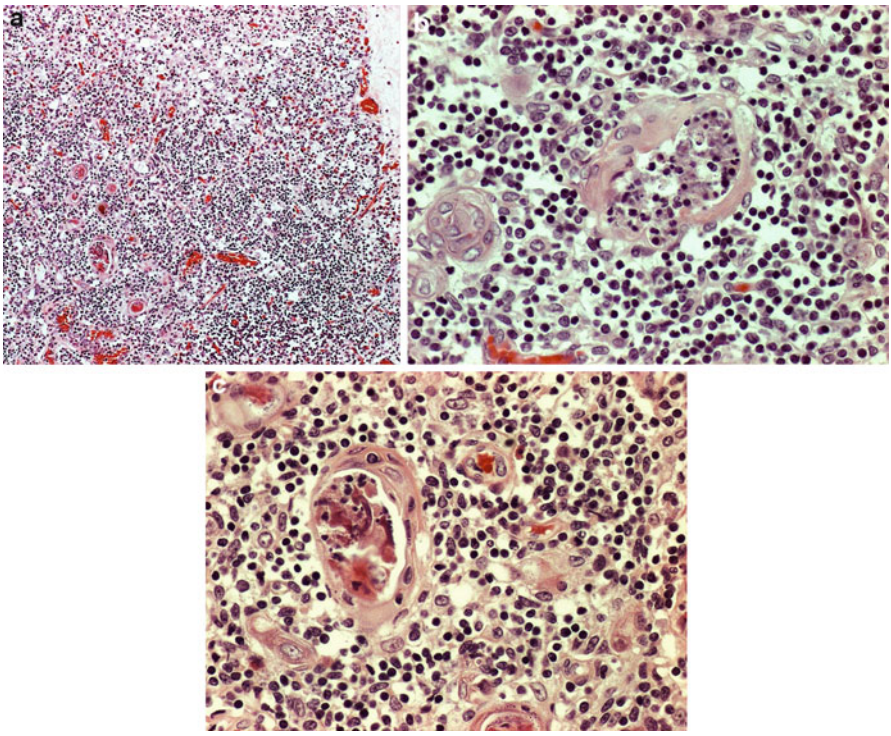

Fig. 4.26 (**a**–**c**) Thymus in a neonate who suffered birth asphyxia and died of hypoxic ischemic encephalopathy. (**a**, Hematoxylin and Eosin, H&E 10×) The thymus demonstrates acute stress involution. The cortex is poorly delineated from the medulla, there is a loss of cortical lymphocytes, Hassall corpuscles are secondarily close together, and (**b** and **c**, Hematoxylin and Eosin, H&E 40×) Hassall corpuscles have necrosis and calcifications

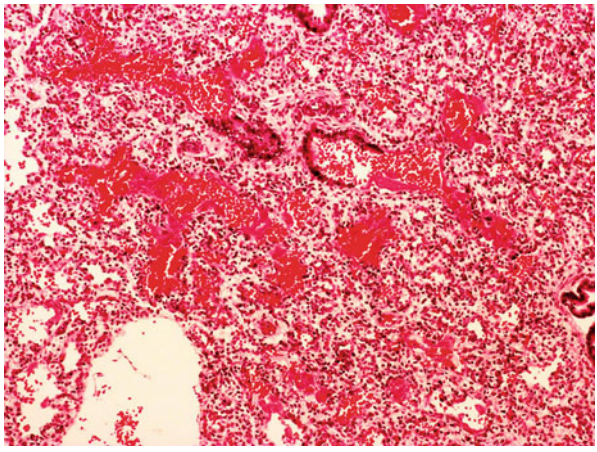

Fig. 4.27 Lung of a premature neonate with respiratory distress syndrome shows vascular congestion, hemorrhage, edema, and hyaline membrane formation (Hematoxylin and Eosin, H&E × 10)

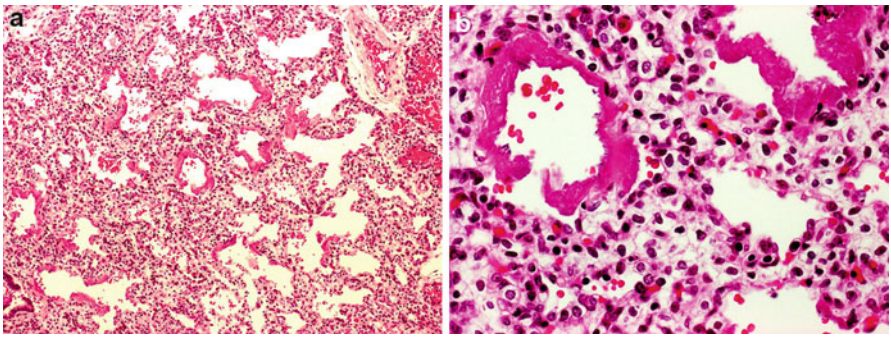

Fig. 4.28 (**a** and **b**) A neonate with respiratory distress syndrome secondary to prematurity. The lungs show hemorrhage and hyaline membranes in the respiratory bronchioles and the alveolar spaces. Of note, hyaline membranes are an indication of live birth (Hematoxylin and Eosin, H&E × 10, 40)

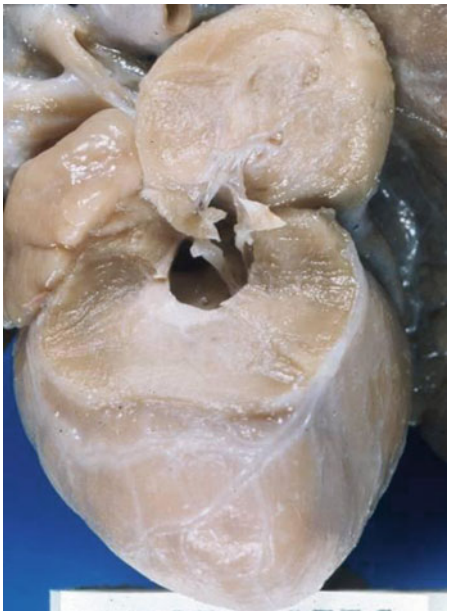

Fig. 4.29 Gross neonatal heart with hypoplastic left heart syndrome. Upward reflection of the left ventricular free wall demonstrates the very small left ventricular chamber. Most of the cardiac mass is right ventricle. Of note, often the mitral valve and aorta are abnormal

deaths throughout the world, especially in areas of poverty and underdevelopment (Bryce et al. 2005). Deaths secondary to aspiration due to dysphagia, metabolic or chromosomal disorders, or a structural abnormality such as a tracheoesophageal fistula or cleft palate also occur (Fig. 4.31a and b).

Of note, intracranial hemorrhages in the neonate have several etiologies including those listed above. The most common presentation is a seizure and many can result in neonatal death (Majeed et al. 2007). These etiologies include

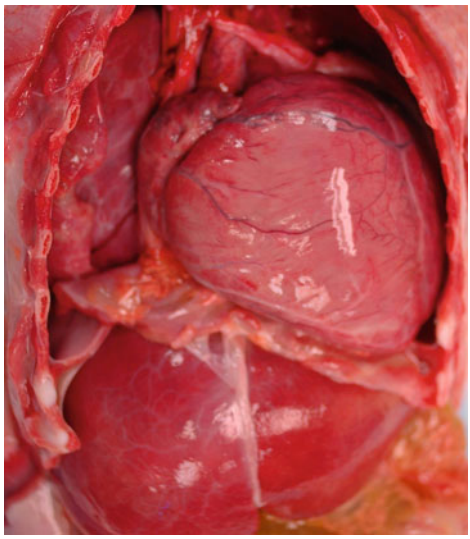

Fig. 4.30 Gross heart. Hypertrophic cardiomyopathy in situ. Cardiomegaly with protrusion of the left ventricle creates a globoid cardiac shape. Compare with the size of the liver below

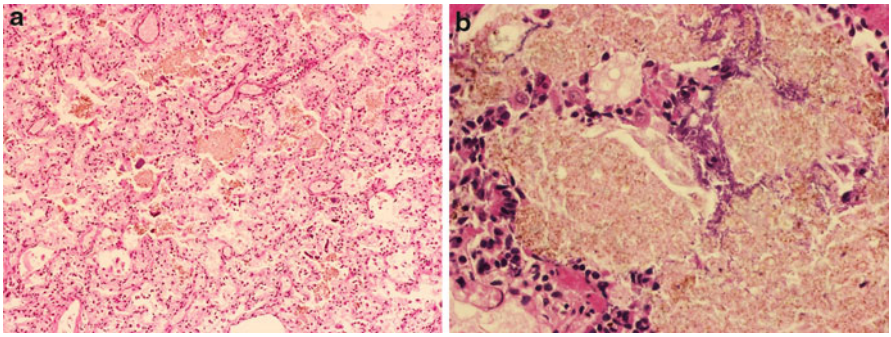

Fig. 4.31 (**a** and **b**) Lung (Hematoxylin and Eosin, H&E × 10) (**a**) and (Hematoxylin and Eosin, H&E × 40) (**b**). Acute aspiration of feeding and/or gastric contents. Granular tan-brown material partially to completely fills the alveolar spaces

intraventricular hemorrhage of prematurity, cerebral infarction, intrapartum asphyxia, birth trauma, inflicted trauma, vascular malformation, coagulopathies, disseminated intravascular coagulation, thrombocytopenia, vitamin K deficiency, hemorrhagic disease of the newborn, neoplasm, sepsis, encephalitis, and sinovenous thrombosis.

Conclusion

Death of a child from the beginning of the fetal period to the end of the neonatal period can be due to numerous causes. Some of these are unavoidable and are

inherent in the fetus. Others are preventable and/or treatable if identified in a timely manner. Most importantly, many of these deaths are associated with known risk factors. Education of healthcare providers, provision of healthcare to underserved areas, and education of the general public can reduce the number of these deaths. In order to accurately determine the cause of death and prevent future morbidity and mortality of these children, a complete autopsy with ancillary studies, examination of the placenta, and assessment of the mother is necessary in every case.

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Placental and Maternal Conditions in Perinatal Deaths

5

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Contents

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Abstract

The placenta provides information about the in utero environment. Abnormalities in the placenta are responsible for many cases of fetal or neonatal deaths, which, without the placenta, may go unexplained. This chapter describes how to examine and section the placenta to yield the best results. The placental abnormalities associated with prematurity, infection, intrauterine growth restriction, intrauterine fetal demise, maternal hypertensive disorders, and diabetes are described.

Introduction

This chapter is designed to aid the evaluation of the placenta associated with a fetal demise or neonatal death, with emphasis on those maternal conditions that may have negative effects on fetal survival. The placenta is a "diary" of the intrauterine environment. Unfortunately, there are many different terms used when describing placental findings and differing opinions about the significance of some of these, which has resulted in confusion. There is no one finding that is diagnostic of a particular maternal or fetal condition. However, combinations of findings in the placenta can yield relatively consistent clinical pathological correlations.

Basic Placental Examination

The gross examination of the placenta should include measurements of the various components and presence of both positive and negative findings. Generally important findings include trimmed weight, location of umbilical cord insertion, cord length and any abnormalities, cord diameter, color of membranes, presence of retroplacental clots, and parenchymal lesions. There are numerous placental textbooks and publications describing the important gross findings, including the guidelines published by the College of American Pathologists (Langston et al. 1997). In general, the placenta has three basic functions which include maternal blood flow, fetal blood flow, and permeability of the villi. If any of these functions is significantly altered, it can jeopardize the fetal well-being.

Adequate sections should be submitted to assure the identification of significant pathology, but in addition, normal tissues must also be examined. It is necessary to assess the development of the placenta in order to determine the significance of pathological features. In general, the placenta has built-in redundancy which allows the fetus to withstand the relative hypoxic intrauterine environment and the stress of labor. If the placenta is developmentally normal (normal weight with appropriate villous maturation), there is approximately a 30 % reserve capacity. However, if the placenta is developmentally abnormal (small for gestation, accelerated maturation), that reserve capacity is reduced to

Table 5.1 Mean expected weight of placenta and length of umbilical cord

Gestation	Mean weight (trimmed gm)	Fetal:Placental (F:P) weight (ratio)	Cord length (cm)	Cord diameter (cm)
8	1.6		6	
10	28.8		10	0.32
12	56.1		13	0.37
14	83.3		16	0.51
16	110.5	1:1	20	0.65
18	137.8		23	0.79
20	163	2.7:1		0.95
22	189	2.9:1	28	1.09
24	190	3.4:1		1.22
26	226	4.1:1	38	1.40
28	254	4.8:1		1.43
30	314	5.2:1	50	1.62
32	338	5.9:1		1.66
34	381	6.2:1	53	1.67
36	447	6.6:1		1.65
38	493	6.9:1	57	1.58
40	510	7.2:1		1.56
42	532	7.1:1	60	1.44

(Ref: Kalousek et al. 1990; Kraus et al. 2004)

as little as 10 %. Therefore the size, location, and type of lesions found within the placenta are important. A gross assessment of percentage of abnormal tissue noted needs to be correlated with the microscopic findings, as grossly normal tissue may also be abnormal. The expected placental weight is based on the disc only after the membranes and cord have been trimmed (Table 5.1).

CAP-Recommended Placental Sections

- Two sections of the umbilical cord from separate areas
- A membrane roll to include the zone of membrane rupture
- Two full-thickness sections of nonmarginal, normal placenta
- Additional sections from abnormalities

The cord sections are primarily submitted to look for fetal inflammation, which may be focal (Katzman and Metlay 2010). There are often hematomas near the fetal end of the cord, secondary to clamping during delivery. These areas should be avoided, as they obscure inflammation. Cord diameter is representative of fetal fluid balance and growth. Thin, flattened, and abnormally spiraled cords are at increased risk of compression.

The zone of membrane rupture has a rolled appearance (Fig. 5.1). In a vaginal delivery, it is the portion of membranes over the cervix that is the most likely to be

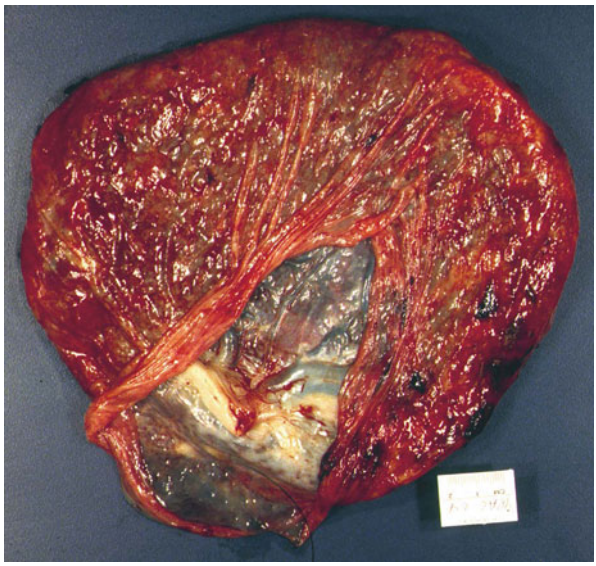

Fig. 5.1 Asymmetric zone of membrane rupture, indicating a low-lying placenta

inflamed as the result of an ascending infection. The zone of membrane rupture is also a clue to the location of the placenta within the uterus. If the membrane rupture is at the placental margin, the placenta was low-lying. Of course, if the delivery is by C-section, the site of membrane rupture usually does not reflect either of these. It has been reported that four membrane rolls have a near-linear increased yield for both chorioamnionitis and maternal vasculopathy (Winters and Waters 2008). One might argue that if the findings are so focal, their significance is diminished.

Terminal villi are the functional unit of the placenta and a feature of a mature placenta. They become the dominant structure around 34 weeks gestation. Appropriate maturation of the placenta is paramount for appropriate transfer of oxygen and nutrients from the maternal to the fetal blood across the vasculosyncytial membranes. Villous development and maturation is a complex topic addressed elsewhere (Popek 1999). In general, throughout gestation, the villi become progressively smaller, there is a decrease in stromal cellularity, and the vessels become larger and move to the periphery to form the vasculosyncytial membrane. Assigning villous maturation is at best an estimate (Fig. 5.2a–d). There is variable maturation within every placenta; the marginal and subchorionic villi are generally less well perfused and appear more mature. The most significant abnormalities include generalized accelerated or delayed maturation.

While the CAP recommends only two full-thickness sections from nonmarginal normal-appearing placenta, many placental pathologists advocate that four sections of parenchyma result in a higher yield of abnormalities. Full-thickness sections show the dichotomously branching fetal vascular tree and the relationship of the villi overlying maternal vessels and are more useful than incomplete sections (Fig. 5.3).

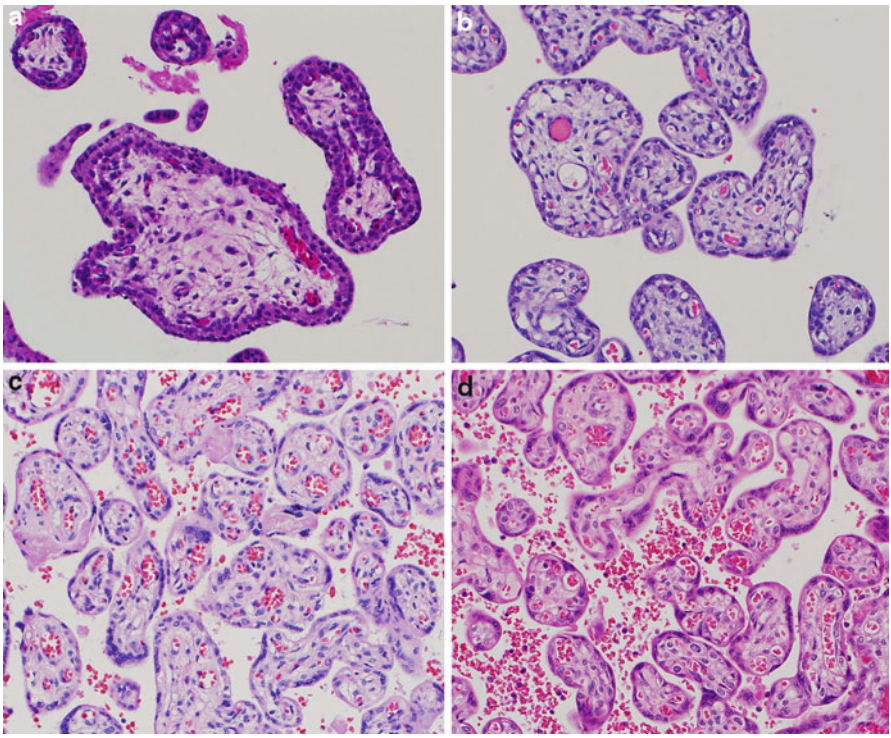

Fig. 5.2 Villous maturation. (**a**) 10 weeks gestation, (**b**) 20 weeks gestation, (**c**) 30 weeks gestation, (**d**) 40 weeks gestation (Hematoxylin and Eosin, H&E × 20)

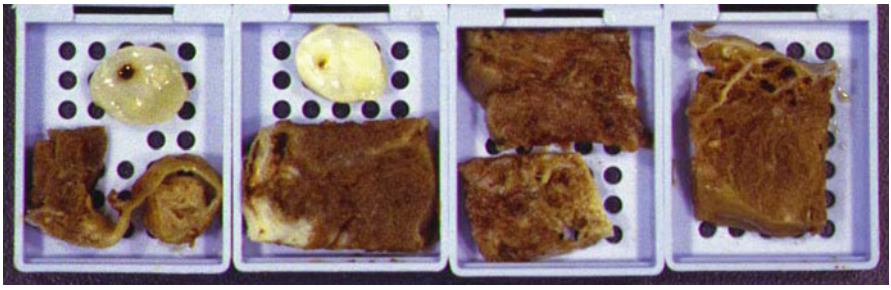

Fig. 5.3 Suggested routine blocks of placental tissues

Estimating Time of Fetal Demise by Placental Examination

Umbilical cord smooth muscle degeneration, villous capillary intravascular karyorrhexis, and intravascular and villous stromal fibroblast proliferation are features that occur after fetal demise but may also be found in live births and may

Table 5.2 Placental changes after fetal demise

Histologic feature	Postmortem interval							
	<6 h	6–12 h	12–24 h	24–36 h	36–48 h	>48 h	>7 days	>14 days
Umbilical cord vascular degeneration	0	33 %	100 %	100 %	100 %	100 %	100 %	100 %
Villous stromal karyorrhexis	0	75	73	64–100	100	100	100	100
Stem vessel luminal abnormalities	0	25	7	21	67	20–60	50–100	100
Villous stromal fibrosis	0	0	0	0	0	20	50	100

(Ref: Jacques et al. 2003; Genest 1992)

be the etiology of fetal demise. There is significant overlap and very broad time intervals with regard to these findings. The most sensitive predictors include degeneration of cord vascular smooth muscle, villous intravascular karyorrhexis, stem vessel luminal obliteration, and villous fibrosis (Jacques et al. 2003; Genest 1992) (Table 5.2). These changes will be discussed more thoroughly in the section on fetal thrombotic vasculopathy. The placenta is the least reliable in estimating the duration of fetal demise.

Umbilical Cord

The umbilical cord is the lifeline for the fetus (Fig. 5.4a–e). Cord accidents probably account for more cases of fetal demise than we can definitively document. Nuchal cord, looped around the neck, is present in at least 20 % of deliveries and most are not significant. Flattening on one side of the cord can sometimes be evident. Knots occur in 1 % of deliveries. As the baby descends during labor, a nuchal cord or knot can become progressively tighter. Cord length also increases throughout gestation and has some relationship to fetal movement (Table 5.1). Short cords are those less than 30–32 cm at term and may reflect neurological or musculoskeletal abnormalities. The cord diameter is a reflection of fetal growth and fluid balance. Thin cords are seen in intrauterine growth restriction (IUGR). Wrinkling of the cord surface is often an indication of decreased amniotic fluid. A thin cord may also be associated with a single umbilical artery (SUA), which is seen in 1 % of deliveries. Congenital malformations are present in 20 % of SUA. Cord spiraling is considered a reflection of fetal movement. The spiraling of the two pulsatile umbilical arteries around the vein also help move oxygenated blood to the fetus. Decreased spiraling, flattened cord, and decreased Wharton's jelly all are risk factors for cord compression. Increased spiraling is often associated with exceptionally long cords and has an increased risk of torsion or stricture and intrauterine fetal demise (IUFD).

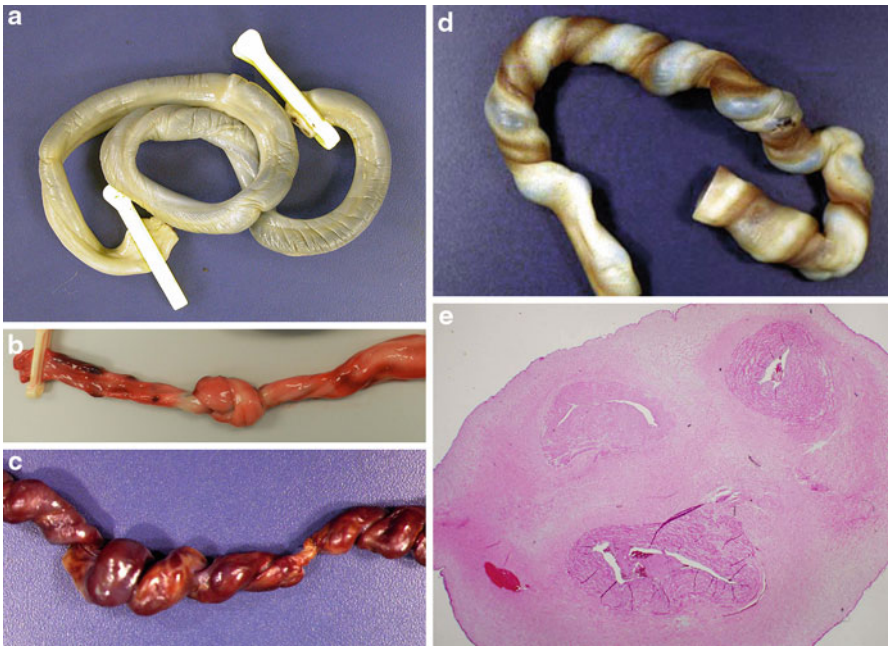

Fig. 5.4 Cord abnormalities. (**a**) Nuchal cord x 3 with one side flattened, (**b**) Tight knot, but no differential congestion on the placental site, (**c**) Excessive spiraling with stricture in IUFD, (**d**) Recent umbilical artery thrombus, with extravasation of hemoglobin pigments, (**e**) Devitalized artery due to recent thrombosis (Hematoxylin and Eosin, H&E × 4)

Preterm Delivery

Preterm delivery is defined as delivery less than 37 weeks gestation and complicates approximately 12–13 % of all births in the United States (USA) (Goldenberg et al. 2008). An increasing number of these, up to 20 %, are iatrogenic, with induced early delivery secondary to either maternal complication or nonreassuring fetal status. Spontaneous preterm births follow labor with intact membranes or after rupture of membranes. Risk factors of preterm births include a previous preterm birth, Black race, periodontal disease, bacterial vaginosis, short cervix, and low maternal body mass index.

Premature rupture of membranes complicates 4.5 % of pregnancies, accounting for 30–40 % of preterm births (Mercer et al. 2000; Menon and Fortunato 2007). In the majority of these cases, the membranes have been weakened by inflammation; however, the remaining have no inflammation, and the etiology of membrane rupture remains unknown. Latency between rupture of membranes and delivery is usually less than 5 days if inflammation is already present but can be weeks in the absence of infection.

Examination of the placenta in spontaneous preterm birth shows two nearly equal and distinct patterns of pathology in preterm delivery: infectious chorioamnionitis and maternal vascular abnormalities typical of hypertensive diseases of pregnancy (Arias et al. 1993; Faye-Petersen 2008).

Infection

Ascending Infection

Chorioamnionitis is the amniotropic migration of maternal neutrophils within the fetal membranes in response to microbial invasion of the amniotic cavity. The fetal inflammatory response within the umbilical cord and chorionic plate vessels is also amniotropic. Various definitions and grading schemes have been proposed, but in general, the diagnosis remains a descriptive one that includes the location and intensity of inflammatory cells (Redline et al. 2003). Maternal inflammation is progressive from the decidua-chorion-amnion. The time necessary for development of full-thickness membrane inflammation is several days, but a number of factors prevent precise timing, including virulence of the bacteria, bacterial load, and maternal immunocompetence. The higher within the membranes and the more severe the inflammation, the worse the outcome. Acute chorioamnionitis is evidence of an ascending infection and is not the result of fetal demise but can occur after fetal demise, as the cervix dilates for delivery. Acute deciduitis at the placental margin is a leading cause of abruption (Darby et al. 1989).

The fetal inflammatory response syndrome (FIRS) is a leading theory for the development of cerebral palsy in preterm infants (Yoon et al. 2007). A fetal inflammatory response is definitive evidence of viability at the time of infection. Caution must be used in interpretation of vasculitis in a severely macerated placenta, as degenerating smooth muscle nuclei may resemble multilobated neutrophils. As with chorioamnionitis, the fetal inflammatory response usually follows a sequential progression over time. The initial response is usually within the umbilical vein, progressing to the arteries. The chorionic plate vessels may be inflamed prior to inflammation of the cord or concurrent with the findings in the cord. The fetal cells begin by margination beneath the endothelium, progressing through the muscular wall out into the surrounding Wharton's jelly. The location and severity of the inflammation should be described, as there is increasing risk for fetal sepsis with increasing severity of the fetal inflammatory response.

Subacute necrotizing chorioamnionitis is a unique form of ascending infection commonly associated with extreme prematurity. Organisms responsible for this type of infection are not unique. It has been proposed that this form of infection has been present for up to 2 weeks, but why there has been a lag time between inflammation and delivery is not known (Ohyama et al. 2003). The gross and microscopic features are characteristic and are often accompanied by necrotizing funisitis (Fig. 5.5a–c).

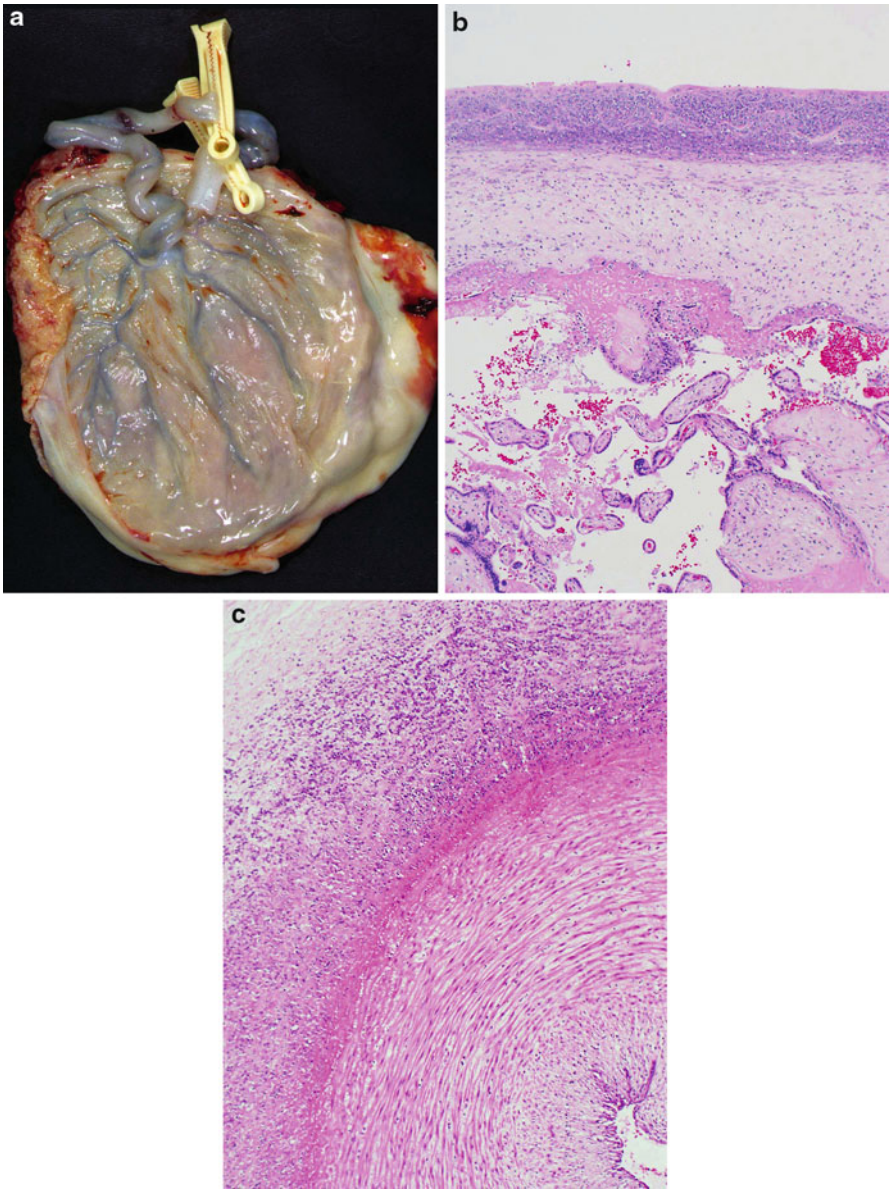

Fig. 5.5 Subacute necrotizing chorioamnionitis. (**a**) Gross appearance, thick opaque membranes, (**b**) Marked necrotic inflammation at subamniotic region (Hematoxylin and Eosin, H&E × 10), (**c**) Necrotizing funisitis (Hematoxylin and Eosin, H&E × 20)

Hematogenous Infection

Hematogenous infection occurs through maternal bacteremia, viremia, or parasitemia. It is much less common than ascending infection. The most common intrauterine viral infection is cytomegalovirus (CMV). There is a 1–2 % risk of CMV seroconversion during pregnancy. Fetal infection occurs in 35 % of primary infection. The earlier the infection, the more severely affected the baby, usually resulting in IUFD or neonatal death (Stagno et al. 1986). The placental hallmark of CMV infection is plasmacytic villitis often associated with hemosiderin-laden macrophages (Fig. 5.6a–c). CMV inclusions are uncommon, and immunohistochemistry is very useful for the diagnosis (Muhlemann et al. 1992).

Other potentially lethal viral infections can be identified by placental examination, but some are not associated with any pathology. Parvovirus B19 is usually associated with fetal anemia and hydrops fetalis. The intranuclear inclusions are easily identified within the nucleated red blood cells circulating within the villi. Immunohistochemistry is also very useful in highlighting the infected cells (Fig. 5.6d, e). Herpes simplex virus, rarely if ever, is a transplacental acquired infection and rarely has any abnormalities.

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy are a major cause of maternal and fetal morbidity–mortality. The incidence ranges from 3 to 7 %. The etiology is multifactorial, poorly understood, and beyond the scope of this chapter. The clinical diagnostic terms used to describe the presence of hypertension that occurs during gestation include pregnancy-induced hypertension, preeclampsia (mild or severe), and chronic hypertension with superimposed preeclampsia. The diagnosis is based on blood pressure elevation prior to or during gestation, degree of blood pressure elevation, and amount of proteinuria.

The basic abnormality identified within the placenta is failed or incomplete remodeling of the maternal spiral arteries at the implantation site of the placenta, resulting in decreased blood flow to the placenta. This is sometimes termed superficial implantation or disorders of deep implantation (Brosens et al. 2011). The spiral arteries are transformed from low-capacity, high-resistance vessels to high-capacity, low-resistance channels and are nearly five times the original diameter. By the end of the second trimester, nearly 90 % of central vessels have adapted, with higher rates near the center of the placenta. Defective vascular adaptation includes retained vascular smooth muscle, residual intraluminal trophoblast, incomplete reendothelialization, fibrinoid necrosis, lymphocytic vasculitis, and atheromas (Fig. 5.7a–e). The vascular lumens may be narrowed or obliterated by intimal proliferation, atherosis, fibrinoid necrosis, or thrombosis. The abnormal vessels are at the junction of the endometrium and myometrium and may not be delivered with the placenta and are often only found in a postpartum curretage (D&C) or placental bed biopsy.

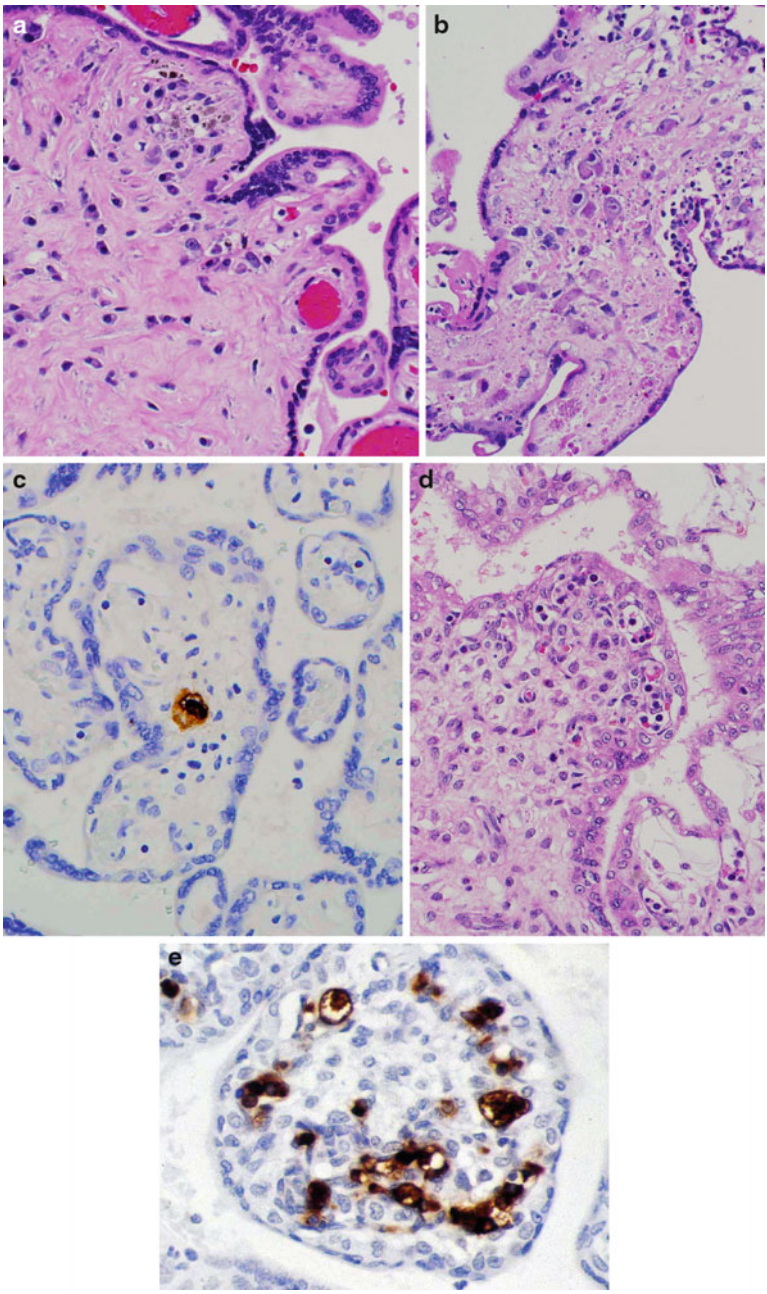

Fig. 5.6 Villitis. (**a**) Lymphoplasmacytic villitis with hemosiderin, consistent with CMV, (**b**) Villous necrosis with CMV inclusions, (**c**) Immunohistochemistry for CMV, (**d**) Erythroblastosis with parvovirus B19 intranuclear inclusions, (**e**) Parvovirus B19 immunohistochemistry (Hematoxylin and Eosin, H&E × 40)

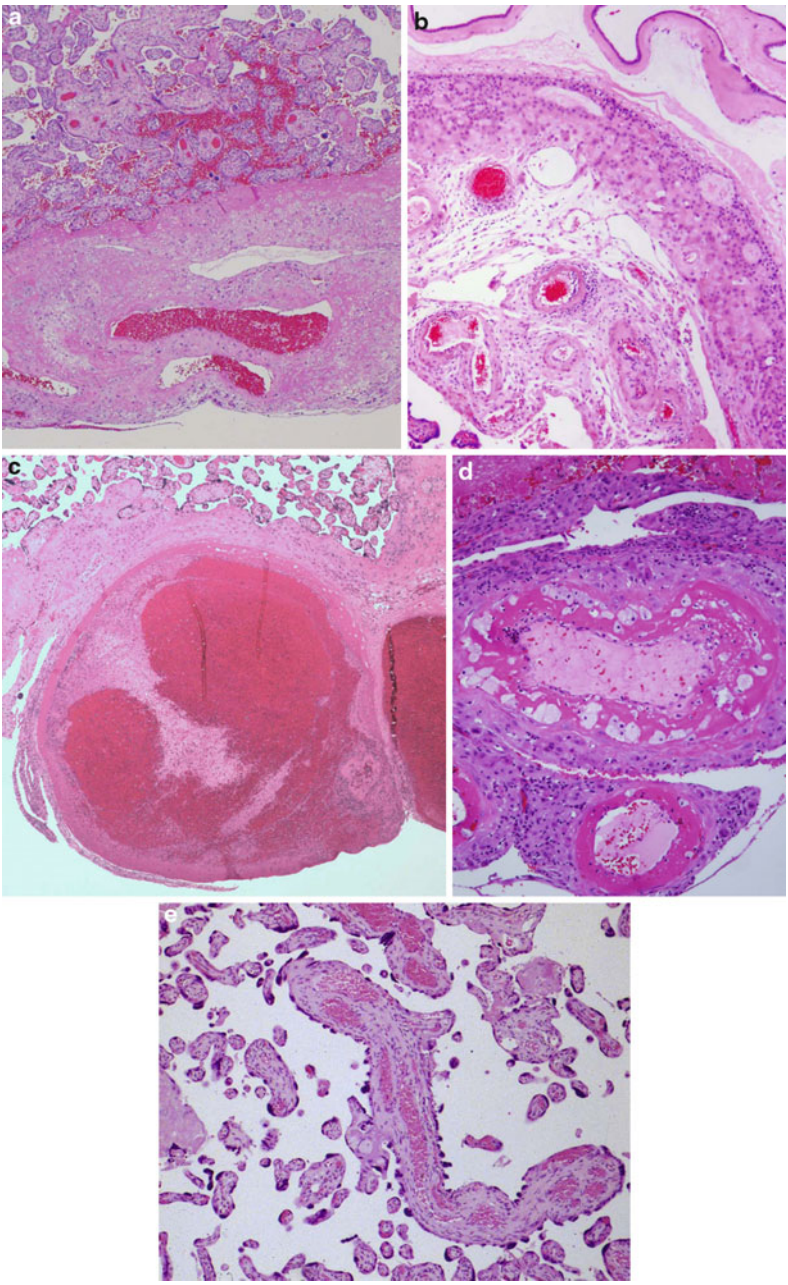

Fig. 5.7 Maternal vasculopathy, (**a**) Normally adapted spiral arteries, (**b**) Fibrinoid necrosis with lymphocytic vasculitis in decidua parietalis, (**c**) Thrombosis, (**d**) Atheroma, (**e**) Accelerated maturation with serrated syncytial knots (Hematoxylin and Eosin, H&E, a, b, c, d × 10; e × 20)

Surrogate markers of poor uteroplacental blood flow, such as accelerated villous maturation or infarcts, are relied on in many cases.

The most severe changes are noted in cases of preterm preeclampsia, preeclampsia associated with IUGR, or abruption. Similar vascular changes with fewer involved arteries are seen in preterm delivery without preeclampsia and in second-trimester pregnancy losses (Khong et al. 1987). In term preeclampsia, the placenta may be completely normal; in fact, the placenta may be slightly heavier than expected for the gestational age. The placenta from preterm preeclampsia characteristically is smaller than expected for gestational age and for the size of the fetus. There are often multiple infarcts of different ages, including infarcts larger than 2 cm with central as well as marginal location. Some infarcts may have central hemorrhage, a particularly poor prognostic feature (Fig. 5.8a–f). The microscopic features include increased syncytial knots, villous agglutination, increased perivillous and intravillous fibrinoid, distal villous hypoplasia, increased invasive or multinucleated trophoblast at the basal plate, maternal vasculopathy, and chronic inflammation (Ghidini et al. 1997; Salafia et al. 1998; Redline et al. 2004a).

Scattered lymphocytes are a normal component of the decidua. Lymphocytes in the decidua are natural killer (NK) cells and have a role in attracting trophoblasts to the decidua and promoting remodeling of the spiral arteries. Increased decidual lymphocytes, extension of the lymphocytes into the chorion or amnion, and cuffing of maternal vessels is considered abnormal and is referred to as chronic chorioamnionitis (Gersell et al. 1991). Plasma cells within the decidua are always considered abnormal. Chronic chorioamnionitis is associated with approximately 37 % of cases of preterm labor or premature rupture of membranes and 23 % of preeclampsia and in 8–19 % of term placentas. It is associated with chronic villitis in approximately 37–70 % of cases (Jacques and Qureshi 1998). Chronic chorioamnionitis, like most chronic villitis, is thought to be an immunological reaction (Kim et al. 2010).

HELLP syndrome – hemolysis, elevated liver enzymes, low platelets – complicates approximately 3/1,000 pregnancies. There is overlap between preeclampsia and HELLP, with some suggestion that they are two different disorders. The major life-threatening complication of HELLP is hepatic hemorrhage and rupture.

Abruption

Abruption occurs in 1–2 % of pregnancies and is the partial or complete separation of the placenta before delivery. Abruption is a clinical diagnosis based on two or more of the following: bleeding after 20 weeks gestation, retroplacental hematoma, uterine tenderness often with tonic uterine contractions, and nonreassuring fetal heart tracings or fetal demise. The etiology of abruption is multifactorial, and there are many risk factors or markers. The most important are preeclampsia, smoking, illicit drug use (cocaine), premature rupture of membranes, multiple gestations doubles the risk (usually affecting the second twin), polyhydramnios, and history of previous abruption increases the risk tenfold (Hladky et al. 2002). There is an association of abruption with inherited and acquired thrombophilias.

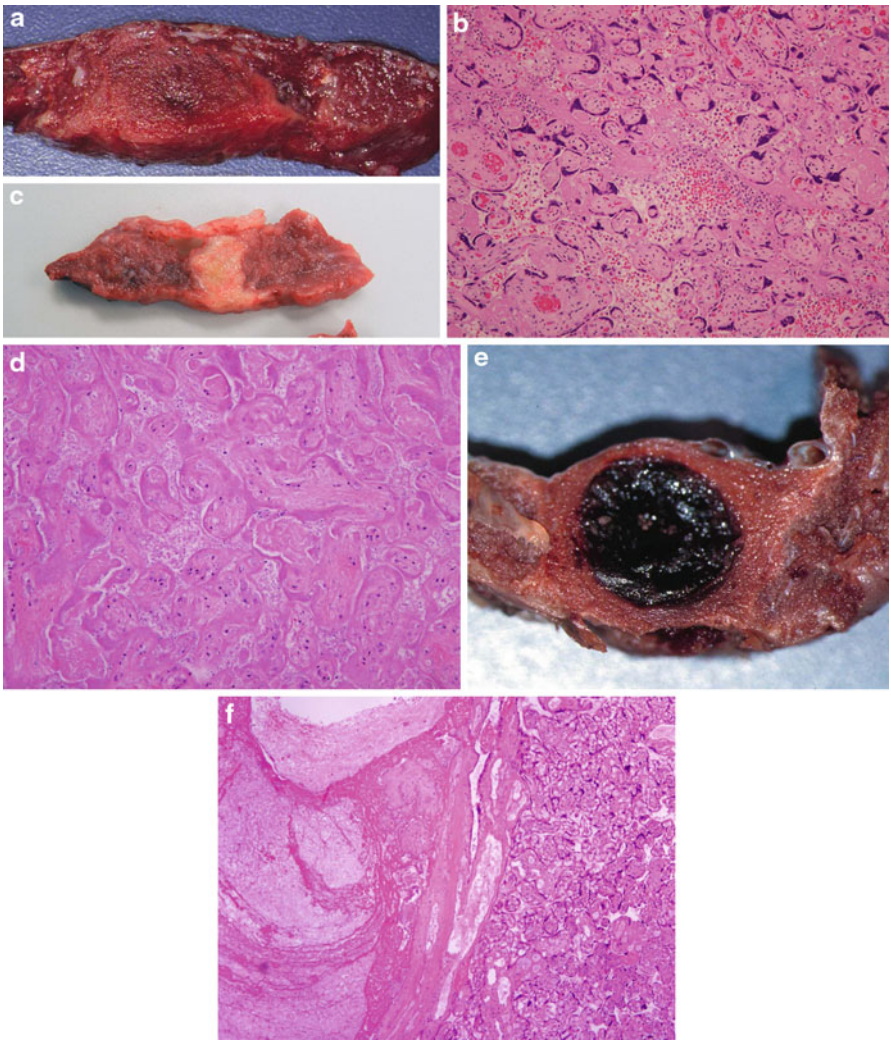

Fig. 5.8 Infarcts, (**a**) Recent, *red* infarct, (**b**) Recent infarct with smudged syncytiotrophoblast and maternal inflammatory reaction to injured tissues, (**c**) Remote, *white* infarct, (**d**) Remote infarct with loss of nuclear chromatin basophilia, (**e**) Infarct with central hemorrhage, gross (Hematoxylin and Eosin, H&E; b, d × 20, f × 10)

Thrombophilias associated with an increased risk of abruption include homozygous methylenetetrahydrofolate reductase, heterozygous factor V Leiden mutation, and heterozygous prothrombin mutations (Tikkanen 2011). Trauma is responsible for abruption in 6 % of minor trauma and 20–25 % of major trauma. The abruption usually becomes manifest 4–6 hours after the trauma, but can occur up to 5 days later (Tikkanen 2011). Most abruptions are associated with major maternal injuries.

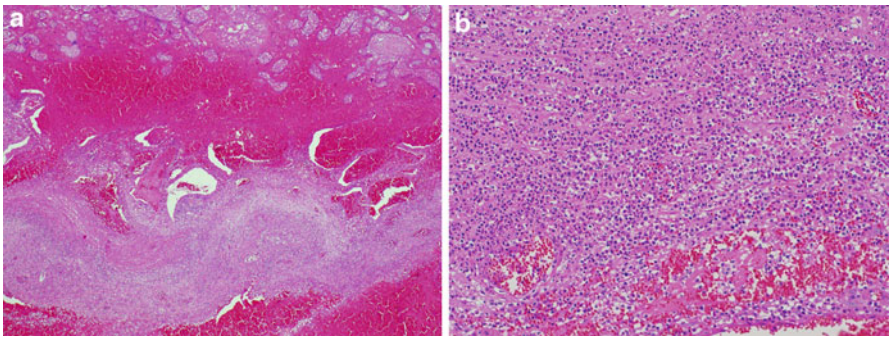

Fig. 5.9 Abruption due to chorioamnionitis, (**a**) Acute hemorrhage into necrotic decidua (**b**) Acutely inflamed decidua (Hematoxylin and Eosin, H&E × 10)

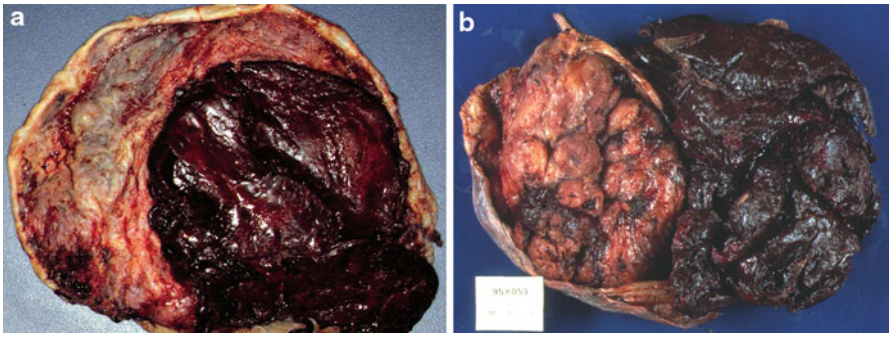

Fig. 5.10 Abruption, (**a**) Retroplacental hematoma, (**b**) Retromembranous hematoma

The fetus can also be injured, and blunt or penetrating injury can be demonstrated. Approximately 25 % of abruptions remain unexplained.

There is a significant risk of preterm delivery, nearly 40 %, even with mild abruptions. IUFD is very common with 50 % separation (Ananth et al. 1999). The risk of abruption is highest at 24–26 weeks, and most occur before 37 weeks. As previously discussed, those mid-gestation abruptions are often related to decidual necrosis and chorioamnionitis (Fig. 5.9a, b). Chorioamnionitis may also be associated with abruption at term (Tikkanen 2011). Abruption is associated with a 15 times increase in fetal mortality compared to stillbirths from other causes (Ananth and Wilcox 2001). Abruption accounts for 10–20 % of all perinatal deaths (Tikkanen 2011; Ananth and Wilcox 2001). Stillbirth is highest when there is maternal PIH, shock, or DIC. Maternal mortality is seven times higher with abruption than with the other causes.

The pathological diagnosis is based on identifying abnormal bleeding at the basal plate of the placenta or sometimes behind the membranes (Fig. 5.10a, b). The more recent the abruption is to the time of delivery, the fewer changes there will be; therefore, a negative placental examination does not rule out a clinical abruption.

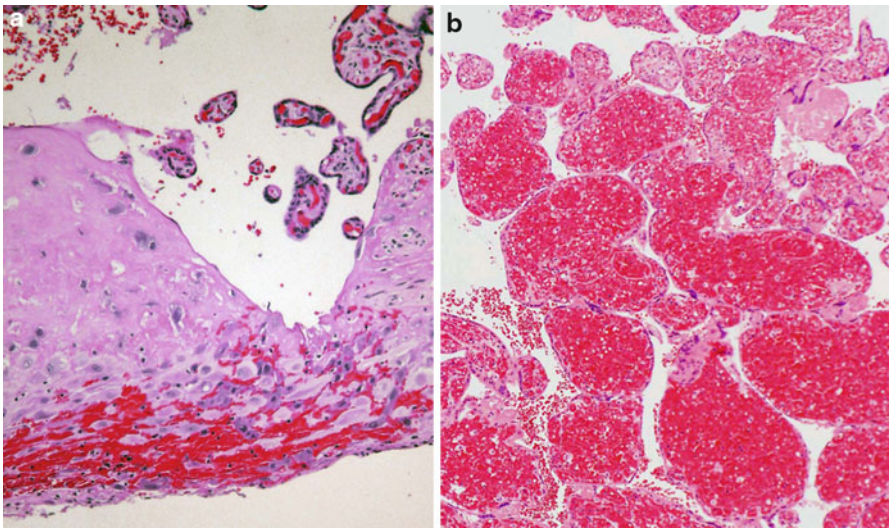

Fig. 5.11 Abruption. (**a**) Blood actively dissecting into the basal tissues (Hematoxylin and Eosin, H&E × 40) (**b**) Intravillous hemorrhage (Hematoxylin and Eosin, H&E × 20)

In approximately one third of cases, there will be a gross retroplacental hematoma. Ultrasound will only identify approximately 50 % of retroplacental hematomas, as there is poor differentiation between recent hematoma and the placental tissue (Glantz and Purnell 2002). However, if the bleeding is allowed to escape the margin of the placenta, then vaginal bleeding will be seen, and there may not be any adherent blood on the maternal surface. A poorly formed retroplacental hematoma may only appear as increased blood in the specimen container, usually greater than 100 cc. Unfortunately sometimes, clots are discarded at the time of delivery. In another one third, there will be abnormal blood actively extending into the basal tissues or into the villi (Fig. 5.11a, b). Villous stromal hemorrhage occurs in abruption when the fetus reacts to the abruption by becoming hyperdynamic. The placental separation results in loss of maternal blood pressure in the intervillous space and rupture of the villous capillaries (Mooney et al. 1994). Less commonly, the blood dissects into the myometrium, resulting in a Couvelaire uterus, which is associated with a worse fetal outcome (Pitaprom and Sukcharoen 2006). The remainder of placentas will be normal, often with features of decreased uteroplacental blood flow.

The villi overlying a retroplacental hematoma will become ischemic and ultimately show characteristic features of infarction. A review of cases by Bendon compared the villous features with duration from abruption to delivery. Neutrophils marginated within decidua within 4 hours, smudged syncytiotrophoblast were found from 4 to 24 hours, and only after 24 hours were pale syncytiotrophoblast nuclei found (Bendon 2011). The timing of infarcts is divided into wide time spans. A very acute abruption will appear red and may only feel slightly firmer than the

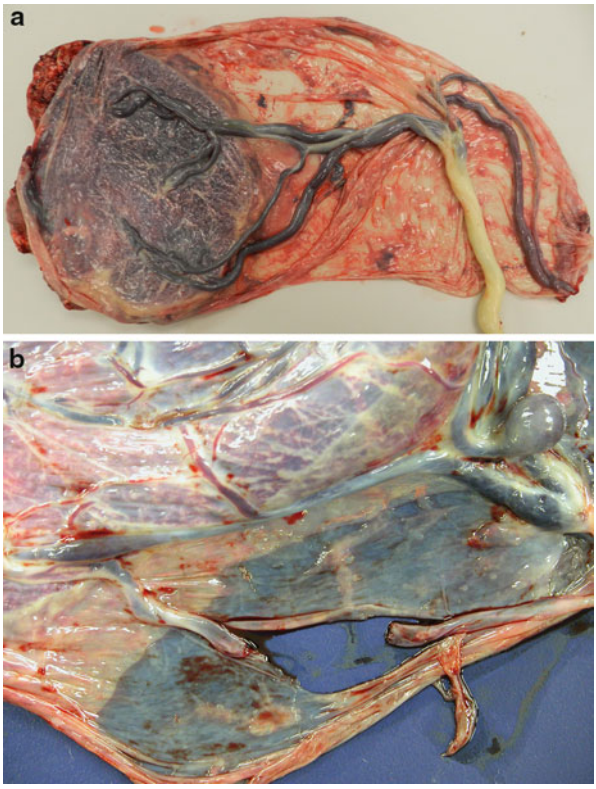

Fig. 5.12 Intramembranous blood vessels. (**a**) Velamentous cord insertion in a "bucket handle" formation, with all vessels entering on the chorionic plate from the outside, (**b**) Disrupted intramembranous vessel, difficult to find after collapse of the thin walled vessels

surrounding tissue. Within 2–3 days, it will be pink, at 3–5 days tan, and greater than 7 days white. Decidual or stromal hemorrhage will eventually break down, and hemosiderin pigment will be present. Hemosiderin begins to appear at 72 hours and will remain present for months (Bendon 2011).

Other etiologies for antepartum vaginal bleeding should be considered. A placenta previa or low-lying placenta can result in painless vaginal bleeding. The origin can also be fetal with rupture of an intramembranous blood vessel, as can occur with a velamentous cord insertion and vasa previa (Fig. 5.12a, b). Careful examination of the fetal chorionic plate vessels should be performed.

Villitis of Unknown Etiology

Villitis of unknown etiology (VUE) is seen in 8–12 % of term placentas, with 17 % incidence in placentas from IUGR (Pitaprom and Sukcharoen 2006; Bendon 2011). VUE is thought to be a heightened maternal immune reaction; it is a disorder usually of the third trimester (Gersell 1993). The inflammatory cells are a mixture of maternal and fetal T-lymphocytes. Maternal risk factors include obesity,

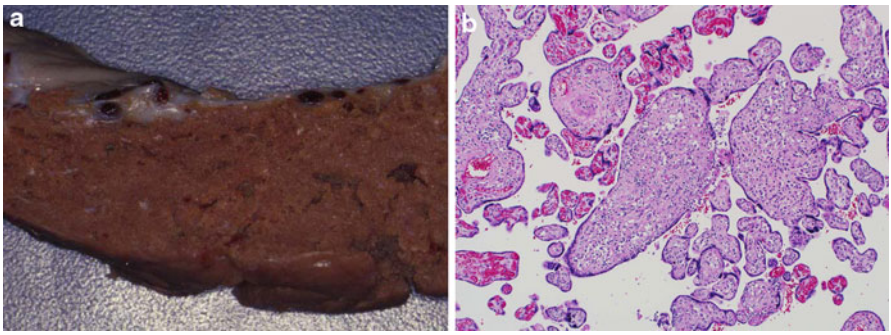

Fig. 5.13 Villitis of unknown etiology. (**a**) Grossly coarse, granular appearance of the villi, (**b**) Lymphohistiocytic villitis (Hematoxylin and Eosin, H&E × 20)

increased parity, increased maternal age, and pregnancy-induced hypertension (Labarrere et al. 1990). There is a significant risk of IUGR and increased neonatal mortality. The abnormal outcome is directly proportionate to the amount of villous tissue involved, with increased severity in IUGR. Recurrence risk is 10–15 %, with increasing severity (Redline 2007). However, recent studies suggest that other factors such as cytokines must influence the IUGR, because even in severe cases, usually no more than 10 % of placental tissue is affected (Becroft et al. 2005; Redline 2007).

Villitis is rarely a gross diagnosis, but occasionally, the parenchyma may appear granular due to aggregation of the villi (Fig. 5.13a, b). There may also be increased fibrinoid material within the placenta or at the basal plate.

Massive Perivillous Fibrinoid (Maternal Floor Infarct)

Massive perivillous fibrinoid is an uncommon placental abnormality, with an incidence of less than 1 %. It is characterized by deposition of eosinophilic material at the decidual plate and throughout the placenta surrounding otherwise normal villi (Fig. 5.14a, b). There may be hyperplasia of extravillous trophoblast within the material as a feature of chronicity. This is frequently mistaken for true infarct, which is a disorder of maternal blood flow. The fibrinoid material interferes with permeability of the villous resulting in IUGR, IUFD, and prematurity (Gersell 1993). There is a significant recurrence risk in some patients, with changes noted as early as 8 weeks gestation.

Histiocytic Intervillositis

Histiocytic intervillositis is characterized by large numbers of macrophages within the intervillous space; some are clearly associated with areas of trophoblast injury.

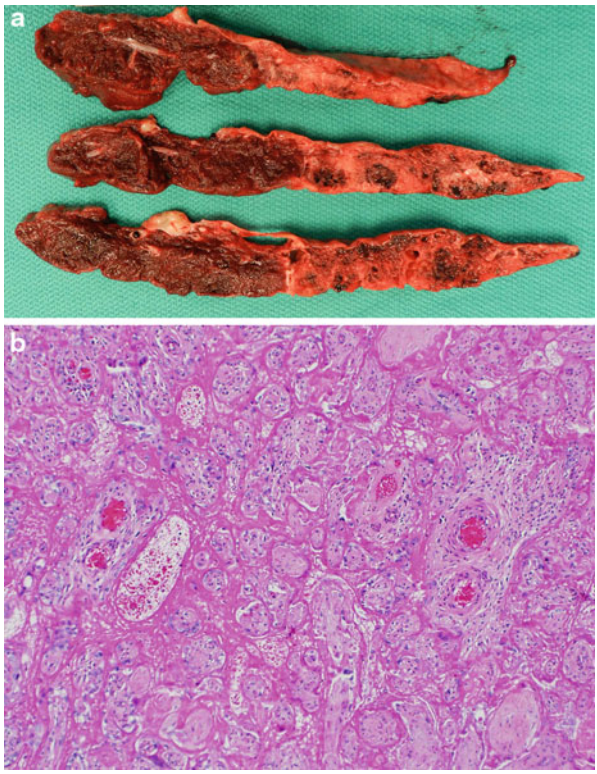

Fig. 5.14 Perivillous fibrinoid. (**a**) Half of the placental surface is involved with perivillous fibrinoid, (**b**) Viable villi, surrounded by eosinophilic fibrinoid (Hematoxylin and Eosin, H&E × 20)

Some, but not all, cases are associated with actual villitis. It is associated with IUGR, prematurity, and IUFD. Recurrence rate in retrospective studies is similar to massive perivillous fibrinoid (Boyd and Redline 2000). Because of significant overlap in pathological features, histiocytic intervillositis and massive perivillous fibrinoid are thought to be ends of the same spectrum.

Diabetes

Diabetes is the most common medical condition complicates 3–14 % of pregnancies. Gestational diabetes mellitus (GDM) is the onset of glucose intolerance during gestation, most commonly at the beginning of the third trimester. Diabetes, particularly pregestational, is associated with a significant incidence of congenital malformations, IUFD, and neonatal morbidity and mortality (Allen et al. 2007). The fetus receives all the glucose across the placental interface by passive diffusion. There is both placental and fetal overgrowth. The fetus produces increased insulin to control the hyperglycemia. Hyperinsulinemia results in acidemia and hyperglycemia in hypoxia, forming a relatively hypoxic intrauterine environment. The placenta in diabetes is large but has suboptimal function, which in conjunction with the hypermetabolic fetus plays a role in the approximately 6 % incidence of IUFD. There is increasing

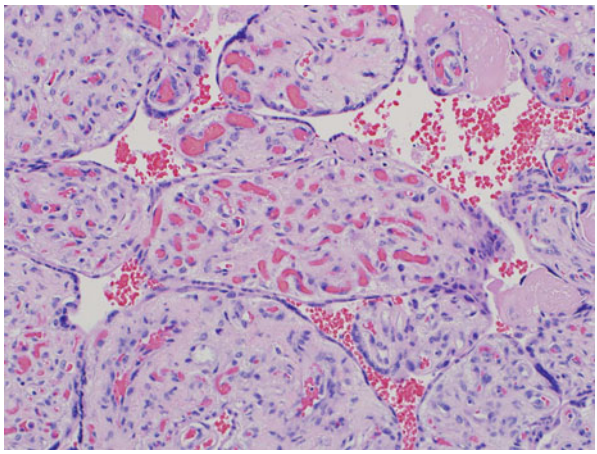

Fig. 5.15 Chorangiosis, marked increase in number of capillaries within terminal villi (Hematoxylin and Eosin, H&E × 20)

evidence of increased oxidative stress in the diabetic placenta and fetus, and this may be important in the worse outcome for male infants (Rajdl et al. 2005).

Grossly, the placenta is large, having increased diameter and weight, for gestational age resulting in a decreased fetal:placental weight ratio. There appears to be generalized overgrowth of all portions of the placenta. There is an increased risk of fetal vascular thrombosis within umbilical cord and stem vessels in up to 25 % of diabetic placentas. Microscopically, the placenta usually has delayed villous maturation, edema, decreased calcifications, thickened trophoblast basement membrane, and hypervascularity (Makhseed et al. 2002). Chorangiosis is defined as diffuse increased villous vascularity when at 10 x magnification, there are greater than 10 vessels, in 10 terminal villi, in more than three nonischemic areas (Altshuler 1984) (Fig. 5.15). Chorangiosis is most commonly associated with diabetes but may also be seen in some cases of congenitally malformed and chromosomally abnormal fetuses in addition to some cases of decreased uteroplacental blood flow. The number of nucleated red blood cells is also increased to approximately double that of a nondiabetic (Green and Mimouni 1990). The placental abnormalities are in general worse with poor glucose control; but this is not universally true. Similar placental findings are noted in obesity without diabetes. Generalized vascular disease found in severe diabetes may also affect the placenta.

Drug Use During Pregnancy

Cocaine and amphetamine use are both associated with abruptions, primarily related to vasoconstriction. The actual participation of these drugs to the pathology is confounded by other risk factors such as lack of prenatal care, smoking, increased risk-taking behavior, and increased chorioamnionitis. Cocaine and amphetamines produce their effects through inhibition of serotonin, norepinephrine, and dopamine transporters, the former two expressed on the syncytiotrophoblast. This is thought

to elevate serotonin and norepinephrine in the intervillous space and cause uterine contractions and vasoconstriction (Ganapathy 2011).

Meconium

Meconium passage is found in approximately 15 % of term deliveries. It is considered to be a feature of fetal stress. Meconium is rarely passed prior to 32 weeks gestation. The more mature the fetus, the less stress is needed to result in passage, whereas at earlier gestation, the stressor is generally more severe. Meconium is most often passed secondary to chorioamnionitis, followed by uteroplacental blood flow issues and fetoplacental blood flow issues, usually cord compression (Incerti et al. 2001). Thick, particulate meconium is associated with significantly more morbidity and mortality. It is not always the meconium that results in the problems, but what caused the meconium passage in the first place. The mechanism for the injury is still unknown, but placental vasoconstriction seems to have been ruled out. Meconium aspiration syndrome occurs in 3–4 % of cases and is associated with significant respiratory distress, pulmonary hypertension, and neonatal mortality (Ahanya et al. 2004).

Grossly pigmented membranes may be secondary to severe chorioamnionitis, hemosiderin deposition, or meconium. Acute meconium is bright green and may only sit on the membrane surface. Subacute meconium is dark green and over time becomes more mucoid. Chronic meconium-stained membranes are dull, muddy brown (Kaspar et al. 2003). Meconium is phagocytized by macrophages in the membranes and is progressively removed from the amniotic fluid. Meconium-laden macrophages can be found within the amnion within 1 h of passage, the chorion in 2–3 hours, and in the decidua parietalis in 6 hours (Miller et al. 1985) (Fig. 5.16a, b). This time sequence is well accepted, but recent studies suggest that the process of uptake may take considerably longer (Funai et al. 2009).

A fetal acute vasculitis is not associated with maternal chorioamnionitis, when the presence of meconium is a feature of meconium aspiration syndrome. It is not the meconium on the placenta that elicits the fetal vasculitis but the presence of the meconium within the lung (Burgess and Hutchins 1996).

Prolonged exposure to heavy meconium may result in meconium-induced smooth muscle injury of the umbilical arteries. Altshuler noted that this feature was not seen in exposure less than 16 h (Wylie and D'Alton 2010) (Fig. 5.17a, b). I find meconium-induced smooth muscle necrosis in approximately 1 % of meconium-stained placentas, and cord ulceration is even less common. It is always associated with neurological injury, and the severity is proportionate to the vascular injury.

Fetal Maternal Transfusion

Massive fetal maternal transfusion (FMT) occurs in 0.3 % of pregnancies and results in perinatal mortality in 1 in 1,000 deliveries. Throughout gestation, fetal

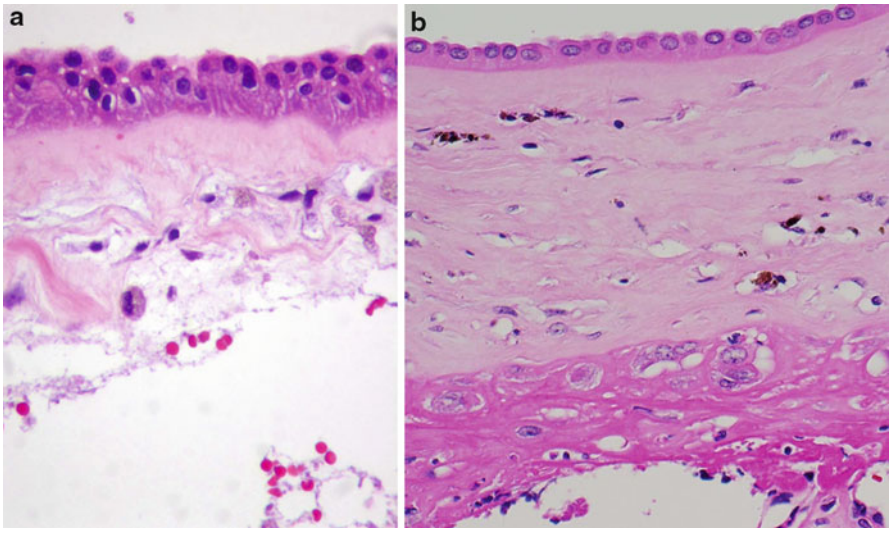

Fig. 5.16 Pigmented macrophages. (**a**) Meconium-laden macrophages in the amnion with mild amnion hyperplasia, (**b**) Hemosiderin-laden macrophages, with more granular appearance (Hematoxylin and Eosin, H&E × 40)

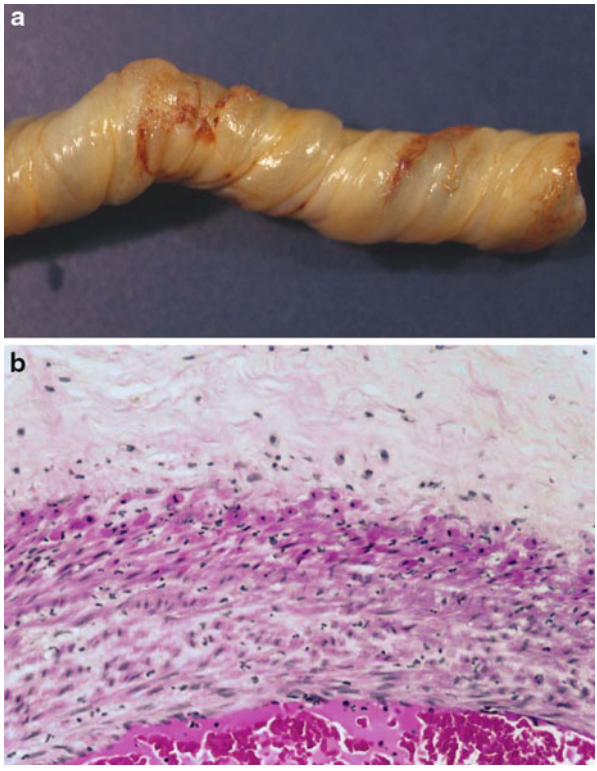

Fig. 5.17 Meconium-induced smooth muscle injury of umbilical cord, (**a**) Superficial ulceration of cord over the arteries, (**b**) Meconium-laden macrophages in Wharton's jelly: rounded up smooth muscle with pyknotic nuclei and vasculitis (Hematoxylin and Eosin, H&E × 40)

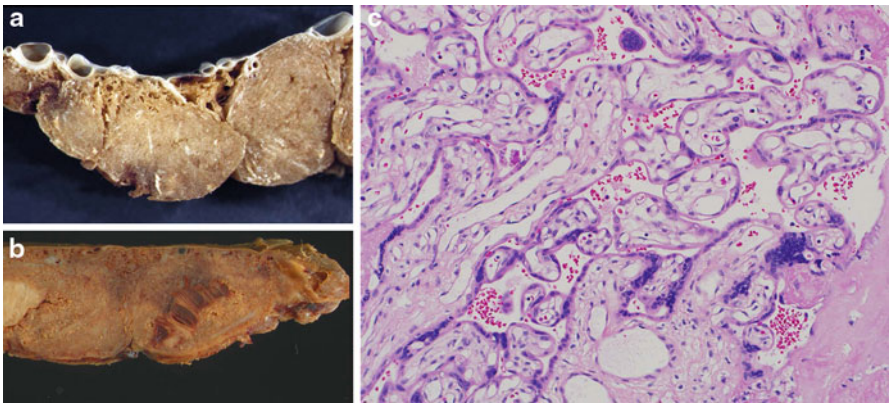

Fig. 5.18 Massive fetal maternal transfusion. (**a**) Pale anemic appearing placenta, with distended chorionic plate vessels, (**b**) Multiple intervillous hematomas, (**c**) Empty fetal capillaries (Hematoxylin and Eosin, H&E × 20)

nucleated and red blood cells gain entrance into the maternal circulation, although their numbers are very small. It is likely that the majority, if not all women, have some fetal red blood cells within their circulation after delivery, which is usually less than 0.5 mL. It is slightly more with C-sections and after placental abruption, particularly if traumatic. The cutoff for "massive" transfusion is variable, ranging from 30 mL to 150 mL.

If the FMT occurs close to the time of delivery or results in immediate fetal demise, the placenta may look completely normal. A Kleihauer-Betke stain performed on maternal blood is the only way to identify circulating fetal cells. If there has been equilibration of the fetal blood volume, the placenta has a characteristic pale appearance with dilated but empty chorionic plate vessels (Fig. 5.18a–c). The villi will also contain increased circulating nucleated red blood cells, within a relatively low hematocrit-appearing blood. In utero equilibration occurs in 4–6 h, much quicker than would occur in a newborn, because of rapid reaccumulation of fluid volume through the placenta (Brace and Cheung 1990).

Fetal anemia must be severe and prolonged before the fetus or placenta becomes hydropic. There is controversy as to whether hydrops occurs within the placental villi before or after the fetus. In my experience, villous edema precedes the onset of fetal hydrops. Severity of the FMT is related to the amount of fetal blood loss, rate of loss, and whether the loss is acute or chronic. Rapid loss of 30 % blood volume is lethal in a high percentage of animal studies, while a greater loss over a longer period of time can be tolerated (Brace and Cheung 1989). In review articles, perinatal death of 36.6 % occurred with hemorrhage above 150 mL, which would be approximately 50 % of the term blood volume (Sebring and Poleksy 1990).

The fetal blood volume changes with gestation. At 20 weeks gestation, the fetal blood volume is approximately 35 mL, while at term, it is approximately

85 mL/kg fetal weight. The placental vasculature will also contain additional fetal blood; at term, this amount is approximately 50 mL. Not only is the amount of fetal blood loss important, whether the loss is over a short or long period of time will also affect the fetal outcome. An estimate of the amount of fetal blood within the maternal circulation can be calculated by using the % of fetal cells from the Kleihauer-Betke stain and multiplying by 5,000 (estimated total maternal blood volume). It is not uncommon to have more than the total blood volume present within the maternal circulation, which may be due to placental blood or indicate some degree of chronicity. Flow cytometry is now being used to automatically measure fetal HbF-containing cells, which is much quicker and more accurate. Delay in testing maternal blood may result in negative results if an ABO incompatibility is present, where maternal blood type O would result in lysis of fetal type A cells.

The placenta may show features of abruption. Other etiologies include chorangiomas and intervillous hematomas/thrombi. Most placentas associated with massive FMT have no lesions. Staining recent and remote intervillous hematomas with immunohistochemistry for fetal hemoglobin can be useful, as is finding fetal nucleated red blood cells within the maternal intervillous space. The placenta may show features of abruption. Other etiologies include chorangiomas and intervillous hematomas/thrombi. Most placentas associated with massive FMT have no lesions.

Fetal Thrombotic Vasculopathy

Fetal thrombotic vasculopathy (FTV) is the result of stasis, hypercoagulability, and vascular damage within the fetal vasculature of the placenta. The lesions can be in any level of the system from the umbilical cord to the villous capillaries. Originally, these lesions were identified in placentas from IUFD and were thought to be secondary to retention of the placenta that is still being perfused by the maternal circulation. However, it is also found in live-born babies with IUGR, neonatal thrombocytopenia, elevated liver enzymes, increased nucleated red blood cells, and neonatal and long-term neurologic deficits. At autopsy, thromboemboli may be found in a small number of cases. The extent of FTV within the placenta to result in morbidity or mortality is unknown, but in some studies, even small lesions were associated with morbidity (Redline and Pappin 1995).

The most common etiology of FTV is obstruction to blood flow through the umbilical cord due to mechanical lesions, velamentous insertion, hyperspiraling, knots, and tight nuchal cord. In the absence of a mechanical lesion, hypercoagulable states such as in an infant of a diabetic mother, and inherited thrombophilias should be considered.

The gross lesions may be seen as firm distended chorionic plate vessels, often with white fibrin thrombi (Fig. 5.19a–d). The stem vessels are frequently distended

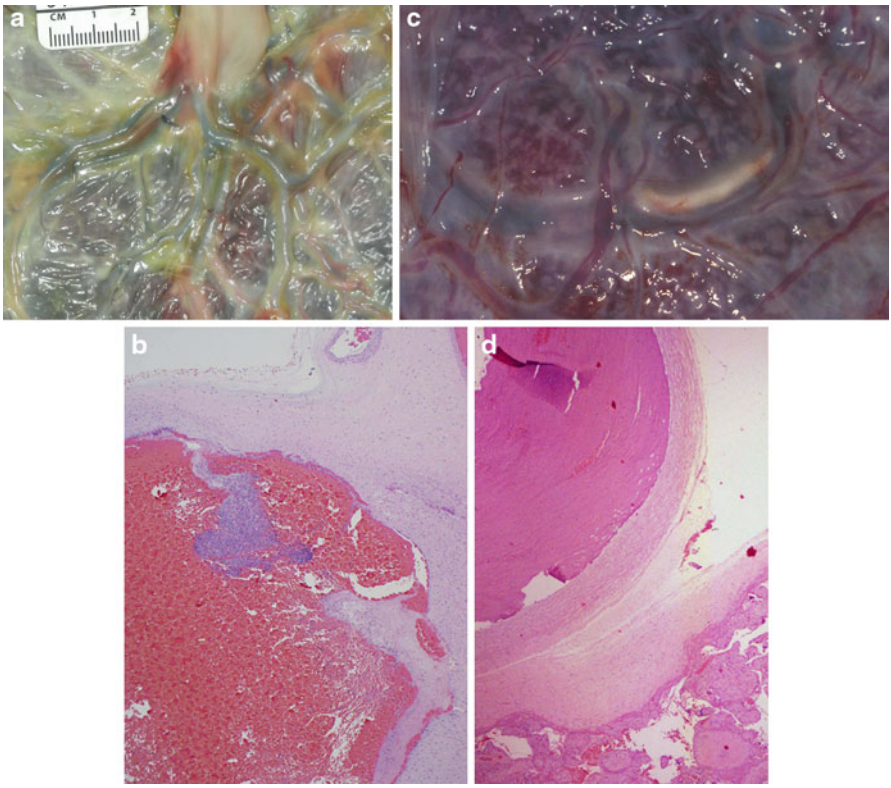

Fig. 5.19 Fetal thrombotic vasculopathy. (**a**) Acute thrombosis of chorionic plate vessels with minimal extravasation of hemoglobin pigments, (**b**) Acute thrombosis with fibrin attached to endothelium, (**c**) Remote thrombosis of chorionic plate vein (arteries cross over veins), (**d**) Remote laminated thrombus (Hematoxylin and Eosin, H&E × 10)

as well. Areas of avascular villi are pale in comparison to the surrounding parenchyma. Microscopic lesions within larger vessels include fibrin thrombi, usually eccentric nonocclusive, frequently with calcification (Fig. 5.20a–d). The stem vessels frequently have varying degrees of fibroblast proliferation, to complete luminal obliteration, and extravasation of red blood cells. Both chorionic plate and stem vessels frequently have eccentric fibroblast proliferation, "cushion" lesions, that can have fibrinoid necrosis, overlying fibrin and inflammation. These may represent vessel branch points in some cases. Villous capillaries show stromal and vascular karyorrhexis, fragmentation, and extravasation of red blood cells and ultimately are completely avascular (Redline et al. 2004b) (Fig. 5.21a–c). These villous lesions are often termed hemorrhagic endovasculosis. It may be possible to distinguish the premortem villous injuries from those that occur after demise by variability of hemosiderin-laden macrophages within villi that were progressively injured prior to fetal demise (Stanek 2010).

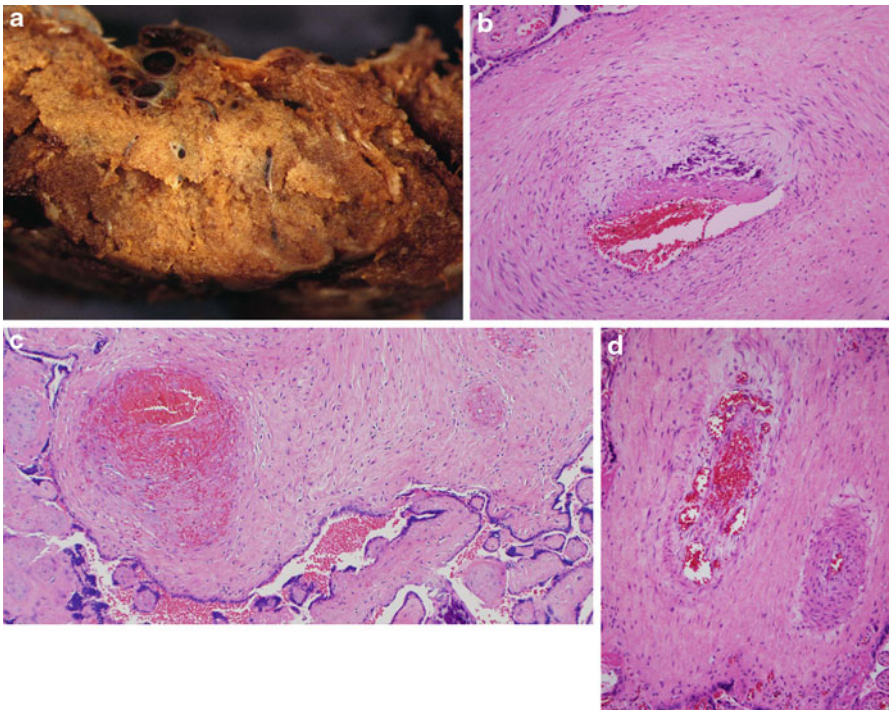

Fig. 5.20 Fetal thrombotic vasculopathy. (**a**) Thrombosed stem vessels, surrounded by pale avascular villi, (**b**) Stem vessel with cushion lesion, fibrinoid, and calcification, (**c**) Stem vessel with fibroblast proliferation and red blood cell extravasation, (**d**) Stem vessel with recanalization (Hematoxylin and Eosin, H&E × 10)

Acquired and Inherited Thrombophilias

Normal pregnancy alters coagulation factors that promoted coagulation, decreased anticoagulation, and inhibit fibrinolysis. There is a marked increase in most of the coagulation factors and a decrease in physiological anticoagulants. There is a significant increased risk of venous thromboembolism (VTE) during pregnancy and the 4–6 weeks postpartum. VTE accounts for approximately 20 % of maternal deaths.

The most common acquired thrombophilia is antiphospholipid syndrome (APS). APS is a heterogeneous syndrome both clinically and in the laboratory. There are several different criteria for the clinical and laboratory diagnosis of APS. Thrombosis may be arterial, venous, or small-vessel. Complications during pregnancy include recurrent early and mid-gestation pregnancy loss and early onset preeclampsia (<34 weeks).

Inherited thrombophilias are usually autosomal recessive, single gene mutations that may lead to a hypercoagulable state. These include factor V Leiden G1691A (FVL), factor II (prothrombin G20210A PGM), methylenetetrahydrofolate

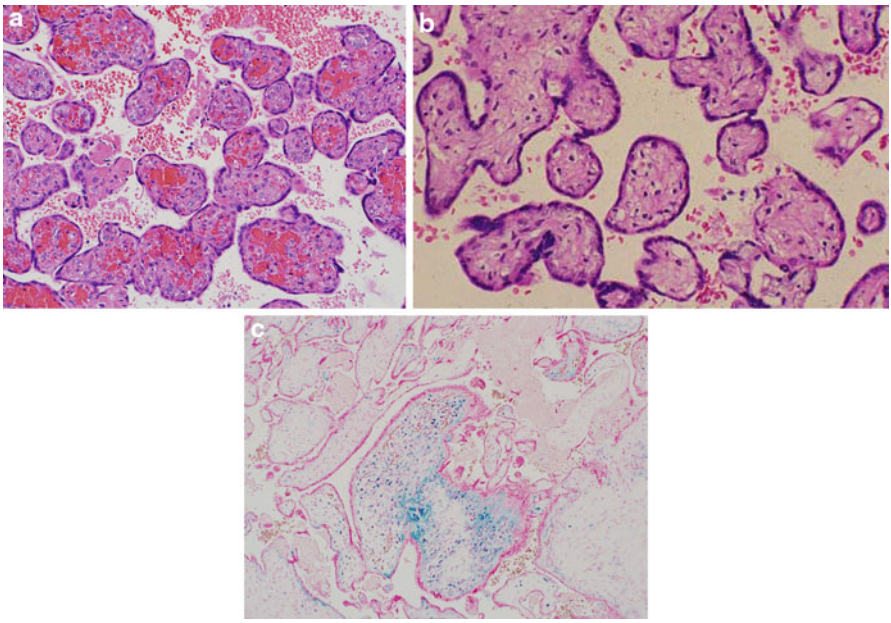

Fig. 5.21 Hemorrhagic endovasculosis. (**a**) Villi with capillary nuclear debris and extravasated red blood cells, (**b**) Avascular villi, (**c**) Variable amount of hemosiderin within villi of a live-born baby with FTV (a, b Hematoxylin and Eosin, H&E × 20; c Perls × 20)

reductase C677T mutation (MTHFR), and protein S and protein C deficiency. With exception of MTHFR, these factors increase the risk of VTE. Most of these are also associated with abnormal pregnancy outcome including early pregnancy loss (MTHFR), late pregnancy loss (protein S deficiency, FVL), preeclampsia (homozygous FVL), abruption, and intrauterine growth restriction (Pierangeli et al. 2011).

Placental pathology includes a small placenta, thrombi in the maternal vasculature, and possibly altered trophoblast interface, resulting in decreased feto maternal oxygen exchange (Pierangeli et al. 2011). The placenta in 105 women, heterozygous for FVL mutation, was found to have increased syncytial knots and increased hypervascular villi. Fifty infants heterozygous for FVL mutation had increased avascular villi (Rogers et al. 2010).

Placenta Without a Baby

Most placentas are passed within 30 minutes of a vaginal delivery. However, there are instances where a woman presents to an emergency department with vaginal bleeding and is found to have a retained placenta, yet no baby is present, and in most cases, its existence is denied. The facts noted above can be helpful to assess gestational age, confirm the presence of a fetus, such as a fetal inflammatory response, and identify abnormalities that could be responsible for fetal demise.

Conclusions

Placental examination is an important part of the evaluation of poor outcome in pregnancy and can yield information concerning a number of questions important to the forensic evaluation of a fetal/neonatal/maternal death: (1) gestational age, based on placental size and maturity of the villi; (2) viability of a fetus also based on gestational age and presence of vital reactions such as fetal inflammatory response; (3) etiology of fetal loss; and (4) assessment of maternal disorders that contribute to poor outcome of both mother and baby.

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Birth Trauma

6

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Abstract

Birth injury is any condition adversely affecting the fetus during labor or delivery, including trauma secondary to mechanical forces or hypoxia. Birth trauma is subcategorized as either injuries produced by the normal force of labor, failure of progression leading to asphyxia, or injuries resulting from obstetric intervention. Not included in this category are injuries from resuscitation, amniocentesis, scalp blood sampling, and accidental puncture of the fontanelle from scalp electrodes. This chapter will cover birth injuries to the head, spinal column, extracranial skeleton, and organs. Complications of fetal death, intrapartum death, neonatal death, and birth asphyxia will be covered in ▶ Chap. 4, "Fetal, Intrapartum, and Neonatal Deaths".

Introduction

Estimates of birth trauma incidence vary widely. Two large population-based studies of births in the United States (USA) estimate the incidence at 2.6–2.9 % of live births (Moczygemba et al. 2010; Sauber-Schatz et al. 2010): 5–8/100,000 infants die secondary to birth trauma, and 25/100,000 infants die secondary to anoxic injury. These two groups account for 2–3 % of all infant deaths. If we look at neonatal deaths only approximately 3 % are due to complications during delivery, and almost 5 % are due to complications of birth asphyxia. In order to predict and hopefully prevent birth trauma, the risk factors, injuries, and resolution times must be understood.

Risk Factors

Although birth trauma can result in many different types of injury, the risk factors are similar for all types. Risk factors for birth trauma include the following:

1. Macrosomia (birth weight >4,000 grams; seen more commonly in diabetic, older, and obese mothers and multiparas)

2. Birth weight <1,500 grams
3. Malpresentation, especially breech
4. Operative/instrumental vaginal delivery (e.g., vacuum and forceps extractions)
5. Maternal–fetal disproportion (cephalopelvic disproportion)
6. Prolonged labor
7. Use of oxytocin during labor (increases the force of contractions)
8. Maternal diabetes
9. Short maternal stature
10. Maternal obesity
11. Oligohydramnios
12. Dystocia
13. Multiple gestations
14. Primagravida, primaparity
15. Fetal tumors
16. Congenital anomalies
17. Prematurity

Although frequently associated with traumatic, difficult, or instrumented delivery, birth injuries often occur in the absence of any of the aforementioned risk factors.

Differential Diagnosis

Injuries due to birth trauma can occasionally resemble those seen in non accidental injury. Difficulty in distinguishing these entities is compounded when the injury is only recognized days or weeks after delivery or when the available history does not reveal risk factors for birth trauma. Patterns of birth trauma can overlap those of non accidental injury, including skull fractures and other head injuries, rib fractures (including posterior rib fractures), fractures of the clavicle, humerus, and femur, and internal organ injury. In unexpected death of a neonate or young infant, it is important to establish the timing of an injury (e.g., by histological examination of a fracture for evidence of healing), as well as examining the birth history for evidence of trauma at birth (Table 6.1). Findings consistent with a remote injury may in some cases be attributed to birth trauma rather than to non accidental injury (Patonay and Oliver 2010).

Occasionally, it is unclear whether autopsy findings in a neonate are due to intrapartum or postpartum trauma to a living infant or as a result of intrauterine demise and maceration. Changes following intrauterine fetal demise include skin slippage, which can be mistaken for burn or scald marks, and loosening of cranial sutures with softening of brain tissue (see ▶ Chap. 4, "Fetal, Intrapartum, and Neonatal Deaths"). Skull compression during delivery of such a fetus can lead to displacement of brain tissue along the spinal cord and into the retroperitoneum. These changes should not be mistaken for birth injury to a live fetus (Reichard 2008).

Table 6.1 Birth trauma injuries, presentations, and resolution times

Birth trauma injury	Approximate resolution time	Clinical presentation(s)
Cephalohematoma	2–3 weeks	Swelling/hematoma does not cross suture lines
Caput succedaneum	Days	Swelling crosses suture lines, pitting edema, ecchymosis
Subgaleal hemorrhage	Depends on severity of hemorrhage. Days to weeks	Boggy scalp, increase HC orbital ridge to nape of the neck; increase HR, dyspnea, shock; onset 0–33 h postpartum
Parietal skull fracture	6 months	Usually assymptomatic; may be associated with cephalohematoma. If depressed, may see increased ICP
"Ping-pong ball" deformation	6–12 months	Round depression/concavity
Occipital osteodiastasis	Usually fatal	Subdural hemorrhage, cerebellar laceration
Retinal hemorrhage(s)	4 weeks	Posterior pole, "dot and blot," "flame"; intraretinal
Scleral/conjunctival hemorrhage	7–10 days to weeks	Uni- or bilateral
Subdural hemorrhage	4–6 weeks (or surgical evacuation)	May compress vasculature and lead to infarction; usually posterior fossa. Seizures within 48 h
Subarachnoid hemorrhage	2–4 weeks	Stiff neck, lethargy, apnea, seizures with 48 h
Epidural hemorrhage	Depends upon site	Often with cephalohematoma, +/− skull fracture, maybe seizure
Cerebral infarction	Depends upon size; weeks to months	Seizures, hypotonia
Cerebral contusion	Depends upon size; days to weeks	Usually temporal lobe and associated with fractures
Spinal cord injury	Months or no resolution	Sudden death; dyspnea, hypotonia, paralysis. Usually C5-7
Brachial plexus palsy, complete (C5-T1)	2 weeks to 2 months	Arm paralysis with no sensation or reflexes
Klumpke palsy (C7-T1)	2 weeks to 2 months	Paralyzed "claw" hand; normal upper arm and shoulder
Erb palsy (C5-6, occasionally C7)	2 weeks to 2 months	Arm adducted and internally rotated, weak shoulder
Facial nerve palsy	Days to months	Ipsilateral facial paralysis, unable to close eye
Phrenic nerve palsy (C3-5)	1–3 months	Asymmetric chest movement, dyspnea, cyanosis
Clavicle fracture	Subperiosteal new bone formation 7–10 days, callus 2–4 weeks	Midshaft; contusion, decreased arm movement. Palpable callus after 7–10 days

(*continued*)

Table 6.1 (continued)

Birth trauma injury	Approximate resolution time	Clinical presentation(s)
Humerus fracture	Subperiosteal new bone formation 7–10 days, callus 2–4 weeks	Midshaft; decreased range of motion, swelling
Femur fracture	Subperiosteal new bone formation 7–10 days, callus 2–4 weeks	Midshaft; decreased range of motion, swelling
Rib fracture(s)	Subperiosteal new bone formation 7–10 days, callus 2–4 weeks	Mid-posterior. Usually with ipsilateral clavicular fracture
Liver hemorrhage/ laceration	2 weeks to months	RUQ mass, pallor, anemia, shock, scrotal swelling. Acute or days later when capsule ruptures
Spleen hemorrhage/ laceration	Often requires surgery	LUQ mass, pallor, anemia, shock, scrotal swelling. Acute or days later
Adrenal hemorrhage	3 months	Flank or abdominal mass; 90 % unilateral (R > L). Anemia, jaundice, scrotal swelling
Genitalia contusion	Varies with extent of contusion	Immediate swelling and discoloration, hyperbilirubinemia

HR heart rate, *HC* head circumference, *LUQ* left upper abdominal quadrant, *ICP* intracranial pressure

Head

Since most deliveries are vaginal and cephalic, injury to the head is the most frequent type of clinically significant birth trauma. Birth injury can involve any of the layers of the head, from scalp skin to cerebral cortex. The layers of the head are as follows:

- Scalp skin
- Aponeurosis
- Connective tissue, emissary veins
- Outer periosteum
- Outer skull table
- Diploe
- Inner skull table
- Inner periosteum, dura
- Leptomeninges
- Cerebral cortex

Scalp

Scalp injuries include bruises, lacerations, and chignon, the latter a collection of interstitial edema fluid caused by vacuum-assisted delivery. Chignon is immediately present following delivery, but resolves within 12–18 h, and is generally not

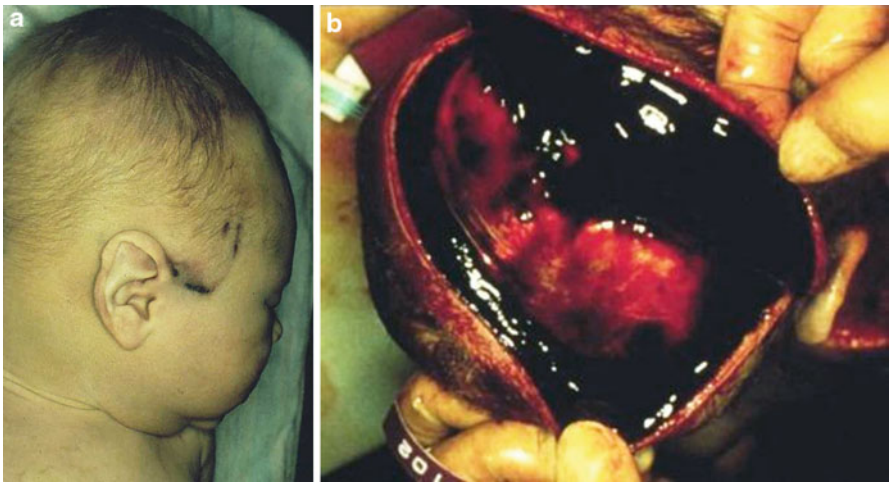

Fig. 6.1 (**a**, **b**) Forceps-assisted vaginal delivery of a cephalic, term, macrosomic neonate. Right side of face (**a**) shows a large forceps abrasion and contusion. Upon reflection of the scalp at autopsy (**b**), massive subscalpular and subgaleal hemorrhage is identified (Image courtesy of Edwina Popek, DO)

clinically significant (Doumouchtsis and Arulkumaran 2008). Abrasions, contusions, and patterned injuries can be seen on the scalp and face secondary to forceps delivery with or without underlying trauma (Fig. 6.1a, b).

Caput Succedaneum

Caput succedaneum is an accumulation of serosanguinous fluid or serum above the outer periosteum which causes fluctuant soft tissue swelling with pitting edema and overlying ecchymosis. Especially in premature infants, the premature fragile vessels rupture easily, leading to ecchymosis. The soft tissue edema may be associated with scalp abrasions and rarely subcutaneous fat necrosis or, later, alopecia (Lykoudis et al. 2007). Unlike a cephalohematoma, the swelling in caput succedaneum crosses the suture lines. Pressure on the head during a prolonged labor is a strong risk factor (Sauvageau et al. 2007). A caput succedaneum usually resolves within 24–48 h, and is rarely clinically significant.

Subgaleal Hematoma

The subgaleal space is located between the scalp aponeurosis and the periosteum of the skull and extends from the orbital ridges to the nape of the neck and laterally to the ears (King and Boothroyd 1998; Chang et al. 2007) (Figs. 6.1, 6.2 and 6.3a–d).

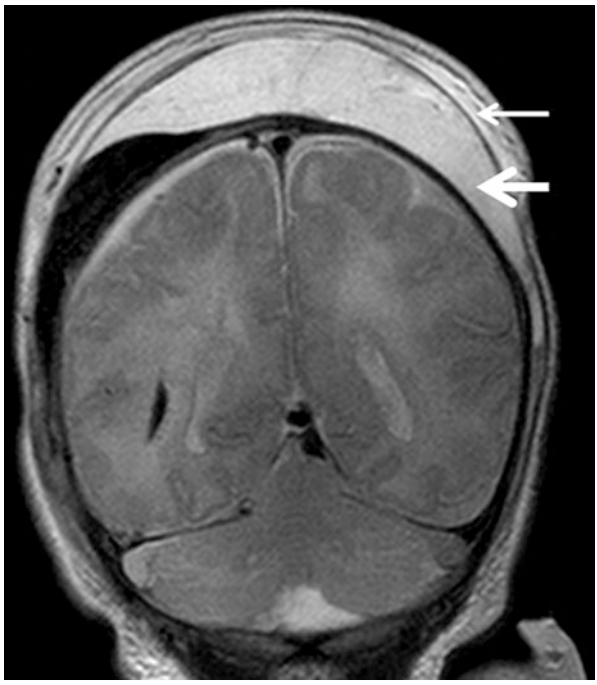

Fig. 6.2 Coronal MRI showing cephalohematoma (*large arrow*) and subgaleal hemorrhage (*small arrow*) in a term infant. Birth history included arrest of descent, failed vacuum extraction, and Cesarean delivery requiring external pressure on the head to dislodge it from the pelvis. Apgar scores were 2, 3, and 6 at 1, 5, and 10 min (Image courtesy of Tara Holm, MD)

This space can accommodate a newborn's entire blood volume (King and Boothroyd 1998; Sorantin et al. 2006). Subgaleal hematoma results from rupture of the emissary veins, especially with vacuum and forceps use (Chang et al. 2007). The incidence with vacuum extraction is approximately 26–45 per 1,000 live births (Uhing 2005; Ali and Norwitz 2009; Kilani and Wetmore 2006). Subgaleal hematomas can be complicated by skull fractures, intracranial hemorrhages, and cerebral compression (Kilani and Wetmore 2006). The condition presents within a few hours postpartum as a firm head mass that may continue to expand and progresses over the next 12–72 h (Uhing 2005). The hemorrhage may be massive, resulting in hypovolemic shock and coagulopathies (Swanson et al. 2012). In cases where a large blood volume is lost, the mortality rate is up to 25 %. Subgaleal hemorrhage is treated by supportive blood product transfusion and, if bleeding is severe, surgical cauterization of bleeding vessels.

Cephalohematoma

The most frequent cranial birth injury is a cephalohematoma, a slow subperiosteal bleed between the outer periosteum and the skull, caused by disruption of the superficial communicating veins between the diploic space and the periosteum. The incidence of cephalohematoma is approximately 0.4–2.49 % of live births (Hughes et al. 1999; King and Boothroyd 1998). The diploic veins of each cranial

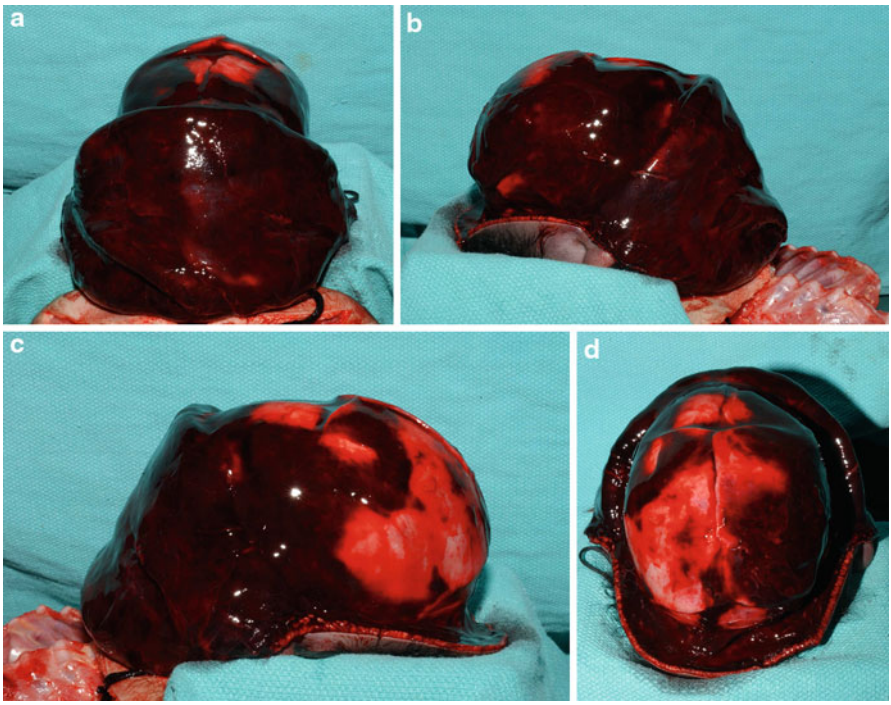

Fig. 6.3 Subscalpular and subgaleal hemorrhage extends from the brow ridge to the nape of the neck following vacuum-assisted vaginal delivery (**a**) Frontal view showing reflected occipital scalp; (**b**) Right side; (**c**) Left side; (**d**) View from above (Images courtesy of Patrick E. Lantz, MD)

bone are separate in infants and so the cephalohematoma does not cross the suture lines (Fig. 6.4). The most common location is the posterior parietal skull. Unlike a caput succedaneum, the overlying scalp is not discolored. Risk factors include prolonged head engagement and instrumentation. Vacuum and forceps delivery result in cephalohematoma 6–10 % and 2–4 % respectively (Doumouchtsis and Arulkumaran 2008; Ali and Norwitz 2009; King and Boothroyd 1998). With vacuum delivery, the outer skull table is elevated, resulting in venous disruption. In 10–25 % of cases, the cephalohematoma is associated with an underlying linear, non depressed skull fracture, especially with the use of forceps (Gresham 1975; Uhing 2005). Cephalohematomas present within the first 24 h and may increase in size over the next 2–3 days. They can begin to calcify within days and usually resolve without treatment within 2–3 weeks (Fig. 6.5). Cephalohematomas can also become infected if drainage has been attempted and may even result in osteomyelitis (King and Boothroyd 1998; Sorantin et al. 2006). If a large amount of blood collects, the infant may develop hyperbilirubinemia and jaundice, but this is rare.

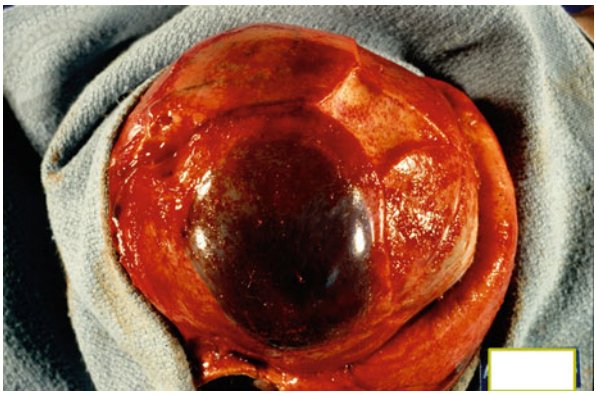

Fig. 6.4 Right parietal cephalohematoma. Note that the hemorrhage does not cross the suture lines (Image courtesy of Richard Conran, MD, JD)

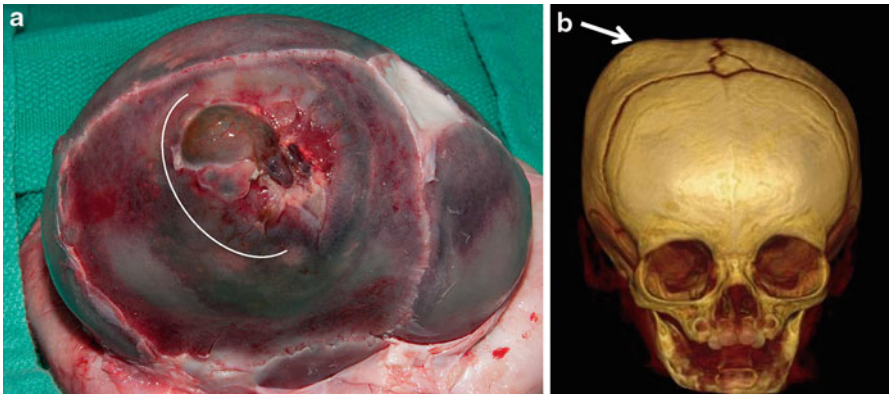

Fig. 6.5 Skulls with calcifying cephalohematomas (**a**) Gross skull, right parietal area after reflection of the scalp shows a calcifying cephalohematoma (*white semicircle*) in an 11-week-old infant who was born at term. She experienced asphyxia and prenatal passage of meconium. She died of periventricular leukomalacia and brainstem gliosis (Image courtesy of Patrick E. Lantz, MD). (**b**) Calcified cephalohematoma (*arrow*) (Image courtesy of Tara Holm, MD)

Skull Fractures

Skull fractures secondary to delivery are not common but the incidence is increased in instrumental deliveries (Sorantin et al. 2006; Fernando et al. 2008) (Figs. 6.6–6.8). Skull fracture complicates 2.3–6.6 % of births, with the higher numbers occurring in primiparous mothers and older mothers (age >35 years). Certain conditions such as craniolacunae (Luckenschadel deformity) can predispose fetuses/neonates to fractures during delivery (Fig. 6.8).

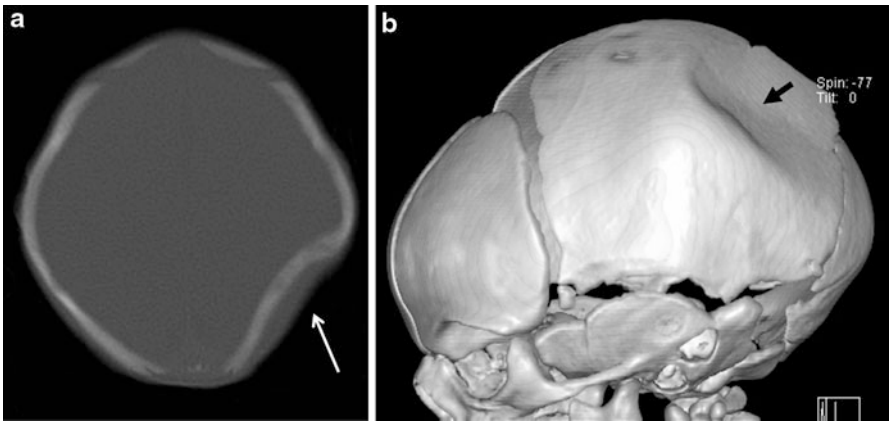

Fig. 6.6 "Ping-pong ball" deformation of the skull (*arrows*) depicted by axial computed tomography (CT) (**a**) and three-dimensional CT reconstruction (**b**). Note continuity of the inner and outer skull tables. The patient was a term infant delivered by non-emergency Cesarean section for non-progressing labor. Caput succedaneum and a skull depression were noted following delivery. Apgar scores were 8 and 9 at 1 and 5 min (Images courtesy of Tara Holm, MD)

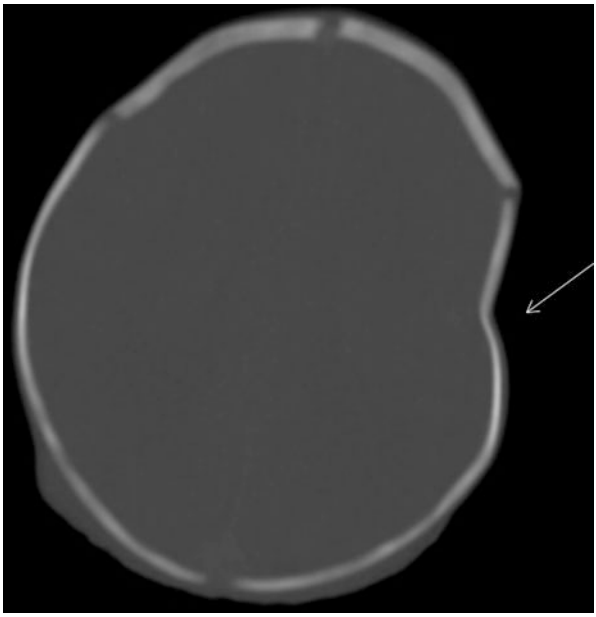

Fig. 6.7 Axial CT showing depressed left parietal skull fracture (*arrow*) (Image courtesy of Tara Holm, MD)

Three types of skull fracture are seen: "ping-pong ball" deformation, linear fracture, and occipital osteodiastasis.

1. *"Ping-pong ball" deformation*: Skull fractures are more frequently a depressed deformation than linear fracture and involve the parietal bone or, less often, the

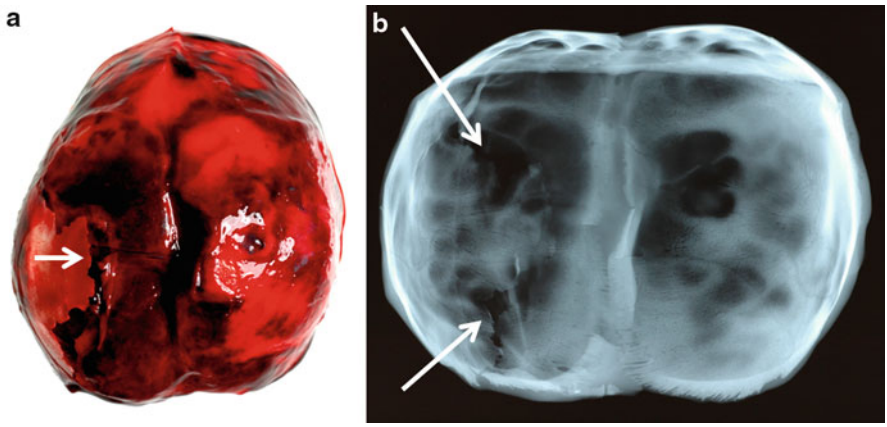

Fig. 6.8 Skull fractures through craniolacunae following vacuum extraction. Skull, gross (**a**) and postmortem radiograph (**b**) demonstrating craniolacunae and skull fractures. A term infant delivered by vacuum-assisted vaginal delivery developed hypoxic-ischemic encephalopathy and died on the second day of life. The craniolacunae are defects in the skull and are seen as oval lucencies on radiographs (Image courtesy of Joseph Siebert, Ph.D.)

frontal bone (King and Boothroyd 1998). The depression does not result in an actual fracture of the skull; there is no loss of bony continuity. Because of its gross and radiographic resemblance to a collapsed ball, this deformation is referred to as a "ping-pong ball" effect (Fig. 6.6). The deformation often occurs with forceps delivery or compression over the maternal symphysis pubis or ischial spines, but has been reported in C-sections. The treatment is to elevate the depression with suction pressure or surgical intervention; some have been reported to heal/resolve spontaneously (Basadella et al. 2011). This type of deformation is worrisome for underlying pathology if the depression is greater than 2 cm.

2. *Linear fracture*: Most linear skull fractures are non depressed and asymptomatic. The parietal bone is most often involved, followed by the frontal bone (Fig. 6.7). There may be an associated cephalohematoma (up to 25 %), but there is usually no underlying intracranial pathology. If the fracture is depressed, it is usually of the parietal bone and often with a forceps delivery. Such a depressed fracture may be associated with increased intracranial pressure and/or intracranial hemorrhage. Linear fractures heal within 2–6 months.
3. *Occipital osteodiastasis*: A more severe fracture which involves separation of the cartilaginous joint between the squamous and the two lateral portions of the occipital bone, a joint which usually fuses by the second year of life (Dixit et al. 2010). The separation is due to excessive pressure over the suboccput in cases of hyperextension, pressure of the occiput on the maternal symphysis pubis, forceps use, and breech malposition (Uhing 2005; Currarino 2000). The anterior squama, the portion of the occipital bone posterior to the foramen magna, is displaced anteriorly and upward. This results in shearing of the bridging veins and subsequent posterior fossa

subdural hemorrhage, cerebellar laceration or contusion, or cerebellar–medullary compression. Occipital osteodiastasis is diagnosed by lateral radiography and/or by careful posterior neck and skull dissection at autopsy. If a careful postmortem dissection is not performed, the diagnosis may only be subdural hemorrhage in the posterior fossa without identification of the underlying etiology. The mortality rate is very high.

Intracranial Hemorrhages

Intracranial hemorrhages of birth trauma (epidural, subdural, and subarachnoid) are seen more often in full-term infants than in premature infants. Intraventricular hemorrhages are seen more often in premature infants with bleeding from the subependymal germinal matrix. Risk factors for epidural, subdural, and subarachnoid hemorrhages include vaginal delivery, macrosomia, cephalopelvic disproportion, prolonged labor, breech presentation, and mechanical assistance. These hemorrhages are also more common in neonates/infants born to mothers who are taking phenytoin. Coagulopathies must be ruled out. Clinically, intracranial hemorrhages usually present within 10 h of delivery (Smit-Wu et al. 2006).

Epidural Hematoma

An epidural hematoma is characterized by bleeding between the skull and the inner periosteum, similar to a cephalohematoma but with an intracranial location (Hamlat et al. 2006). The hemorrhage/hematoma is due to cleavage of the dura from the skull with or without instrumentation during delivery, and there is often tearing of the middle meningeal artery. An epidural hematoma in the newborn secondary to birth trauma is rare and is linked to excessive molding, cephalohematoma, and/or skull fracture (Uhing 2005; Sorantin et al. 2006; Sharma et al. 2005; Hamlat et al. 2006; Noetsel 2006; Doumouchtsis and Arulkumaran 2008). Most reports are of infants of normal weight after a difficult delivery with or without instrument use. Unlike adults, a skull fracture is not always present. The clinical presentation is asymptomatic scalp swelling, bulging anterior fontanelle, or, in 50 % of cases, a seizure (Scheibl et al. 2012; Noetsel 2006). Treatment can include surgical decompression in cases of large hematoma or expectant management in smaller bleeds.

Subdural Hemorrhage

Bleeding between the dura mater and the leptomeninges defines subdural hemorrhage (Fig. 6.9). Subdural hemorrhage is the most common clinically significant form of intracranial hemorrhage in neonates, affecting 2.9 per 10,000 spontaneous deliveries and 8.0–25.7 per 10,000 instrumental deliveries. Risk factors are vaginal

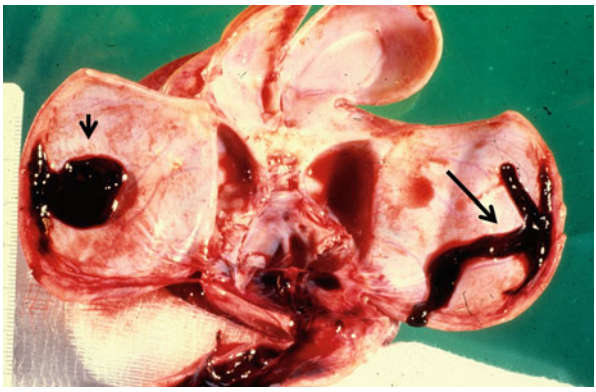

Fig. 6.9 Neonatal skull opened and brain removed. Subdural hemorrhage (*arrows*) secondary to birth trauma (Image courtesy of Richard Conran, MD, JD)

delivery, malpresentation (especially breech), prolonged labor, and instrumentation (Looney et al. 2007; Squire and Cowan 2004). By contrast, most subdural hemorrhages secondary to inflicted, non accidental, abusive head trauma are in the interhemispheric fissure over the cerebrum. Of note, subdural hemorrhages have been identified on prenatal sonography, and asymptomatic, thin subdural hemorrhages are sometimes seen in the posterior fossa. The usual mechanisms of subdural hemorrhage are molding of the fetal head and/or injury leading to tearing of veins and venous sinuses associated with the dura of the tentorium cerebelli and falx. Occipital osteodiastasis is another cause (Looney et al. 2007; King and Boothroyd 1998; Whitby et al. 2004). Clinical symptoms include a full fontanelle, increased head circumference, and/or signs of brainstem compression such as apnea, eye deviation, or altered consciousness and usually appear within 12–72 h. Surgery is required in 30–50 % of cases (Parker 2005). The mortality rate is 5–7 %, and prognosis depends on the size of the hemorrhage and whether intraparenchymal bleeding is also present (Doumouchtsis and Arulkumaran 2008). Subdural hemorrhages usually resolve within 4–6 weeks (Fernando et al. 2008).

Subarachnoid Hemorrhage

Unlike subarachnoid hemorrhages in adults, subarachnoid hemorrhages from birth trauma result from torn bridging veins (King and Boothroyd 1998). They are associated with vaginal birth and vacuum delivery and complicate 1.3–10.7 births per 10,000, with the higher incidence in instrumental deliveries (Doumouchtsis and Arulkumaran 2008; Looney et al. 2007; Noetsel 2006). Many researchers believe that small, clinically insignificant subarachnoid hemorrhages are the most common type of intracranial hemorrhage. However, symptomatic subarachnoid hemorrhages are less common than symptomatic subdural hemorrhages. The most common clinical presentation is a transient seizure within the first 48 h postpartum; apnea and depressed consciousness are other presentations (Doumouchtsis and Arulkumaran 2008).

Cerebral and Cerebellar Parenchymal Injury

The cerebrum can be damaged by difficult vaginal delivery and/or instrumentation as the head is compressed during rapid and extreme deformation (Looney et al. 2007; Sorantin et al. 2006; Huang and Robertson 2004). As opposed to typical cerebral gray-matter contusions of older children and adults, these injuries are more often white-matter hemorrhagic tears. These injuries are usually of the temporal cerebrum in proximity to the open sutures. Rarely, isolated parenchymal injuries are associated with depressed skull fracture, subarachnoid hemorrhage, and epidural hemorrhage (Noetsel 2006). In preterm infants, intraventricular hemorrhage arising from the vascular subependymal germinal matrix is more common within the cerebrum and usually occurs 6–48 h after birth.

Embolism of brain tissue into the systemic circulation has been described in a series of nine infants who died intrapartum or within 8 h of delivery. All had an instrumental delivery, and most had evidence of cranial trauma, including hemorrhage and, in a minority, skull fractures. Tissue emboli included cerebellar and glial tissue, confirmed by glial fibrillary acidic protein (GFAP) immunohistochemical staining, and emboli were most often seen in pulmonary vasculature. Of note, three patients developed disseminated intravascular coagulation and pulmonary hemorrhage, suggesting that the embolic tissue may be a contributor to death rather than an incidental finding (Cox et al. 2009).

Cerebral infarction has also been noted following birth trauma. The mechanism is uncertain but may be due to stretching of the carotid and middle cerebral arteries during a difficult delivery (King and Boothroyd 1998). Subdural hemorrhage can also cause direct compression or spasm of the posterior and middle cerebral arteries, resulting in infarction (King and Boothroyd 1998; Govaert et al. 1992).

Spinal Cord and Nerves

Damage to the spinal cord and nerves is associated with macrosomia, cephalopelvic disproportion, difficult delivery requiring forceps, breech presentation, shoulder dystocia, and obstruction (e.g., from fetal abdominal tumors) (Sheil and Collins 2007). Spinal cord injuries carry a very high mortality rate of 70–90 % (Parker 2006). By contrast, most nerve traumas are transient palsies, but some damage can result in permanent disability.

Spinal Cord

The spinal cord can be injured or disrupted during delivery secondary to spinal column flexion and longitudinal stretching and traction of the infant during delivery, especially when the neck is hyperextended and pulled laterally as the shoulders are delivered (Ross and Beall 2006). Lateral traction at the level C5-T3 is the most

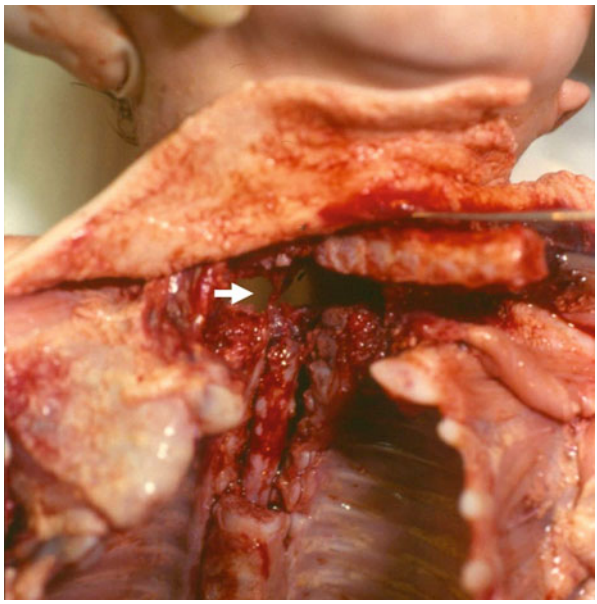

Fig. 6.10 A C5-C7 fracture and subtotal transection of the spinal cord due to forced neck traction during a difficult vaginal delivery with cephalic presentation. An undiagnosed abdominal teratoma in the fetus created an obstruction during delivery. The anterior cervical vertebral column is lifted to show a thin remnant of spinal cord (*arrow*)

common, especially in breech deliveries. The spinal cord can also be compressed against the maternal pubis. The upper cord, especially at the level of C4, is more often injured than the lower cord (Uhing 2005). Upper cord injuries are seen more often in cephalic deliveries (often with forceps use), and lower cord injuries are seen in breech deliveries (Parker 2006; Sorantin et al. 2006). If a vertebral fracture occurs during delivery, the most common location is C5-7 (Fig. 6.10). However, the spinal cord can be injured or even transected without a vertebral fracture. Signs and symptoms are immediate. Lesions in the lower spinal cord present with hypotonia and areflexia. Lesions above C4 are associated with apnea. The mortality rate is approximately 70–90 %.

Brachial Plexus Palsy

The brachial plexus includes nerve roots C5-T1. Brachial plexus palsy occurs in approximately 0.1–2 % of live births. It is associated with macrosomia, lateral neck traction, shoulder dystocia (17–45 % of cases), and breech delivery but can also occur in Cesarean section deliveries (Foad et al. 2008; Alfonsa 2001). In breech deliveries, brachial plexus damage occurs when the arms are extended over the head. In one study, half of the neonates/infants with brachial plexus palsy had at least one risk factor (shoulder dystocia, macrosomia, forceps delivery) (Foad et al. 2008). Of neonates sustaining brachial plexus injuries at birth, approximately 20–25 % sustain permanent impairment of the affected limb. Three common

types of brachial plexus palsies, in descending order of frequency, are Erb palsy, Klumpke palsy, and complete brachial plexus palsy. Erb palsy involves C5-6 and possibly C7 and is by far the most common type of brachial plexus injury, comprising 90 % of injuries. Klumpke palsy involves C7-T1, and complete brachial plexus palsy involves C5-T1. Full recovery usually occurs within 2 weeks to 2 months. Some cases require therapy and/or surgery.

- *Erb palsy*: Injury of C5-6 and possibly C7 presents with the arm adducted, prone, and internally rotated. The shoulder is weak. The hand muscle innervation remains intact. Erb palsy is often associated with phrenic nerve palsy, as the phrenic nerve arises from C3-5 (Uhing 2005; Parker 2006).
- *Klumpke palsy*: Injury of C7-T1 results in a normal upper arm and shoulder, but the wrist and hand are paralyzed in a "claw" position. Klumpke palsy is sometimes associated with Horner syndrome (ptosis, miosis, anhidrosis) if T1 is involved (Gottlieb and Galan 2007; Parker 2006).
- *Complete brachial nerve palsy*: With palsy of the entire brachial plexus C5-T1, the arm is paralyzed with no sensation or reflexes.

Phrenic Nerve Palsy

The phrenic nerve arises from C3-5. Damage to the phrenic nerve is due to lateral hyperextension of the neck, which stretches the cervical nerve roots; the damage is usually unilateral (Uhing 2005). The palsy is often associated with ipsilateral brachial plexus palsy and/or humeral fracture (Parker 2006; Stramrood et al. 2009). Breech presentation and shoulder dystocia increase the risk of phrenic nerve injury (Stramrood et al. 2009). Clinically, the infant is dyspneic, may be cyanotic, and has asymmetric or paradoxical movements of the diaphragm (Fig. 6.11). Recovery usually occurs within 1–3 months.

Facial Nerve Palsy

The facial nerve, cranial nerve VII, innervates the facial musculature. The facial nerve is most often damaged during vaginal deliveries requiring forceps use or those with compression of the facial nerve against the maternal sacrum. Facial nerve injury is usually unilateral and often associated with ipsilateral clavicular fractures (Hughes et al. 1999). Clinically, the infant presents with ipsilateral drooping of the face and an open eye that will not close, most prominent when crying. The palsy typically improves within a few days but may take months to fully resolve.

Ocular Trauma

The eyes can be traumatized during delivery. The cornea may be lacerated, especially with the use of forceps. Scleral or subconjunctival hemorrhages, unilateral or

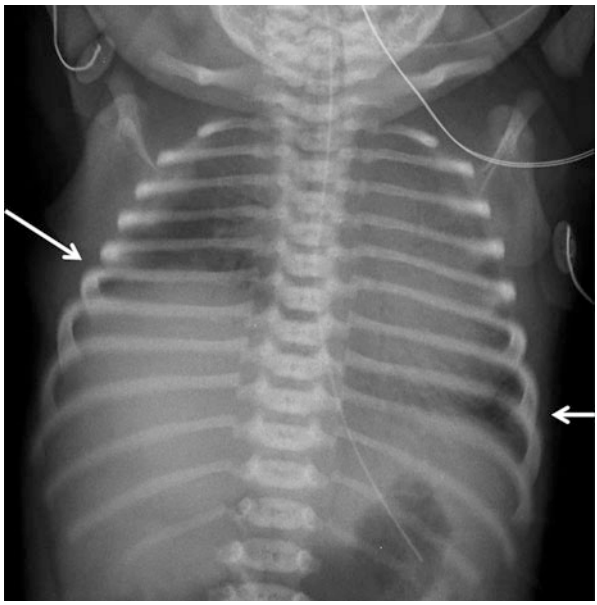

Fig. 6.11 Right hemidiaphragm paralysis due to traumatic injury of the phrenic nerve. *Arrows* demonstrate the height of the left and right hemidiaphragms (Image courtesy of Tara Holm, MD)

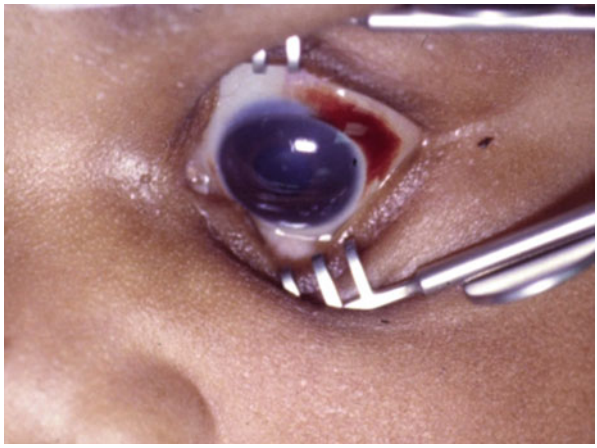

Fig. 6.12 Scleral subconjunctival hemorrhage of the left eye secondary to birth trauma

bilateral, are associated with increased intrathoracic pressure from the contractions of vaginal delivery (Fig. 6.12). This results in an increase in venous pressure in the head and neck and rupture of vessels. The hemorrhage usually resolves within 7–10 days but may be evident up to several weeks (Katzman 1992; Parker 2006). Retinal hemorrhages occur during delivery in 20–40 % of births (Hughes et al. 2006). Most resolve within a week; others last up to 4 weeks. Upon ophthalmoscopic

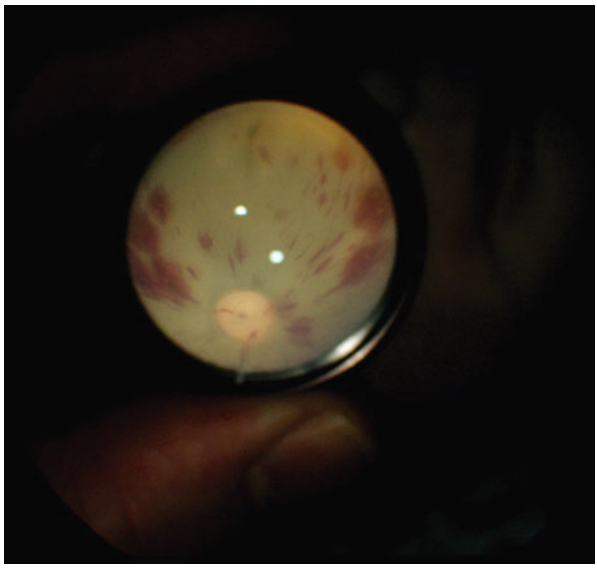

Fig. 6.13 Postmortem indirect ophthalmoscopy of the right eye allows examination of the fundus and posterior retina, demonstrating projected aerial image of birth-related retinal hemorrhages over the posterior pole. No clinical fundal examination was documented in the medical record (Image courtesy of Patrick E. Lantz, MD)

examination, they appear as "dot and blot" or "flame" hemorrhages in the posterior retina (Figs. 6.13 and 6.14a–c). Postmortem examination of the posterior fundus and peripheral retina can be conducted by indirect monocular ophthalmoscopy, utilizing a light source and hand held lens (Lantz and Adams 2005; Lantz 2009). The frequency of retinal hemorrhages varies by delivery route: vacuum > forceps > spontaneous vaginal > Cesarean section (Ali and Norwitz 2009).

Nasal Trauma

The nose can be injured with slight deformity or complete dislocation of the cartilaginous portion of the septum with septal deviation (Hughes et al. 1999; Uhing 2005; Parker 2006). The clinical presentation is of a flattened nose, septal deviation, asymmetrical nares, possible discoloration, and possible dyspnea due to the fact that infants are obligate nose-breathers (Parker 2006).

Extracranial Fractures

The most common extracranial fractures secondary to birth trauma are of the clavicle, humerus, and femur in descending order of incidence. The main risk factor is high birth weight. Of note, fractures in infants heal much faster than those in older children and adults; for example, healing with subperiosteal new bone formation and calcification occurs within ten days. Therefore, any fracture in an infant more than 11 days old that does *not* have calcification suggests postnatal trauma. Premature infants have

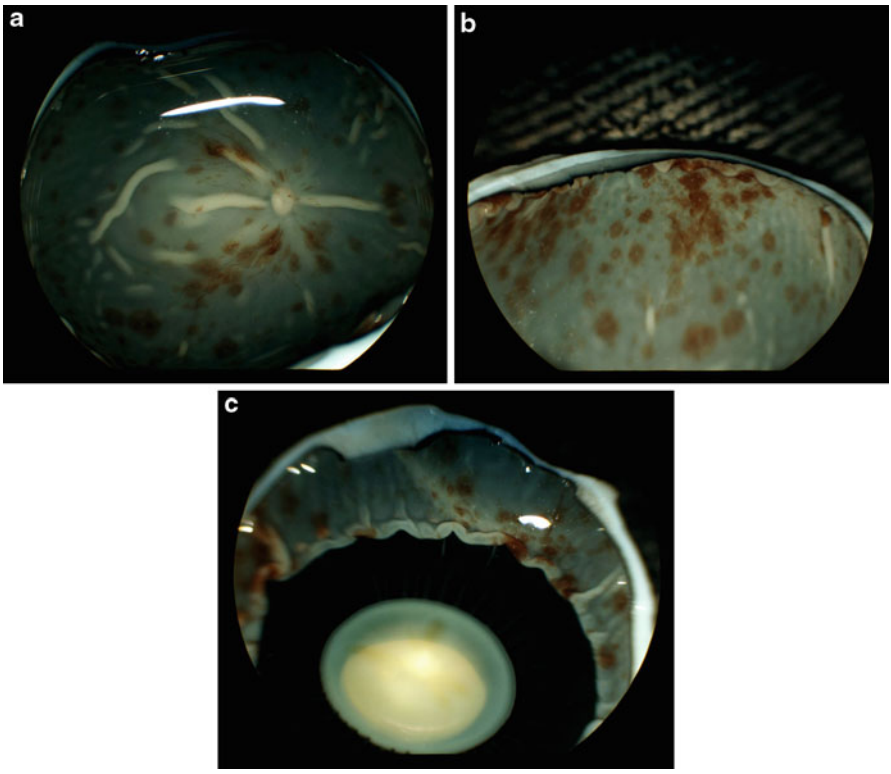

Fig. 6.14 Retinal hemorrhages secondary to birth trauma. (**a**) Sectioned globe (cornea, ciliary body, and lens removed) demonstrating birth-related splinter, flame-shaped, dot, and blot retinal hemorrhages over the posterior pole and extending to the equator. (**b**) Too-numerous-to count birth-related peripheral retinal hemorrhages. (**c**) Extensive hemorrhages in the right eye abutting the ora serrata (Images courtesy of Patrick E. Lantz, MD)

been reported with long bone fractures due to osteopenia. Skeletal dysplasias such as osteogenesis imperfecta and hypophosphatemia predispose to multiple fractures before and during delivery (Fig. 6.15).

Clavicle

The most common bone to fracture at birth is the clavicle, with an incidence of 0.2–4.4 % of term deliveries (Parker 2006; Uhing 2005; Bhat et al. 1994; Hughes et al. 1999, Mavrogenis et al. 2011). The risk factors include macrosomia and shoulder dystocia. The fracture is usually in the midshaft or at the junction of the middle and distal third of the bone (Figs. 6.16–6.18). Clinically, fractures may be asymptomatic, or the infant may have swelling and possible discoloration over the site and decreased movement of the ipsilateral arm (Monjok 2008; Mavrogenis et al. 2011).

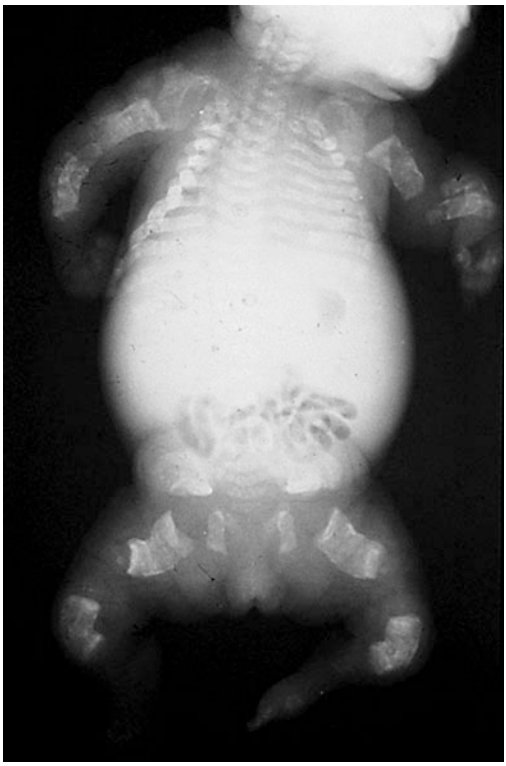

Fig. 6.15 Postmortem radiograph of osteogenesis imperfecta. The long bones are short and thick with numerous fractures and poor mineralization

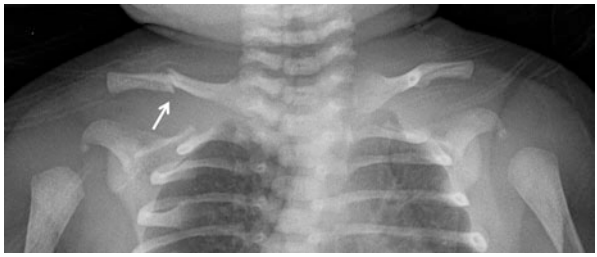

Fig. 6.16 Right clavicular fracture in a neonate (*arrow*) (Image courtesy of Tara Holm, MD)

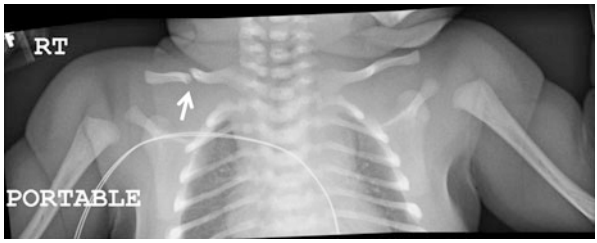

Fig. 6.17 Right clavicular fracture (*arrow*)

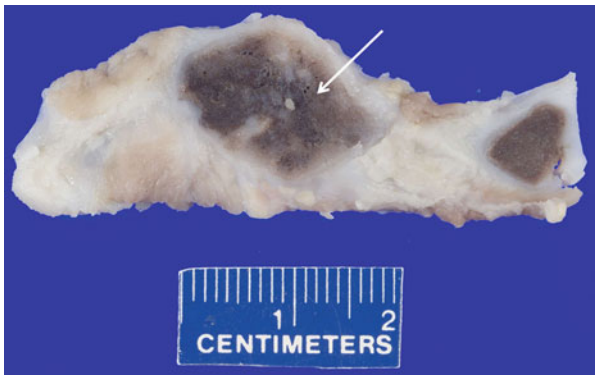

Fig. 6.18 Right clavicle from a 7-week-old infant who died of sudden infant death syndrome (SIDS). Resection and bisection of the clavicle at autopsy shows a healing birth-related fracture exhibiting hard callus (*arrow*) and loss of fracture line (Image courtesy of Patrick E. Lantz, MD)

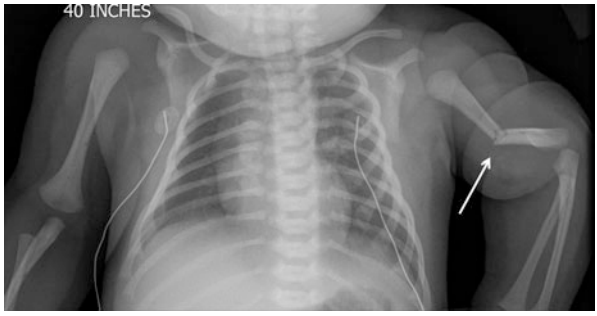

Fig. 6.19 Midshaft left humerus fracture (*arrow*) in a 4,300 grams term neonate with shoulder dystocia and resultant contralateral Erb palsy (Image courtesy of Tara Holm, MD)

Rarely, pneumothorax can result from a fractured clavicle. These fractures show subperiosteal new bone formation within 7–10 days and mature callus within 2–4 weeks (Fig. 6.18).

Humerus

The humerus is the second most frequent long bone fractured during birth. A humerus fracture most often occurs in breech deliveries, difficult deliveries, high forceps deliveries, and even in C-sections. Most fractures are of the midshaft and are due to tractional and torsional forces as well as hyperextension of the elbow (Figs. 6.19 and 6.20). Proximal epiphyseal separation with lateral displacement can occur as the arm is twisted and pulled with hyperabduction of the shoulder. Physical findings are evident immediately after birth with a decreased range of motion and swelling. Subperiosteal new bone formation can be seen within 10 days and mature callus within 2–3 weeks.

Femur

Most perinatal femoral fractures are of the shaft but can also be of the metaphysis and upper epiphysis. Risk factors are breech presentation and a difficult delivery.

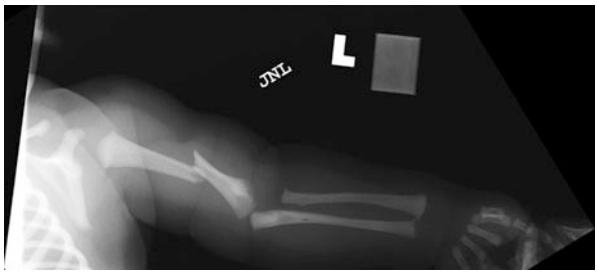

Fig. 6.20 Midshaft left humerus fracture

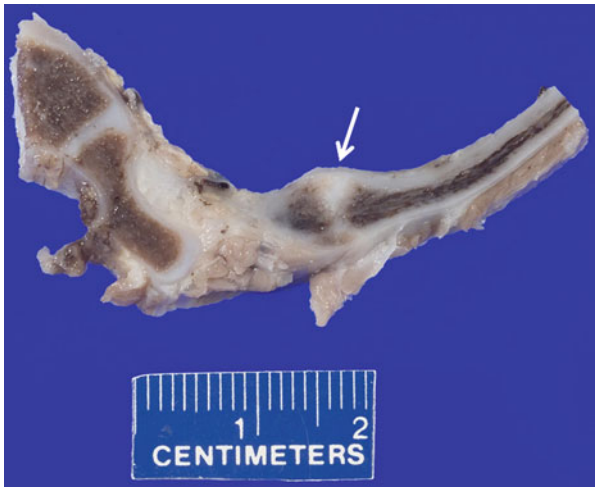

Fig. 6.21 Resection and bisection of left posterior rib T11 at the time of autopsy. The *arrow* demonstrates a healing birth-related fracture (Image courtesy of Patrick E. Lantz, MD)

A femoral fracture can occur when the femur is held in the extended position for a prolonged period in breech deliveries. External version maneuvers can also result in femoral fracture. Femoral fractures, unilateral and bilateral, have been reported in C-section deliveries (Cebesoy et al. 2009, Matsubara et al. 2008). Physical findings are evident immediately after birth with decreased range of motion and swelling. Subperiosteal new bone formation can be seen within 10 days and mature callus within 2–3 weeks.

Ribs

Rib fractures secondary to birth trauma are rare, and in some studies none of the birth injuries are rib fractures (Rubin 1964). In cases of rib fracture, the setting is a difficult vaginal delivery of a large infant (macrosomia), shoulder dystocia, and/or vacuum extractions. The fracture(s) are mid posterior in location and are very often associated with ipsilateral clavicular fractures (Van Rijn et al. 2009) (Figs. 6.21 and 6.22). The fractures are due to leverage or upward flexion against the maternal

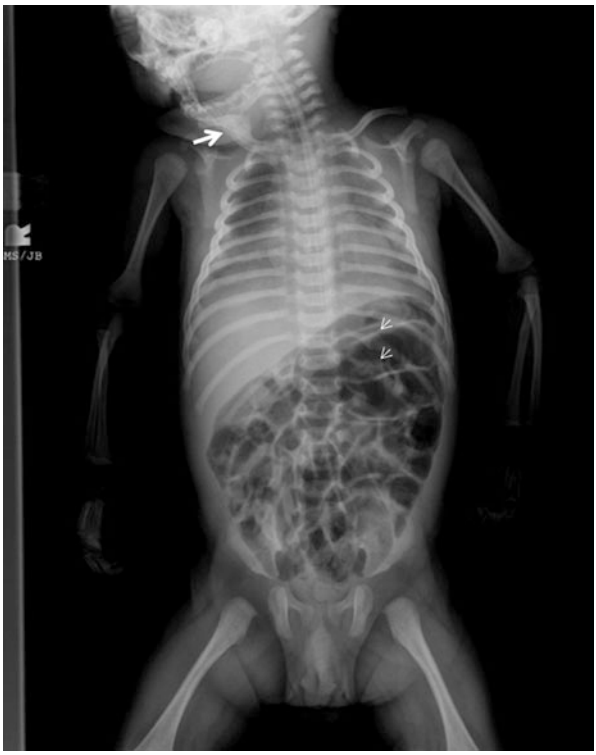

Fig. 6.22 Healing birth-related right clavicular (*arrow*) and posterior left rib fractures (*arrowheads*) from a 6-week-old infant who died suddenly and unexpectedly at home (Image courtesy of Patrick E. Lantz, MD)

pubis symphysis as the child passes through the birth canal. Predisposing factors for birth fractures are osteopenia due to prematurity (especially <1,500 grams), hyperparathyroidism, rickets, hypocalciuric hypocalcemia, and mothers who have taken magnesium sulfate (Bulloch et al. 2000; Van Rijn et al. 2009). Of note, infants with osteogenesis imperfecta rarely have posterior rib fractures (Lachman et al. 1998).

Internal Organs

Aside from the brain, organ injury associated with birth trauma usually involves the liver, spleen, and adrenal glands. The presenting event is usually hemorrhage, and infants may present with pallor, abdominal distention, or unexplained anemia (Parker 2006).

1. *Liver*: The liver is the most common extracranial organ injured during delivery. Infants with hepatosplenomegaly (e.g., due to extramedullary hematopoiesis or syphilis), breech delivery, sepsis, or hypoxia are especially at risk (Parker 2006).

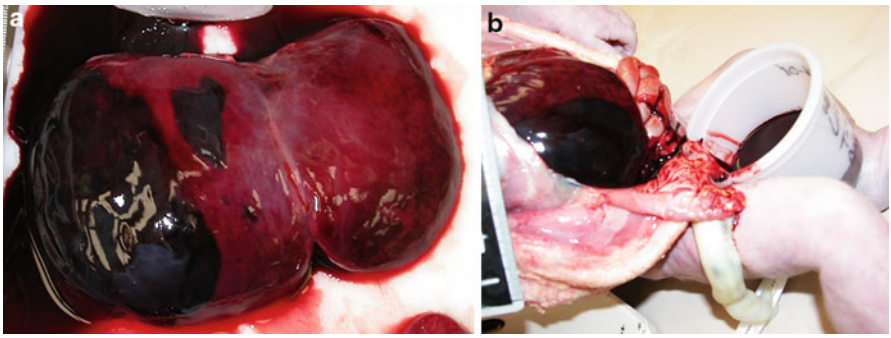

Fig. 6.23 (**a**, **b**) A newborn has a large hepatic subcapsular hematoma with hemoperitoneum secondary to birth trauma. (**a**) Liver, gross, with large subcapsular hematoma; (**b**) Opened abdomen showing the traumatic subcapsular hematoma of the liver and resultant hemoperitoneum

Mechanical forces on the capsule cause a subcapsular hematoma, which can easily rupture (Ting et al. 2006). Often these hematomas span 4–5 cm. Clinically, the infant presents with a right upper quadrant mass, pallor, anemia, and/or hypovolemic shock (Figs. 6.23a, b). Delayed bleeding of a subcapsular hematoma can occur 1–3 days later. The hepatic parenchyma can also be damaged during delivery, resulting in a more rapid presentation of internal hemorrhage without an abdominal mass (Akin et al. 2011). Upon rupture, the hemoperitoneum can lead to rapid hemorrhagic shock and can cause scrotal or labial swelling and ecchymosis.

2. *Spleen*: The spleen is less commonly ruptured during birth, and rupture may occur in conjunction with hepatic rupture. Risk factors include macrosomia, erythroblastosis fetalis, and increased thoracic pressure during a difficult delivery, pressing the spleen downward. A subcapsular hematoma develops at the medial aspect near the implantation site of the supporting splenorenal ligament (Ting et al. 2006). Clinically, the infant will have a left upper quadrant mass, pallor, anemia, and possibly hypovolemic shock. The capsule may rupture hours to days after delivery, leading to hemoperitoneum and rapid hemorrhagic shock (Ting et al. 2006). As with the liver, intraperitoneal hemorrhage may present with scrotal or labial swelling and ecchymosis (Lee and Im 2011). The mortality rate is high.
3. *Adrenal glands*: In the infant, the adrenal glands are large and vulnerable to vascular damage and hemorrhage (Parker 2006; Adorisio et al. 2007). Risk factors for adrenal injury are macrosomia, infants born to diabetic mothers, and breech position. In 90 % of cases of adrenal hemorrhage, the hemorrhage is unilateral, and in 75 % of these it involves the right adrenal gland. Clinically, the infant presents with an abdominal mass, anemia, jaundice, and/or scrotal or labial swelling and ecchymosis (Parker 2006; Adorisio et al. 2007). Complete recovery usually occurs within 3 months. Adrenal insufficiency can result from hemorrhage or surgical adrenalectomy with hypoglycemia, hypotension, and hyponatremia (Parker 2006).

Genitalia

Genital injury is a rare complication of breech presentation (Carceller et al. 2002). Risk factors are primiparous mothers, prolonged labor, and difficult breech deliveries. The labia in girls and the scrotum in boys can show swelling and diffuse ecchymoses. As mentioned, abdominal organ injury with hemoperitoneum can also result in scrotal or labial swelling and ecchymosis (Carceller et al. 2002).

Complications of Cesarean Section

Although Cesarean delivery is generally considered a "safer" method of delivery in a difficult labor, fetal injury can occur by this route. One large study estimated fetal injury in 1.1 % of Cesarean deliveries; other studies suggest a somewhat higher incidence (Alexander et al. 2006). The most common injury is a fetal laceration, occurring in 0.7–1.9 % of Cesarean deliveries, with increased risk in emergent procedures for fetal distress and in second-stage deliveries with rupture of membranes (Alexander et al. 2006; Gajjar and Spencer 2009). Non vertex presentations also increase the risk of fetal injury. The majority of lacerations (70 %) involve the head and face, while most of the remainder are on the buttocks and legs (20 %) and back (10 %). Fetal lacerations involving only the skin heal rapidly, while involvement of muscle and deeper structures requires cosmetic surgery intervention (Gajjar and Spencer 2009). Other injuries during Cesarean delivery include cephalohematoma, clavicle fracture, facial nerve and brachial plexus palsy, and skull fracture. Cephalohematoma complicates 2.4 per 1,000 Cesarean deliveries, while the rest occur in fewer than 1 per 1,000 deliveries (Alexander et al. 2006).

An unusual setting for birth injury following Cesarean section involves the Zavanelli maneuver, used in refractory shoulder dystocia. The fetal head is replaced into the vagina before or during the Cesarean section. There is a case report of cervical spinal cord dislocation (at C5-6) and intrapartum death in a term infant following this maneuver. Birth asphyxia, brachial plexus injury, and clavicular and humeral fractures have also been described in cases delivered by this route, although it is not clear whether the risk of these injuries is greater than in other cases of severe shoulder dystocia (Ross and Beall 2006).

Toilet Deliveries

Births into toilets raise a differential diagnosis of stillbirth, precipitous live delivery, and neonaticide, the latter including blunt force trauma, asphyxia by drowning, and neglect of the newborn (Mitchell and Davis 1984). Determining whether an infant delivered into a toilet was live-born or stillborn can be challenging (Table 6.2). A number of tests have been utilized to make this determination;

Table 6.2 Toilet deliveries

Neonaticide toilet delivery	Accidental toilet delivery
Term gestation	Preterm gestation
Live-birth	May be stillbirth
Not precipitous delivery	Precipitous delivery
Concealment and denial of delivery	No concealment or denial of delivery
Cut umbilical cord	Possible torn umbilical cord
Does not seek help	Seeks help immediately
Possibly signs of birth trauma or prolonged labor	No birth trauma or signs of prolonged labor
May have inflicted blunt force trauma	No postpartum blunt force trauma
Cause of death = drowning, inflicted trauma, neglect	Cause of death = prenatal cause, infection, drowning

however, no single test is conclusive. Often the cause of death of a live infant born into the toilet is asphyxia, with or without aspiration of excreta. The question is whether this was a rapid, unavoidable delivery or a delivery followed by neglect of the live newborn resulting in drowning. Case history and the investigation of facts surrounding the delivery play a major role in answering this. This includes history of the pregnancy and prenatal care, determination of neonatal neglect versus seeking help immediately, follow-up obstetric records of the postpartum mother, placental examination, examination of the umbilical cord for signs of cutting as opposed to tearing, and full autopsy of the infant including radiographs. Denial of pregnancy and concealment of delivery are important facts to determine. Mothers may conceal their pregnancy for several reasons, for example, personal, religious, social, cultural, and financial. This does not equate to neonaticide. However, concealment of a delivery with disposal of the body is of more concern and raises the possibility of neonaticide. Cases of neonaticide with delivery into a toilet are usually term livebirths with evidence of asphyxia and drowning and possibly concurrent blunt force trauma (see ► Chap. 7, "Neonaticide") (Fig. 6.24a, b).

A precipitous delivery is one that occurs less than 3 h from the start of contractions. Precipitous deliveries into toilets can happen. Often precipitous deliveries involve preterm and/or stillbirths, there is no denial of the pregnancy or concealment of the delivery, and the mother seeks help immediately. Precipitous deliveries most commonly occur in multiparous women. Findings of birth trauma indicative of a difficult or prolonged labor will not be seen in such cases.

Examination of both term and preterm newborns delivered into toilets indicates that the toilet delivery itself is not a cause of appreciable blunt force trauma. Cases of rescued infants delivered into the toilet do not have skull fractures. One investigation into infant skull fractures indicated that in order to result in a skull fracture, an infant must generally fall from a height of at least 2 meters, onto a hard surface (Holck 2005). Another study of falls in six neonates showed a linear parietal skull fracture in 66 % after falling approximately a meter onto a hard surface (Ruddick et al. 2010).

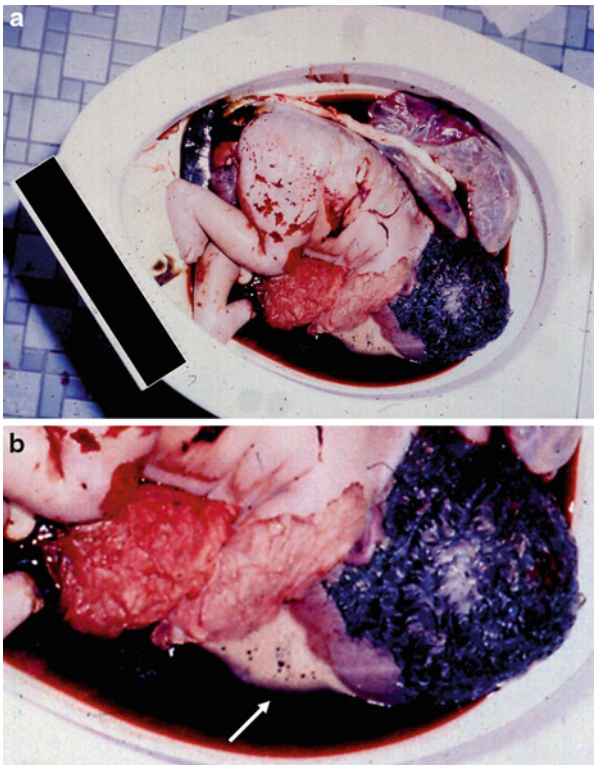

Fig. 6.24 Toilet delivery (**a**, **b**). (**a**) A full term neonate was found in a public toilet. The placenta was still attached. The face was submerged. No physical trauma was identified. (**b**) Note the froth indicative of breathing in toilet water and a live birth. Radiographically no trauma was identified. A complete autopsy showed no natural diseases that could have caused or contributed to the death. The cause of death was classified as asphyxia due to drowning. The manner of death was listed as homicide

Water Births

Underwater birth, either intentional or unplanned following labor in water, can occasionally lead to complications resulting from aspiration of water. Contrary to the belief that neonates will not breathe while immersed in water, there are documented cases of water inhalation leading to drowning, near-drowning, and hyponatremia. Additionally, exposure to water borne pathogens can lead to infection, including lethal Pseudomonas and Legionella pneumonias, and umbilical cord and ear infections (Byard and Zuccollo 2010).

Conclusion

Birth trauma can result in temporary injuries, permanent damage, or the death of an infant. All organ systems can be affected by birth trauma. Fortunately, many injuries can be prevented and/or predicted since risk factors are well documented. Clinicians and forensic pathologists must be able to differentiate traumatic birth injuries from postnatal accidental or inflicted injuries. Investigating the birth

history, assessing the biomechanics of the delivery and instrumentation, and understanding the resolution times of various injuries enable investigators to determine how or if a traumatic birth injury occurred.

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Neonaticide

7

Michael Tsokos

Contents

Abstract

Neonaticide, a crime almost exclusively committed by the biological mother, occurs throughout the world and seems to be one of the least preventable crimes. Mothers who commit neonaticide usually give birth to the child alone and kill their newborn very soon after delivery, most commonly within the first 24 h of life. The majority of newborns are killed by smothering, strangling, head trauma, drowning, or neglect. In most cases, the scene where the dead neonate is found is not consistent with the scene of delivery, and a broad variety of methods of disposal can be observed. Issues that have to be addressed by the forensic pathologist during autopsy include (i) estimating the gestational age and physical maturity of a neonate; (ii) determining whether there are indications

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of live birth or stillbirth; (iii) answering the question as to whether the child was viable and able to survive, and if so for how long; (iv) documenting lethal and nonlethal injuries as well as underlying (potentially lethal) organic diseases; (v) helping to establish the identity of the mother; and (vi) determining cause, mechanism, and manner of death if possible. In addition to the flotation test for lungs and the stomach, to determine whether the neonate was born alive, postmortem computed multislice tomography assists with the distinction between live and stillbirth but also the differentiation between artificially aerated lungs (resulting from resuscitation attempts) and naturally aerated lungs, making this presently the gold standard in postmortem imaging techniques in addition to autopsy in cases of neonaticide.

Introduction

Since terminology and legislation vary among different countries, a number of terms have been used to classify the killing of very young children, including *infanticide* (killing of an infant between 1 month and 1 year of age), *neonaticide* (killing of a newborn within its first 24 h of life; other definitions extend this to 28–30 days after birth), and *filicide* (killing of a child by a parent). This chapter deals with neonaticide, the practice of intentionally causing the death of a neonate.

The crime of neonaticide is one of the most common forms of murder committed by women and is almost exclusively carried out by the biological mother (Porter and Gavin 2010). Neonaticide occurs throughout the world and seems to be one of the least preventable crimes, irrespective of the intellectual ability of the mother and the socioeconomic setting or the geographic region where it occurs.

Due to the unique nature of the immediate postpartum period and the fact that women are more likely to experience mental disorders after childbirth than at any other time in their lives (Nesca and Dalby 2011), the crime of neonaticide has been incurring and still incurs lesser penalties than for murder in some jurisdictions. For example, legislation in the United Kingdom has reflected the possibility of a puerperal association with mental illness by stating that a mother's mental state may be "disturbed by reason of her not having fully recovered from the effect of giving birth" (Kellett 1992; Byard 2004). In Finland, to give another example, the crime committed by a woman who in a postpartum state of exhaustion or anxiety kills her child will be ruled a neonaticide, and she will be subject to not less than 4 months and not more than 4 years of imprisonment (Putkonen et al. 2007). However, today the prevailing forensic standpoint is that the vast majority of women who kill their newborn do not have an incapacitating mental illness at the time of the criminal act (Porter and Gavin 2010). In Germany, the respective law was abrogated in 1998. However, Germany has still one of the highest rates of neonaticide in European countries, with an estimated rate of at least 40–50 cases per year (Gheorghe et al. 2011).

Typically, mothers who commit neonaticide (i) give birth to the child alone and without any professional assistance; (ii) kill their newborn very soon after delivery, most commonly within the first 24 h of life; (iii) are unmarried; (iv) have either

concealed their pregnancy and subsequent delivery or were unaware that they were pregnant (denial of pregnancy); (v) are living with their parents; (vi) are 25 years of age or younger (in 90 % of cases); and (vii) do not suffer from a major mental illness such as psychosis or depression at the time of the killing of the newborn (Wissow 1998; Putkonen et al. 2007; Porter and Gavin 2010; Gheorghe et al. 2011).

The majority of newborns killed within their first 24 h of life are (i) born out of hospital and delivered secretly, (ii) unwanted, and (iii) killed by smothering, strangling, head trauma, drowning, or neglect (are forced to die by omitting adequate supportive care, such as feeding) (Pitt and Bale 1995; Saunders 1989; Byard 2004; Putkonen et al. 2007; Porter and Gavin 2010; Gheorghe et al. 2011; Guddat et al. 2013).

Despite media attention usually received in cases of neonaticide, official estimates for this type of crime are quite low. However, the exact incidence of neonaticide is difficult to determine since it depends on sociocultural structures of different communities, and there is probably underreporting in official statistics worldwide because cases are (i) never discovered, (ii) classified under different charges, or (iii) lost in statistics due to various reasons such as lack of proof and forensic evidence of the offense or pretrial plea bargains. One study surveying retrospectively all cases of suspected neonaticide in Finland from 1980 to 2000 estimates the rate of neonaticide in this country to be about 0.07–0.18 per 100,000 live births (Putkonen et al. 2007). However, statistics probably represent only the tip of the iceberg since many such deaths are not registered in official records.

Reasons for mothers killing their newborn children include fear of job loss, not wanting to raise a child, waiting too long for an abortion, poverty, and psychosis. While unmarried women may fear revealing the pregnancy to their families because of shame or fear of punishment or rejection, married women may wish to eliminate an unwanted extramarital pregnancy or just fear the financial disadvantage of having another mouth to feed. Over the last decades, greater tolerance of pregnancy outside marriage in industrialized countries has seen a reduction in the numbers of neonaticides, as have improvements in contraceptives and contraception advice.

Though multiple neonaticides conducted by one mother are rare, these killings do occur (Fig. 7.1a–d), with one report documenting a woman killing nine newborns (Funayama et al. 1994).

Scene Findings

In most cases, the scene where a body is found is not consistent with the scene of delivery (Fig. 7.2a, b). Different methods of disposal can be observed, depending on availability and access. Usually, the newborns are completely naked and are most often enclosed in blankets, towels, or bathrobes and then wrapped up in plastic bags or other similar material (Fig. 7.3a, b). Bodies or their remains may be dumped in trash bins, garages, lofts, freezers, big flowerpots, and coin-operated railway lockers or, if outside, dropped in rivers, concealed in woodlands, or buried. In a number of cases, the bodies of the newborns might never be found. The placenta is often disposed of separately.

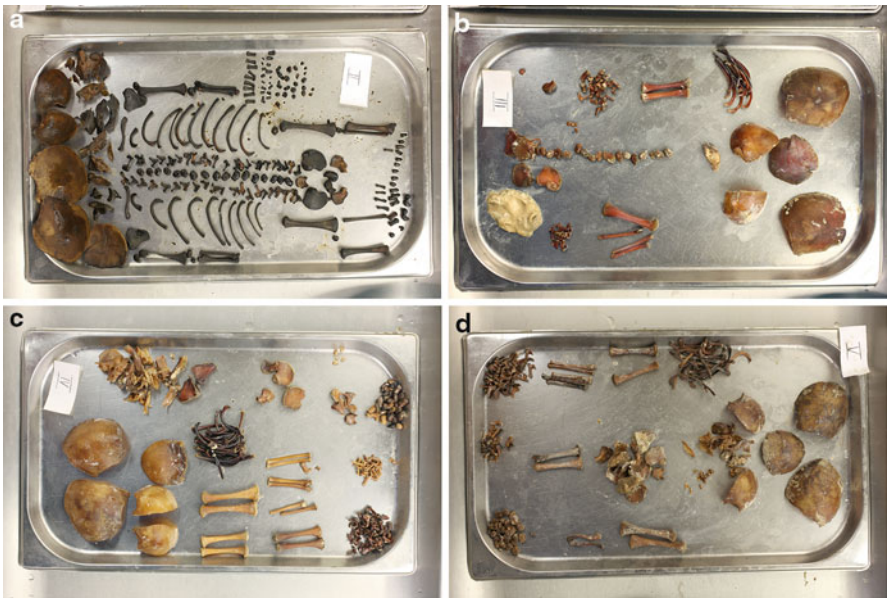

Fig. 7.1 Multiple neonaticides by one mother: (**a**–**d**) Skeletal remains of four out of a total of five newborns that were killed by their biological mother over a period of 12 years. The remains were concealed in furniture in her apartment for nearly two decades and then found after she had committed suicide

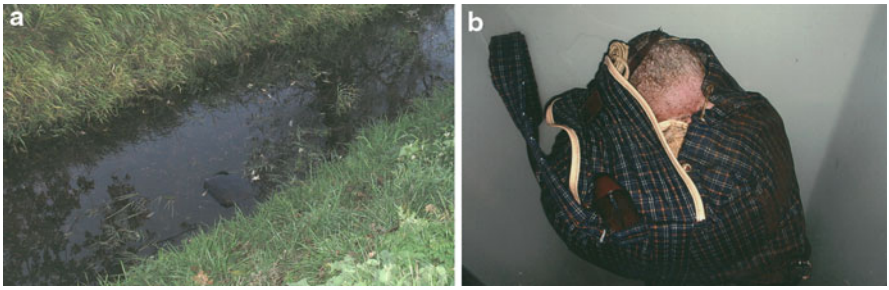

Fig. 7.2 (**a**) Backpack floating in a brook. (**b**) Inside the backpack, the body of a newborn was found

The remains of newborns that have been concealed indoors may be found years or even decades after the crime when residences are left by the tenants for various reasons and the housing space is vacated.

Careful examination of the scene may provide relevant information linking a dead newborn to its mother since material used to wrap or transport the infant, such as blankets or supermarket bags, may help to identify or locate the maternal residence. Domestic waste may also help in this regard (Fig. 7.4).

Fig. 7.3 (**a**, **b**) Completely naked neonate with placenta enclosed in blankets and found inside a plastic bag

Fig. 7.4 Three-dimensional computed tomographic scan of a plastic garbage bag showing a variety of domestic rubbish and the body of a newborn infant

If the body is not found immediately, there may be mummification, adipocere formation, or skeletonization (Fig. 7.5). On occasion, mothers may retain fetal/neonatal remains for decades in close proximity to them in their household, e.g., in freezers, flowerpots, or hidden in sealed bags in furniture (Fig. 7.6a, b).

Fig. 7.5 Skeletonized remains of a newborn infant that was disposed of in a plastic garbage bag

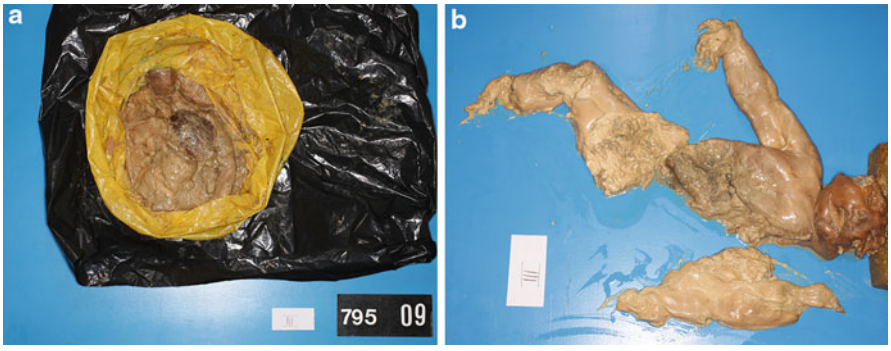

Fig. 7.6 (**a**, **b**) The remains of a neonate had been hidden by the mother in different places (e.g., in a freezer) in her apartment for many years

Autopsy

A variety of issues need to be addressed by the forensic pathologist handling a case of suspected neonaticide. These include (i) estimating the gestational age and physical maturity of a neonate; (ii) determining whether there are indications of live birth or stillbirth; (iii) answering the question as to whether the child was viable and able to survive, and if so for how long; (iv) documenting lethal and nonlethal injuries as well as underlying (potentially lethal) organic diseases; (v) helping to establish the identity of the mother; and (vi) determining cause, mechanism, and manner of death if possible.

The autopsy of such neonates has to include subsequent histological, neuropathological, and toxicological investigations and has to be accompanied by a full photographic documentation of each step undertaken by the forensic pathologist.

Postmortem computed tomography investigation or at least a full radiological examination of the neonate before commencing with the autopsy is mandatory for various reasons, not only to locate injuries. Postmortem multislice computed tomography (pmMSCT) visualizes aeration of the lungs to enable distinction between live and stillbirth, differentiation between artificially aerated lungs (resulting from resuscitation attempts) and naturally aerated lungs, and discrimination between putrefaction gases and natural air (Guddat et al. 2013). In addition, estimating the gestational age and physical maturity of newborns is easily performed using CT (Sakurai et al. 2012). Although pmMSCT is presently the gold standard in postmortem imaging techniques in addition to autopsy, it cannot replace a conventional autopsy performed by an experienced forensic pathologist.

External Examination

Sampling of DNA swabs from the neonate's body (Fig. 7.7) as well as from the objects the corpse is wrapped in is needed for later comparison with DNA of the probable mother. Swabs have to be taken at the very beginning of the external examination to avoid contamination with DNA from a third party.

The external examination includes weighing and measuring the newborn. Routine parameters assessed include head circumference, crown-heel, crown-rump, foot length, as well as the length of the portion of the umbilical cord remaining attached to the body. The insertion site of the umbilical cord has to be inspected, as well as the end to see if it has been cut or torn, the latter possibly indicating a precipitate delivery.

The anterior and posterior fontanelles are measured and palpated to assess whether they are sunken or tense. The ears are examined with particular attention to the form of the helix, their position on the head, and if the cartilage of the auricle is normally developed. The mouth including the gingival ridges and the mucosa as well as the hard and soft palates are checked for injuries or congenital defects. The number of digits on each extremity is noted. If dysmorphic features or any other physical abnormalities are present, these should be documented with photographs, and if possible, two additional blood samples for later chromosome analysis (apart from those blood samples taken for possible matching with maternal DNA if this becomes available at a later time) should be collected during the subsequent autopsy, as well as samples of fascia, cartilage, and tendon for the same purpose.

Descriptions of the body should include the presence or absence of vernix caseosa and blood indicating recent delivery (Fig. 7.8a, b) or washing of the body before disposal. Vernix caseosa is a white material composed of sebum, desquamated epithelial cells, and lanugo hair that is normally adherent to the skin of a fetus. The presence of vernix and blood merely indicates that delivery has occurred recently; their absence may simply mean that a neonate has been cleaned postpartum.

Fig. 7.7 Sampling of DNA swabs for later comparison with DNA of the probable mother is an essential part of the external examination of a body of a newborn

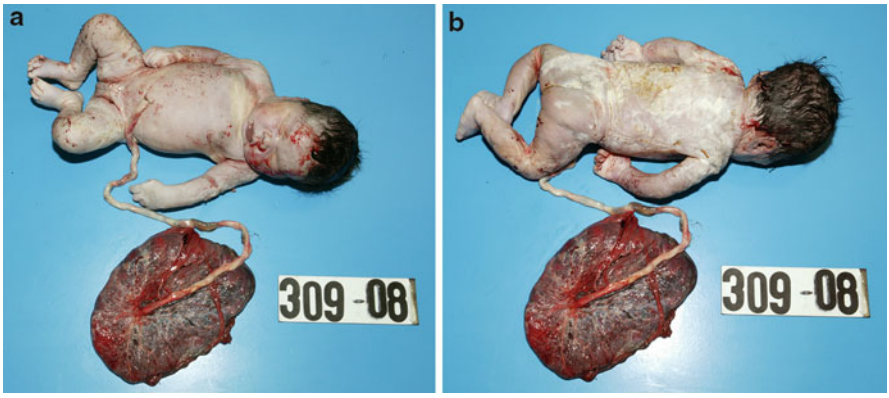

Fig. 7.8 (**a**, **b**) Vernix caseosa and blood on the body of a newborn with the placenta still attached to the body indicating recent delivery

If the placenta is still attached to the body via the umbilical cord, this is another indicator of recent delivery.

The body has to be examined carefully for injuries. Injuries that may have been inflicted with the aim of killing a newborn include (i) strangulation marks around the neck with bruising from hands or parchmented abrasions from ligatures that may have been left in situ, (ii) stab wounds to any part of the body, (iii) craniocerebral trauma that may include bruising with subgaleal, extradural, and subdural hemorrhages as well as skull fractures and cerebral lacerations.

Strangulation and smothering are common methods involved in neonaticide. While the first may be associated with facial petechiae, the latter usually leaves either no or only subtle marks such as superficial abrasions or drying of the skin around the mouth and nose.

One has to be aware that facial petechiae are not a rare finding in newborns, and therefore, their presence has to be interpreted carefully. Since facial petechiae occur

Fig. 7.9 Caput succedaneum

in 20 % of all newborns, most often seen on the skin of the eyelids, this finding alone can never give sufficient evidence of inflicted asphyxia after delivery in cases of suspected neonaticide (Wisser et al. 2012). On the other hand, when hemorrhage from coagulation disorders or vasculopathies can be excluded, the combination of extensive petechial hemorrhage of the skin of the face, upper thorax, and shoulders as well as of the mucosa of the mouth can only be explained by hemodynamic factors such as obstruction of the airways with simultaneous chest compression (Oehmichen et al. 2000).

Inflicted injuries such as abrasions with underlying swelling of the soft tissue of the scalp and scalp lacerations with or without associated skull fracture have to be carefully distinguished from injuries due to birth trauma such as *caput succedaneum* (edema and minor hemorrhage within and under the scalp) or *cephalhematoma* (subperiosteal hematoma). Both findings are frequent types of "normal" birth trauma associated with prolonged labor that usually resolve within the first days of life. Since caput succedaneum (Fig. 7.9) and cephalhematoma indicate prolonged labor, their presence may give investigators a useful hint in analyzing the circumstances of delivery in the light of the story given by the mother ("I was unaware of my own pregnancy and the child birth came to me as a bolt from the blue" is a highly unlikely version of the events of delivery when caput succedaneum and cephalhematoma are found).

However, scratch marks or even a ligature around the neck may not necessarily indicate attempted strangulation, as these may be found if a mother has attempted to manually extract a fetus or has used a loop of cloth to assist with traction. Similarly, pressure from an umbilical cord wrapped around the neck (Fig. 7.10) may also leave circumferential grooving which should not be confused with ligature indentation. When an entangled umbilical cord is removed prior to external examination by a third party, circumferential grooving may be confused with ligature indentation. Normal fat folds may also produce circumferential markings, especially upon refrigeration (Fig. 7.11).

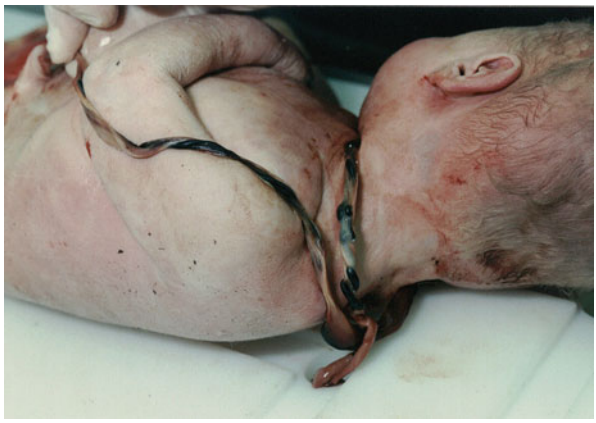

Fig. 7.10 Umbilical cord entanglement

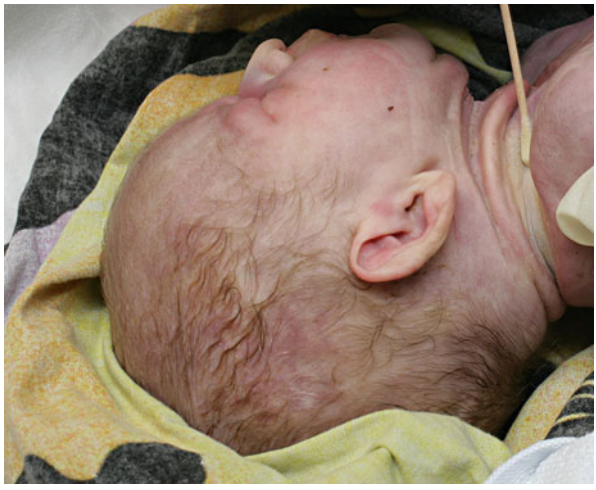

Fig. 7.11 Normal fat folds producing circumferential markings that may be confused with marks from ligature strangulation

A newborn may have sustained head injuries if a mother has delivered in a standing or squatting position with an umbilical cord long enough for the child to strike the ground or floor.

Exposure of a newborn's body to carnivore, rodent, or insect activity indoors or outdoors may also result in quite extensive soft tissue trauma (Byard et al. 2002; Tsokos 2005). Putrefaction and autolysis are additional factors complicating assessment of the presence or absence of injuries.

Physical Maturity of the Neonate and Gestational Age

Estimation of physical maturity and gestational age of a neonate is important to assess viability and ability to survive. The chance of fetal survival increases with gestational age, with otherwise healthy neonates born at 28 weeks now expected to live. The age of

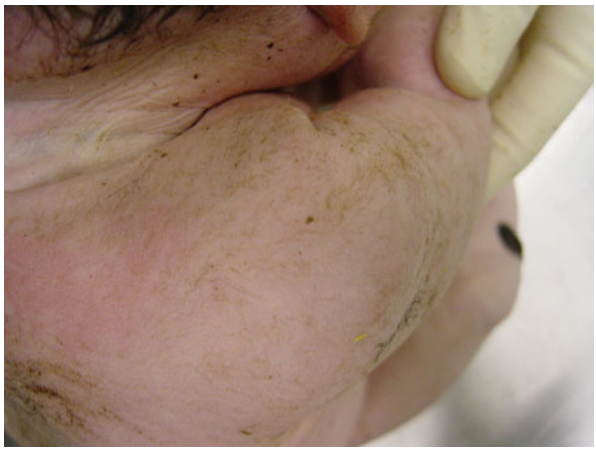

Fig. 7.12 Lanugo hair only present over both shoulders indicating physical maturity of this newborn

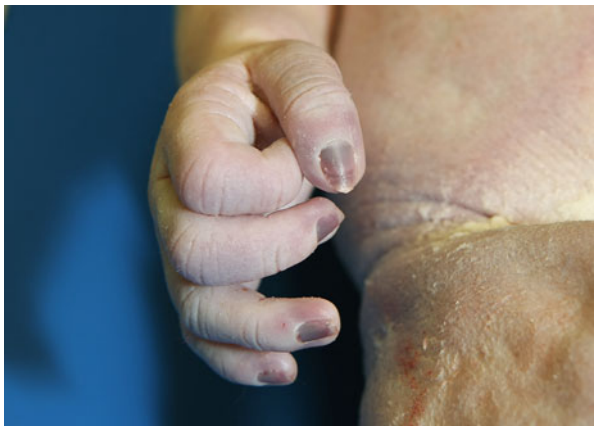

Fig. 7.13 Fingernails superior to the finger tips indicating physical maturity of this newborn

viability varies among jurisdictions with 24 and 28 weeks being cited as the lower limits of potential survival. Physical maturity means that the body corresponds to that of a term newborn of 38–40 weeks. This physical maturity of the neonate can be determined by the following parameters: body length (≥48 cm), body weight (≥2,500 g), head circumference (34–35 cm), shoulder-to-shoulder length (≥12.5 cm), foot length ≥6.5 cm, complete descent of both testicles into the scrotum, distribution pattern of lanugo hair, fingernail length, and size of epiphyseal ossification centers.

In mature newborns, lanugo hair is only still present over both shoulders but absent on the rest of the body (Fig. 7.12). The fingernails are superior to the finger tips in physically mature neonates (Fig. 7.13).

Dissecting of the knee joints followed by a cut through the distal epiphysis of the femur gives access to the ossification site located there (Fig. 7.14); in German textbooks, this is termed Beclard's ossification site. A diameter of this epiphyseal ossification center of ≥5 mm indicates physical maturity of the newborn.

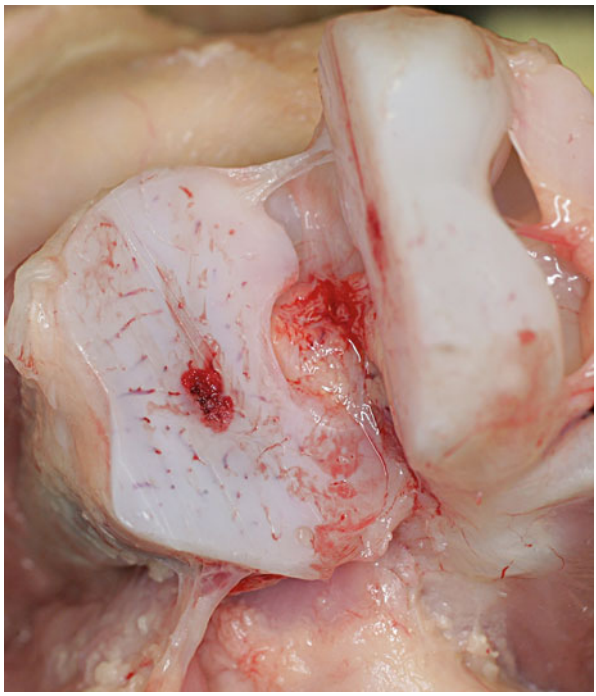

Fig. 7.14 A cut through the distal epiphysis of the femur gives access to the ossification site located there (Beclard's ossification site) indicating physical maturity when the diameter is 5 mm or more

Radiological evaluation will also be a useful adjunct by enabling ossification sites to be assessed against known developmental data.

Recent advances in postmortem imaging using computed tomography (Fig. 7.15) and its widespread introduction in forensic pathology worldwide have provided new methods for estimating gestational age (Sakurai et al. 2012). However, as practiced for decades and still carried out in this way, gestational age can reliably be determined by comparing measurements of the child to standard growth charts or of skeletal remains with respective skeletal system charts.

Differentiation Between Live Birth and Stillbirth

Determination of whether a child was born alive or dead is not only the most important aspect of these cases, since further legal proceedings inevitably depend on this, but it is also one of the most difficult aspects. The definition of what constitutes *live birth* legally differs from jurisdiction to jurisdiction. Requirements have included complete expulsion from the birth canal with a heart beat and/or respiratory efforts. Unfortunately, pmMSCT imaging and autopsy examination cannot determine whether the heart has functioned or not or if a newborn's body was completely expelled prior to death. Signs of intrauterine death, caused by a process of sterile tissue breakdown or maceration, may be present, indicating that live birth has not occurred. During this process, the body undergoes a series of characteristic changes beginning with

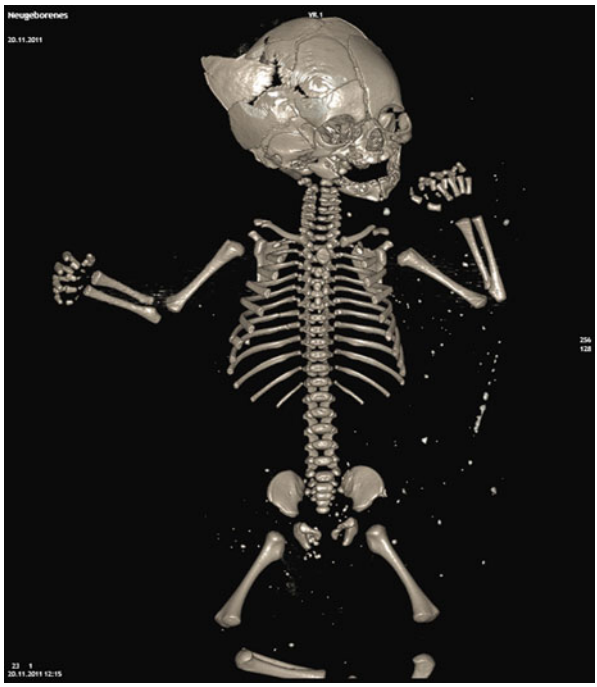

Fig. 7.15 CT scan enabling an estimation of the gestational age of a newborn

reddening, slippage, and peeling of the skin after 12 h, followed by purple discoloration and blister formation after 24 h (Fig. 7.16). After several days, the body has lost tone, joints become hypermobile, and cranial bones collapse. A child with changes of maceration has not been alive outside the uterus. The forensic pathologist's opinion often relies upon an assessment of the degree of pulmonary inflation, the presence or absence of a vital reaction in the tissues, or evidence of feeding.

The presence of milk within the stomach indicates that the newborn had been alive for long enough to be fed. However, its absence does not indicate that the child was stillborn.

Methods for Determining Live Birth

Flotation Test

The main test, still in use in most jurisdictions, is the flotation test for lungs and the stomach including the duodenum. The history of the flotation test for the lungs goes back to 1667 when the Dutch scientist Jan Swammerdam demonstrated that the aerated lungs of a neonate, who had breathed at birth, floated in water, while those of neonates that did not visibly draw breath sank. The test was later expanded to include the stomach and duodenum to demonstrate air in the upper gastrointestinal tract, which is swallowed by the infant during the first respiratory attempts.

The test involves placing the lungs in water (Fig. 7.17) to determine whether they float or sink. This has to be done after careful dissection with occlusion of the airways by string prior to exenteration to avoid environmental (artificial) air

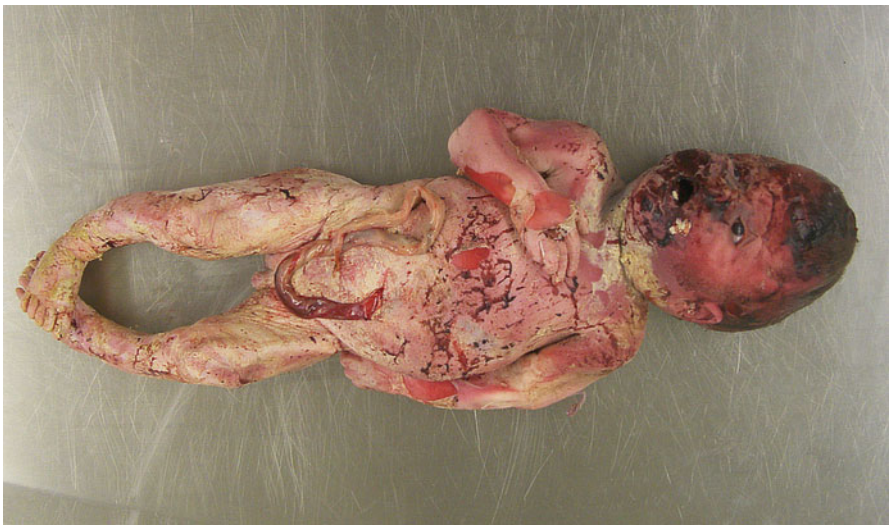

Fig. 7.16 Intrauterine death with maceration of the fetus

Fig. 7.17 Positive flotation test of the lungs

producing a false-positive result. The flotation test is based on the hypothesis that the lungs from a neonate who has breathed will be expanded and filled with air and therefore will float in water, in contrast to the non inflated lungs of a stillborn that will sink. It is recommended first to attempt to float the lungs and heart en bloc before the lungs alone are tested to increase the sensitivity of the test.

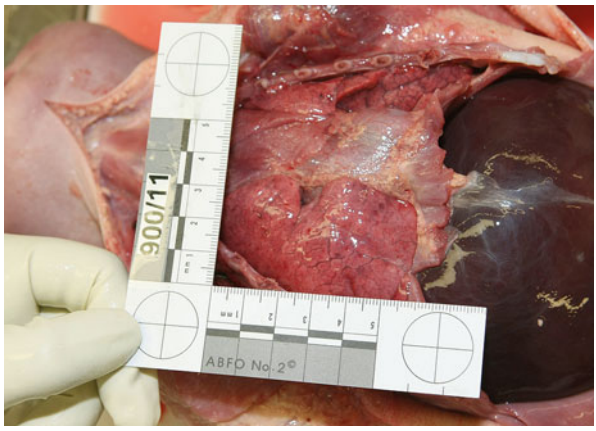

Fig. 7.18 Typical appearance of the lungs of a neonate that has breathed. The lungs appear spongy and salmon pink in color

Lungs of a neonate who has breathed will usually appear spongy and salmon pink in color at autopsy (Fig. 7.18), with expansion of the distal airspaces. This contrasts with the morphology of lungs of a stillborn which are collapsed and feel quite dense and heavy and appear dark red in color.

In Germany, law mandates the flotation test to be performed by forensic pathologists to assist with the determination of live birth. Every forensic pathologist is therefore required to use it in cases of neonatal deaths. However, any conviction based on the flotation test alone must be regarded with caution. The flotation test is not without controversy as different aspects have to be considered when a positive result is obtained, particularly the potentially severe legal consequences for someone found guilty of neonaticide. In many cases, the flotation test has to be excluded as proof of a live birth due to the presence of putrefaction or the fact that cardiopulmonary resuscitation was performed. In cases where putrefactive tissue changes are suspected, a simultaneous liver section flotation test may provide an evaluation of the level of decomposition present within the internal organs. In the German literature on neonaticide, the liver section test as well as a spleen section test is recommended because putrefaction gases may develop in these organs at a rate similar to lung tissue.

Some authors view the flotation test of the lungs to be of limited value and should only be used as a "suggestive pointer" (Saukko and Knight 2004). This attitude is understandable in view of the many possible false-positive and false-negative results which may be obtained when the test is administered incorrectly or under the wrong circumstances.

One of the problem scenarios which has led to denial of the validity of the lung flotation test occurs in cases with cardiopulmonary resuscitation. It is argued that resuscitation attempts artificially introduce air and produce some lung expansion. However, this may not have the same appearance as lung expansion from natural respiration because this lies in the extent of peripheral alveolar expansion, which is usually not achieved by mouth-to-mouth resuscitation efforts in the same quantity when compared to naturally aerated lungs (Kellett 1992).

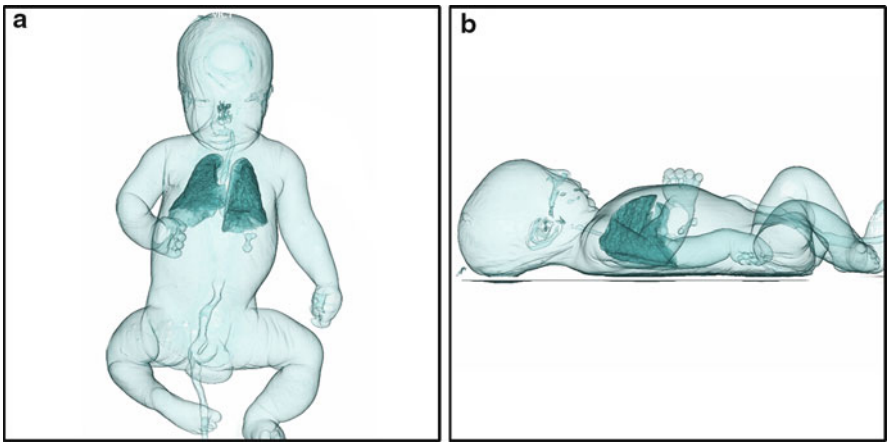

Fig. 7.19 (**a**, **b**) Three-dimensional CT reconstruction of a live birth with visualization of fully aerated lungs

However, during the conventional autopsy, it is almost impossible to make this distinction morphologically. Histological examination may be of use in some cases, with pulmonary interstitial emphysema in combination with aerated alveolar spaces being proposed as another histological marker of live birth (Lavezzi et al. 2003).

Postmortem Multislice Computed Tomography (pmMSCT)

A recent study successfully compared pmMSCT scans of live birth signs with conventional autopsy results of the flotation tests for lungs and the GI tract, thereby demonstrating the possibility of radiological visualization of complete aeration in cases of live birth (Guddat et al. 2013). pmMSCT also seems to be advantageous over conventional autopsy techniques in the possible differentiation between complete aeration of the lungs and partial artificially aerated lungs as a result of resuscitation attempts. The same study also demonstrated that pmMSCT can be used with ease to detect the presence or absence of putrefactive gases within the vascular system.

Where available, pmMSCT should be used as an additional tool to the flotation test to differentiate between live birth and stillbirth (Fig. 7.19a, b). The usual caveats pertaining to the flotation test should still be considered when applying the virtual method.

Survival Time

Air or gas may also be present in the stomach and adjacent small intestine if the newborn has swallowed air after delivery which means that the child was (i) born alive and (ii) survived for at least a short period of time. The flotation test of the

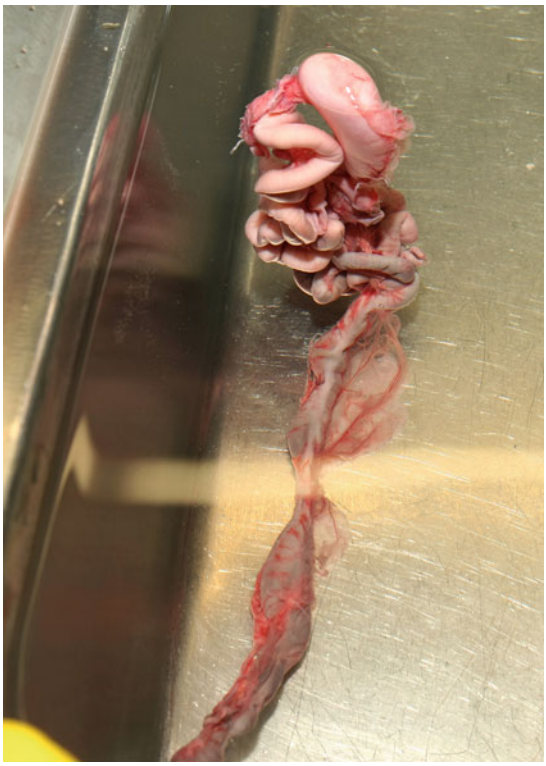

Fig. 7.20 Positive flotation test of the stomach and adjacent duodenum indicating a survival time between a few and 30 min

stomach and intestine tract may provide a useful hint toward the survival time of a neonate with (i) a positive flotation test of the stomach and adjacent duodenum indicating a survival time between a few to 30 min (Fig. 7.20), (ii) a positive test of the complete small bowel and stomach indicating a survival time of up to 6 h (Fig. 7.21), and (iii) a positive test for the large bowel with small intestine and stomach indicative of a survival time of at least 12 h (Podolsky and Jester 1954; Hirvonen et al. 1969; Madea and Dettmeyer 2007).

If meconium is found within the entire large bowel, this indicates a survival time of less than 2 days; if small portions of meconium are only still apparent within the folds of the large bowel, this means the neonate did live up to a maximum of 5 days (Madea and Dettmeyer 2007).

Special Autopsy Considerations

The process of delivery may cause a number of characteristic injuries to infants. Separation of parts of the occipital bone (*occipital osteodiastasis*) is a feature of breech deliveries that causes cerebellar lacerations and tearing of dural venous sinuses with subdural bleeding. Birth trauma with rupture of bridging veins may

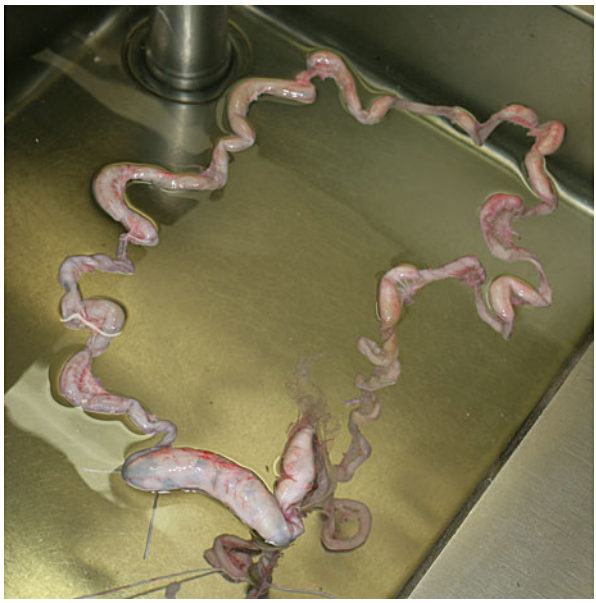

Fig. 7.21 Positive flotation test of the small bowel and adjacent parts of the large bowel

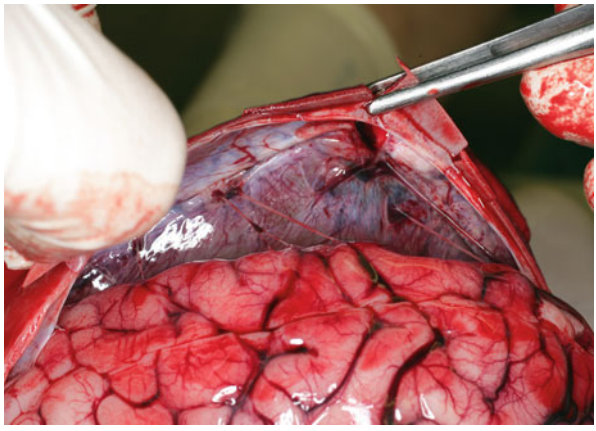

Fig. 7.22 Inspection of bridging veins at autopsy

occur during nearly every stage of parturition. Therefore, the careful inspection of bridging veins (Fig. 7.22) is a prerequisite to determine whether craniocerebral injuries are intentionally inflicted or may be a result of birth trauma.

Precipitate delivery with excessive molding of the head may also cause intracranial hemorrhage. Unfortunately, assessment of the likely significance of these lesions may be difficult due to a lack of delivery history.

Asphyxia may also complicate traumatic labor and delivery from shoulder dystocia or cephalopelvic disproportion in larger infants. Evidence of acute asphyxia at autopsy includes thymic, pleural, and epicardial petechiae with

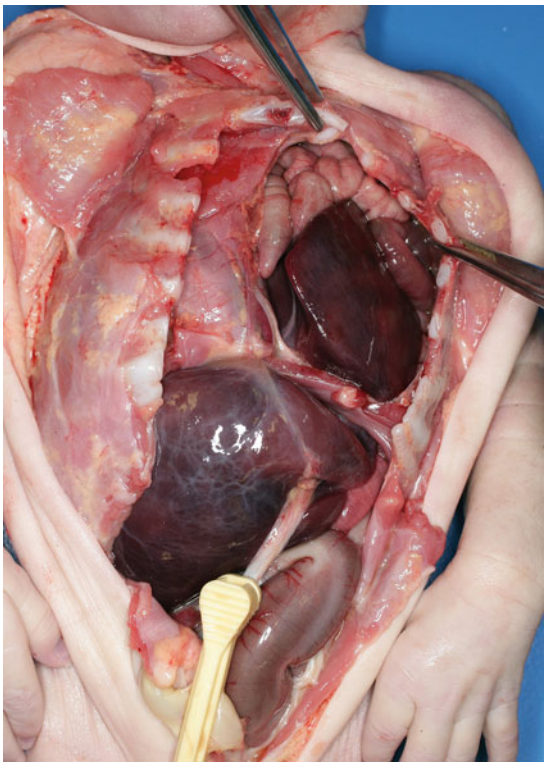

Fig. 7.23 Congenital diaphragmatic hernia with displacement of the abdominal organs into the left chest cavity causing fetal death by asphyxia during birth

intra-alveolar hemorrhage and meconium and numerous shed fetal skin (squamous cells) within distal air passages.

Another important part of the autopsy is to check for the presence or absence of natural diseases. Congenital diaphragmatic hernia with compression of the lung due to displacement of the abdominal organs into one or both chest cavities is also occasionally observed as a cause of fetal death by birth asphyxia (Fig. 7.23).

Complete dissection of the posterior trunk and upper and lower limbs to detect subcutaneous or intramuscular hemorrhage as a sequel of trauma (e.g., from a blow, kick, fall, or forceful grip) that has left no cutaneous marks is also necessary (Fig. 7.24).

Certain conditions such as anencephaly and other abnormalities of brain development, significant pulmonary hypoplasia, congenital malformations of the cardiovascular system, or extracardiac anomalies of inner organs should be easily identified at autopsy. Subtle cardiovascular or metabolic abnormalities are often difficult to diagnose, even in the nonputrefied body of a newborn. If the postmortem interval is less than 4–5 days, a full microbiological workup of both the infant and the placenta, if available, should be undertaken along with histological examination of all major organs and tissues.

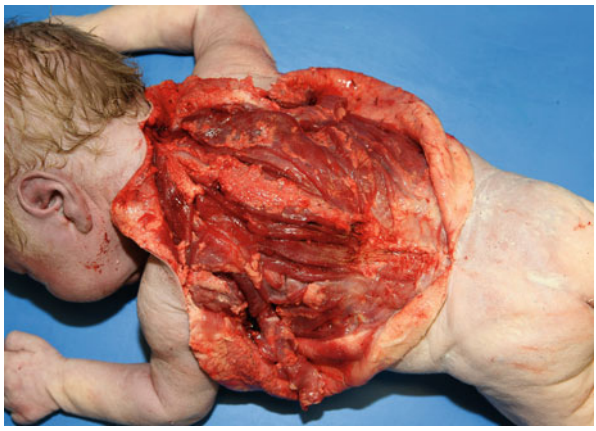

Fig. 7.24 Complete dissection of the posterior trunk to detect subcutaneous or intramuscular hemorrhage from trauma is a prerequisite in the investigation of the death of a newborn

Examination of the Placenta

Placental examination is a vital part of any perinatal autopsy. Due to the unusual circumstances surrounding concealed deliveries and possible neonaticides, the placenta may not always be available for pathological assessment.

The placenta is a complex organ that receives circulations from both mother and fetus. Examination of the placenta is best performed by an experienced pediatric pathologist, as forensic pathologists may not handle enough cases to develop or maintain their expertise. The primary purpose of the examination of the placenta is usually to identify conditions in either the mother or the fetus that may have negatively impacted the viability or survival of the newborn. A variety of placental conditions may result in the stillbirth of otherwise completely normal fetuses. For example, premature separation of the placenta from its uterine attachments (*abruptio placentae*) may cause extensive retroplacental bleeding and compromise of placental and infant oxygenation (see ► Chap. 5, "Placental and Maternal Conditions in Perinatal Deaths").

Examination of the Umbilical Cord

The average umbilical cord length is 54–61 cm.

Umbilical cord length is dependent on the stretch provided by fetal intrauterine motor activity. Accordingly, short cords may be a marker of abnormal fetal brain development (Khong 2001). An abnormally short cord is defined as being less than 32 cm, which is the minimum length considered to permit unrestricted vertex activity. An abnormally long umbilical cord is considered to exceed 100 cm (Khong 2001).

Umbilical cord problems may cause precipitate deterioration in a fetus's condition from a variety of mechanisms. Excessively long cords may cause blood flow obstruction if prolapse, torsion, or knotting occur. Long cords may also lead to entanglement around the fetus's neck. Conversely, blood flow in short cords may

also be compromised if there is excessive traction during delivery. While possible twisting or knotting of cords may be difficult to assess, true knots should be tight, with congestion of vessels on one side and pallor on the other.

The umbilical cord is often edematous in maternal diabetes or when there is fetal or placental hydrops (Khong 2001).

Drying and separation of the umbilical cord stump which occurs after 24–48 h, with histological evidence of a tissue reaction, may also be useful, but does not help with deaths in the immediate post-delivery period.

Examination of the ends of the cord must be undertaken macroscopically and microscopically. This will reveal whether the ends of the cord have been cut or have been torn, possibly indicating a precipitate delivery.

Causes of Death

Deaths are most often due to airway obstruction from strangulation or smothering (Byard 2004; Gheorghe et al. 2011). A neonate's nose and mouth may be covered with a hand in an attempt to prevent the infant's cries from being heard with subsequent suffocation. Neonates may also asphyxiate if placed in plastic bags and hidden while a mother cleans up after delivery and determines what she is to do (Byard 2004). Drowning may occur if a newborn is delivered into a toilet bowl and left there, held under water in a bath, or intentionally immersed in a water basin or a bathtub. Blunt head trauma is also common as well as hypothermic deaths of neonates exposed to cold ambient temperatures or from failure of the mother to adequately clothe or place an infant in a warm environment (Byard 2004; Guddat et al. 2013). While stabbing is very rare as a form of killing a newborn, occasionally the throat may be cut (Saunders 1989; Pitt and Bale 1995; Mendlowicz et al. 1999).

Deaths may also occur from failure to provide appropriate care of a vulnerable newborn. Failure to tie off the cut umbilical cord may result in lethal blood loss, and airway occlusion from secretions may compromise respiration if not cleared, but these two causes of death are exceptionally rarely seen in cases of neonaticide.

Conclusions

Denial of pregnancy, concealment of delivery, and neonaticide are rare but particularly concerning, given the potential legal outcomes of the latter. Much depends on the autopsy findings. The central questions in such cases are the following:

1. Was the newborn mature and what was the gestational age?
2. Was the newborn born alive?
3. Was the newborn viable and able to survive?
4. How long did the newborn survive?
5. What is the cause of death?

The autopsies of suspected cases of neonaticide should therefore be performed by forensic pathologists with experience in this area. Neonaticides are often

difficult cases to investigate as injuries may be extremely subtle or nonexistent and proof of live birth may not be possible when the forensic pathologist has to deal with decomposed or mummified newborns or skeletal remains.

Given the fact that the causes of death may not be found at autopsy in unexpected near-term stillbirths that occur in hospitals under highly controlled conditions, it is perhaps not surprising that determination of lethal mechanisms may not be possible in cases where dead infants have been found abandoned some days after delivery. In these cases, stillbirth cannot be ruled out until there is firm evidence to the contrary.

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8 Sudden Infant Death Syndrome (SIDS), Sudden Unexpected Death in Infancy (SUDI), and Sudden Unexplained Death in Childhood (SUDC)

Henry Krous

Contents

Abstract

This chapter is a brief review of sudden unexpected death in infancy (SUDI), sudden infant death syndrome (SIDS), and sudden unexplained death in childhood (SUDC). Sudden unexpected death occurs in infants and young children alike. In both age groups, establishing the cause and manner of death often presents a difficult but important challenge. Accurate determination of the cause and manner of sudden unexpected death of infants and toddlers

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alike requires comprehensive review of the medical and family history, reconstruction of the death scene with evaluation of the circumstances of death, and thorough autopsy examination with extensive ancillary studies. If the cause of death is not established after comprehensive postmortem evaluation, then it generally defaults to SIDS in infants and SUDC in children beyond the first birthday.

Introduction

Sudden unexpected death in infancy (SUDI) and childhood has many causes including natural diseases, accidents, and inflicted injuries, but the majority in both age-groups remain unexplained after review of the medical history, scene investigation with reconstruction, and postmortem examination that includes ancillary laboratory and radiographic studies (Byard 2010; Krous et al. 2005a; Weber et al. 2008a). Therefore, the diagnosis in most of these cases defaults to sudden infant death syndrome (SIDS) in infants and sudden unexplained death in childhood (SUDC) in cases beyond 1 year of age (Krous et al. 2005a). In the mid-1970s more than half of unexplained sudden infant deaths were ascribed to SIDS (Hauck 2001). More recently, nearly two thirds of 546 cases presenting as sudden unexpected infant deaths at a single institution remained unexplained (Weber et al. 2008a).

During recent years, recognition of possible asphyxia challenges imposed upon infants at the death scene has been recognized and resulted in a diagnostic shift away from SIDS toward undetermined suffocation or asphyxia (Malloy and MacDorman 2005). These asphyxial challenges can be a consequence of infants sleeping prone and/or having their head covered by bedclothes, sleeping on surfaces not designed for infants (e.g., adult beds, sofas, recliner chairs, large pillows), soft sleep surfaces, and bed sharing; all of these factors increase the risk of sudden death and SIDS. However, it would be simplistic to consider accidents as the sole cause of these deaths, especially since the vast majority of infants sleeping in similar environments do not die. With this recognition, the triple-risk model for SIDS, which was first proposed in the mid-1990s, has been progressively validated with identification of an ever-increasing number of deficits in the medullary serotonergic system that predispose a vulnerable infant to sudden unexpected death especially during sleep when homeostatic mechanisms are developmentally unstable (Kinney 2009).

SUDC is sudden *unexplained* as opposed to *unexpected* death in children beyond the first birthday, especially toddlers 1–4 years of age; is extraordinarily rare; and as such has received far less attention than SUDI. Data from the CDC indicate that sudden unexpected death in toddlers has an incidence of approximately 1 in 100,000 compared to SIDS with an incidence of 1 in 2,000 live births, a nearly 50-fold difference. SUDC accounts for the majority of sudden unexpected deaths in toddlers (Krous et al. 2005a).

This chapter is a brief review of SUDI, SIDS, and SUDC.

Sudden Unexpected Death in Infancy

Sudden unexpected death in infancy (SUDI) is an umbrella label, the meaning of which depends upon its user, that is, the forensic or pediatric pathologist or the researcher. Unfortunately endorsement of an international and consistently used SUDI definition has not been achieved. As a result, some may use SUDI to encompass all sudden unexpected infant deaths, whether or not explained, while others restrict its use to cases in which the cause of death is uncertain. This confusion is often compounded by publications often failing to provide clear and specific meanings for SUDI.

An inevitable interface exists between SUDI and SIDS since the former is occasionally and the latter is always a diagnosis of exclusion. This interface is especially blurred as there is a lack of definitive, easily identifiable postmortem marker(s) for SIDS. Therefore, present SIDS definitions are imprecise, and its diagnosis remains one of exclusion. The continuing controversy regarding SUDI and SIDS will remain until SIDS definitions become more precise, the causal relationship of intrinsic and extrinsic risk factors and underlying pathology in SIDS is further unraveled, scene investigation improves universally, and affordable diagnostic postmortem testing for SIDS and other disorders masquerading as SIDS becomes widely available.

SIDS accounts for approximately 80 % of SUDI deaths, the remaining 20 % having another cause established by postmortem evaluation. Genetic cardiac ion channelopathies and inherited disorders of fatty-acid oxidation, especially mutations in the medium-chain acyl–coenzyme A dehydrogenase (MCAD) gene, account for approximately 5–10 % and 1 % of SUDI cases, respectively. Molecular and metabolic testing are required to establish these diagnoses. Finally, intentional suffocation has been estimated as the cause of death in less than 5 % of SUDI cases. If undertaken with a soft object, intentional suffocation is virtually impossible to distinguish from SIDS at autopsy, but it deserves consideration especially if the infant is older than 6 months with a history of recurrent life-threatening events while under the care of the same caretaker, and if there is a history of a previous death of an infant with the same caretaker.

Sudden Infant Death Syndrome

Definition

PubMed, the National Library of Medicine (USA) search engine, at the time of this writing, cites greater than 100 publications when “SIDS and definition” are used as keywords. That none of the currently published SIDS definitions enjoy universal acceptance is illustrated by a recent audit of 50 papers published in 2005 on SIDS found that 29 either had not specified any definition or had used nonstandard or idiosyncratic ones (Byard and Marshall 2007); 15 used the NICHD definition (Willinger et al. 1991), five used the San Diego definition (Krous et al. 2004), and one used the Seattle definition. The dilemmas and challenges involved in

achieving a universally accepted SIDS definition have been recently discussed (Krous 2010). Conversely, some have suggested that universal acceptance of a SIDS definition is neither possible nor advisable.

The most widely used SIDS definitions are those emanating from the NICHD and the San Diego conferences. The NICHD definition of SIDS is "the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Willinger et al. 1991). The more recent San Diego SIDS definition is "the sudden and unexpected death of an infant under 1 year of age, with onset of the lethal episode apparently occurring during sleep that remains unexplained after a thorough investigation including performance of a complete autopsy, and review of the circumstances of death and the clinical history" (Krous et al. 2004). This general "San Diego" definition has also been stratified into categories SIDS IA, IB, and II to accommodate the certainty of a SIDS diagnosis based upon the available information; these categories specifically include consideration of an asphyxial challenge either contributing to or actually causing sudden infant death (Krous et al. 2004). They are intended to facilitate research. Another category, Unclassified Sudden Infant Death (USID), was created by the San Diego panel for "deaths not meeting the criteria for Category 1 or II SIDS, but where alternative diagnoses of natural or unnatural conditions are equivocal. This includes cases where autopsies have not been performed." It should also be noted that this new scheme also allows cases that have undergone cardiopulmonary resuscitation to be classified as SIDS. More recently, yet another classification focusing upon asphyxia contributing to or causing sudden infant death was proposed (Randall et al. 2009).

Until the mechanisms of death are completely delineated, SIDS will continue to be a diagnosis of exclusion, that is, if another cause of death is not established, then it defaults to SIDS.

Epidemiology

SIDS rates vary considerably between industrialized countries. Prior to the 1990s, SIDS rates were generally at least 1.5 deaths per 1,000 live births. Current SIDS rates per 1,000 live births in Japan, England and Wales, the United States (USA), and New Zealand have decreased to 0.09, 0.41, 0.57, and 0.80, respectively, in response to national public educational programs aimed at altering infant care practices that will reduce infants' exposure to SIDS risk factors. Nevertheless, SIDS is still the most common cause of postneonatal infant mortality.

In the USA, SIDS rates are as much as seven times the national averages among Native Americans and African Americans; increased rates are also observed among Maoris in New Zealand and Aboriginal Australians.

The recent diagnostic shift away from SIDS toward other diagnoses, especially undetermined or positional asphyxia, may partially explain plateauing of SIDS rates since approximately 2000.

Ninety percent of the cases occur primarily between 1 and 5 months of age. The male-to-female ratio is generally 2:1. Premature birth, low birth weight, lower socioeconomic class, young maternal age, and short intergestational interval place an infant at increased risk of SIDS.

Triple-Risk Model for SIDS

Introduced by Filiano and Kinney in 1994, the triple-risk hypothesis for SIDS continues to be refined as the importance of potential asphyxial challenges at the death scene and identification of an ever-widening array of serotonergic abnormalities in the brainstem have occurred (Filiano and Kinney 1994; Kinney et al. 2009a). The triple-risk model hypothesizes that a SIDS event requires the simultaneous occurrence of three factors: (1) an infant sleeping during a critical stage of development; (2) an underlying vulnerability, such as an abnormal medullary serotonergic system; and (3) the presence of an exogenous homeostatic stressor, such as prone sleeping on a soft mattress. As such, SIDS is not a specific cause of death in normal infants, but occurs only in vulnerable infants who have an underlying abnormality. For example, supine as opposed to prone sleep position is protective against SIDS since the exogenous stressor (e.g., facedown position) is removed allowing the vulnerable infant to safely pass through the critical period.

Risk Factors

Factors that increase an infant's risk of SIDS are divided into extrinsic and intrinsic categories. Extrinsic risk factors are physical stressors that could expose a vulnerable infant to asphyxia or another homeostatic derangement and include side or prone sleep position, soft bedding, bed sharing, and mild infections, including colds. Conversely, intrinsic factors increase an infant's risk of SIDS by their effect on its underlying vulnerability with medullary serotonergic deficiency being perhaps the most important (see below). Intrinsic risk factors are divided into genetic and developmental groups; the former includes male sex, possibly polymorphism in the gene encoding the promoter region of the serotonin transporter, and African–American or Native American ethnic groups, while the developmental group includes premature birth, cigarette smoke exposure, parental ethanol intake or drug use, and disadvantaged socioeconomic status. It should be emphasized that cigarette smoke exposure increases SIDS risk whether it be prenatal, gestational, and/or postnatal and is becoming increasingly important given the decline in the incidence of prone sleep position. At the same time, bed sharing has emerged as an increasingly important SIDS risk factor given its progressively increasing incidence.

National educational programs, such as the Back to Sleep campaign in the USA and Reduce the Risk campaign in Australia, have led to dramatic decreases in SIDS rates by altering infant care practices to avoid potentially asphyxial sleeping conditions.

Pathology

General Findings

There are a variety of findings in the majority of SIDS cases that are neither specific nor explain the cause of death. The blood is typically liquid and the bladder is empty. Oronasal secretions are common. Gastric contents may also be observed on the infant and/or the bed surface at the site of its face when found. Evidence of acute trauma is not identified. Rather commonly observed microscopic findings include pulmonary and visceral congestion, focal mild pulmonary edema, and mild focal interstitial lymphocytic infiltrates in the tracheobronchial tree and pulmonary interstitium. Focal atelectasis is also often identified. Significant stress changes are not seen in the thymus and adrenal cortex.

Medullary Serotonergic Deficiency in SIDS

The triple-risk hypothesis requires that a SIDS infant must be vulnerable as a result of an underlying abnormality. Discovery of abnormalities in serotonin (5-HT) metabolism in the medulla is perhaps the most important underlying vulnerability that increases an infant's risk of SIDS. The reader is referred to comprehensive discussions of serotonin (5-HT) abnormalities in SIDS provided by Kinney et al that are beyond the scope of this chapter (Kinney et al. 2009a). Briefly, extensive data support the hypothesis that SIDS represents the convergence of numerous factors primarily involving 5-HT-mediated mechanisms in the medulla. 5-HT neurons in the medulla modulate breathing, blood pressure, temperature, and arousal by detecting CO_2 levels and altering hypercapnic and hypoxic responses. Thus, SIDS is currently viewed as a consequence of the simultaneous intersection of a critical period of infant development during sleep, exogenous stressors, and dysfunctional and/or immature cardiorespiratory and/or arousal systems involving abnormal 5-HT mechanisms. A SIDS event might be characterized, for example, by the combination of an infant with an abnormal medullary 5-HT system during a critical phase of development and an asphyxial challenge while sleeping face down on a soft sleep surface. Hence, the importance of investigating and reconstructing the death scene for possible asphyxial challenges in cases of sudden infant death is immediately obvious.

Intrathoracic Petechiae

Despite the frequent presence of minor pathologic findings in SIDS cases, routine autopsies supplemented by current ancillary studies do not identify a specific cause or mechanism of death. Intrathoracic petechiae are the most common naked-eye finding, but their presence is neither pathognomonic nor does their absence exclude a diagnosis of SIDS. Their distribution suggests they occur as a result of agonal breathing against an obstructed upper airway (or deep gasping) as opposed to external oronasal obstruction (Krous 1984; Poets et al. 1999). Conjunctival and scleral petechiae are not a feature of SIDS, and their presence should prompt investigation for an asphyxial cause of death. In contrast to the intrathoracic localization in SIDS, petechiae simultaneously affecting the serosal surfaces of

the pleural, pericardial, and peritoneal cavities collectively may be seen in infections, coagulopathies, and severely disordered acid–base imbalance.

Infection

Although a history of upper respiratory infections, microscopic inflammatory infiltrates in the airways and lungs, and positive postmortem bacterial cultures are common in SIDS, their rates are not different from those cases who had died of accidental or inflicted suffocation control cases (Krous et al. 2003). In other studies, *Staphylococcus aureus* or *Escherichia coli* have been isolated significantly more often from postmortem cultures taken from SIDS cases than from infants dying suddenly without clinical evidence of infections and suggested these organisms may be important in triggering the fatal sequence of events (Weber et al. 2008b). Given the inflammatory infiltrates are typically lymphocytic, it is not surprising that a variety of viruses have been isolated from SIDS cases. However, given the mild and focal nature of these lymphocytic infiltrates, they are rarely considered to be the cause of death. Activation of the mucosal immune system in subsets of SIDS cases compared to controls, perhaps in response to minor infections, has been proposed on the basis of immunohistochemical studies of selected tissues.

Oronasal Blood

Oronasal secretions, often pink in color, are a common observation in SIDS cases. In contrast, oronasal blood (ONB) *in the absence of, or prior to, cardioplumonary resuscitation (CPR)* is rarely observed, being described in only 1 (0.3 %) of 300 SIDS cases found supine and alone in a safe crib (Krous et al. 2001). Conversely, ONB is common in cases of attempted but unsuccessfully inflicted suffocation as shown in a study wherein it was observed in 11 of 38 patients undergoing covert video surveillance for a history of acute life-threatening events, but none of 46 controls (Southall et al. 1997). ONB was described in less than 10 % of all of the cases in the San Diego SIDS/SUDC Research Project database and could not be attributed to resuscitative efforts among 14 of 28 cases including only 10 of 300 SIDS cases, 2 of 14 accidental suffocation cases, and 2 of 13 undetermined cases. ONB in the absence of attempted CPR suggests local origin from oronasal skin or mucus membranes; therefore, postmortem otoscopic examination of these tissues is recommended. Since very little blood arising from the lungs is required to stain oronasal secretions some shade of pink, one should not automatically assume that their reddish color is a result of local oronasal hemorrhage from mucus membranes that were traumatically damaged in an effort to inflict death by suffocation.

Pulmonary Intra-alveolar Siderophages

Pulmonary intra-alveolar siderophages (PS) form as a consequence of intra-alveolar hemorrhage at least 48 h prior to death; PS have been proposed as a morphological marker to identify past efforts to suffocate an infant. Therefore, some investigators have suggested that when PS are present in large numbers, SIDS is an inappropriate diagnosis, especially when other potentially lethal findings are absent. We were unable to confirm this view after retrospective assessment of siderophages in

iron-stained lung sections in 91 SIDS cases and 27 cases of accidental and 2 cases of inflicted suffocation (Krous et al. 2006). Only 6 % of each group had a history of prior apparent life-threatening events and approximately three fourths of the families from both groups had no prior referral to Child Protective Services. The number of PS varied widely in the SIDS and suffocation control cases. The medians of the PS counts were not significantly different between the SIDS and control suffocation groups, but the range was wider in the SIDS group. Thus, it is apparent that PS cannot be used as an independent variable to unequivocally confirm previous attempts at suffocation (Krous et al. 2006).

Pulmonary Intra-alveolar Hemorrhage

Pulmonary intra-alveolar hemorrhage (PAH) has also been suggested as a morphological marker of suffocation. Again, we were unable to provide confirmation of this hypothesis in our study wherein we compared the severity of pulmonary hemorrhage in 34 SIDS cases that were found supine, alone, and on a safe sleep environment, with 40 cases of suffocation that was either accidental (37 cases) or inflicted asphyxia (3 cases) (Krous et al. 2007a). Importantly, age and the duration of CPR and postmortem interval had no effect on the severity of PAH in SIDS.

Aspiration of Gastric Contents

The finding of gastric contents on the faces of infants dying suddenly and unexpectedly or on the sleep surface where their faces were when they were discovered raises the question whether they may have died as a result of gastric aspiration. It is extremely common for infants to "spit up" after feedings, but actual aspiration is rare in neurologically intact infants. Resuscitative efforts can force gastric contents into the distal lung parenchyma and can confound the interpretation of this finding. Additionally, gastric contents through their effect on pH-sensitive laryngeal receptors are capable of causing laryngospasm and upper-airway occlusion that may be lethal. Incidentally, it is important to separate gastric contents from clusters of bacterial colonies associated with groups of squamous cells in pulmonary alveoli; these latter materials are very commonly associated with resuscitation and should not be considered as either evidence of aspiration or a cause of death. Gastric contents in the lungs are occasionally observed microscopically in SIDS cases, but their significance has received limited attention. Efforts at CPR prior to death can force gastric contents from the pharynx into the distal lung after death thereby confounding interpretation of their significance at autopsy and has rarely been considered in previous studies. In our study of 69 SIDS cases that had not undergone CPR prior to death, only 10 (14 %) revealed microscopic evidence of gastric aspiration, but these cases were not otherwise clinically or pathologically different from SIDS cases without gastric contents in their lungs. This finding suggests that gastric aspiration may be a terminal event that a subset of SIDS cases cannot overcome (Krous et al. 2007b). In the final analysis, the significance of gastric contents in distal airways and alveoli requires careful consideration of the medical history, circumstances of death, and all of the postmortem findings, especially those that may be present in the central nervous system.

Disorders Mimicking Sudden Infant Death Syndrome

Asphyxia

The complex relationship of SIDS and asphyxia has been reviewed in detail elsewhere (Krous and Byard 2011). Characterized by simultaneous inadequate oxygen and excessive carbon dioxide in the blood, asphyxia can cause death at any age. The lack of pathognomonic postmortem markers makes the diagnosis of asphyxia difficult not only in adults but even more so in infants. The combination of facial and conjunctival petechiae can be found at autopsy in asphyxiated individuals but are less common in infants than adults. Florid cutaneous petechiae of the face and upper body suggest possible chest and/or neck compression (Oehmichen et al. 2000). The small size and lack of muscle strength of infants render them vulnerable to accidental or deliberate asphyxiation. Bruises or abrasions that might assist in determining the circumstances surrounding the lethal episode are usually not present. Also, less pressure is necessary to occlude the external oronasal airways of infants compared to adults and older children given their softer nasal cartilages and increased mandibular mobility. Consequently, markings on the skin may not be present in infants dying as a result of accidental or inflicted suffocation.

The limited range of activities during infancy dictates that the most common types of asphyxial deaths involve feeding and sleeping accidents including smothering. Certain factors such as soft abundant bedding, young infant age, larger adult(s) body mass compared to infants, and caretaker intoxication, sedation, or fatigue can increase an infant's risk of asphyxiation while bed sharing with adults. Other causes of infant asphyxiation are wedging, head entrapment in a plastic bag, foreign body aspiration, air displacement by noxious gases, and hanging (see ▶ Chap. 9, "Pediatric Asphyxial Deaths").

Cardiac Channelopathies

Cardiac sodium and potassium ion channel mutations leading to prolongation of the QT interval cause 2–5 % of sudden unexpected infant deaths (Tester and Ackerman 2005). To date, mutational analyses have revealed approximately 103 distinct mutations in the sodium channel gene SCN5A (Moric et al. 2003). Confirmation of the diagnosis requires either characteristic findings on an antemortem electrocardiogram, which is rarely available, or molecular testing of blood or fresh tissues taken at autopsy. Electrocardiographic demonstration of long QT intervals in either parent may be helpful, but negative results do not exclude the diagnosis in infants since approximately half of the cases of long QT syndrome are the result of a new mutation (see ▶ Chap. 31, "Cardiac Channelopathies and the Molecular Autopsy").

Metabolic Disorders

It is now estimated that approximately 5 % of sudden infant deaths are a result of metabolic disorders, especially those disrupting energy metabolism and glucose homeostasis (Boles et al. 1998). The various forms of disordered fatty-acid

oxidation are the most frequently encountered, and among these, medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common. Very-long-chain acyl-CoA dehydrogenase deficiency, long-chain acyl-CoA dehydrogenase deficiency, and short-chain acyl-CoA dehydrogenase have also been documented in cases of sudden infant death. Other diseases that can cause sudden infant death are defects in carnitine uptake and glutaric acidemia type 2 (Boles et al. 1998). Conversely, disordered amino and organic acid metabolism are rarely associated with sudden unexpected death; rather death associated with these disorders is typically preceded by varying periods of clinically evident deterioration. Blood and/or filter paper blood spots obtained either shortly following birth (newborn blood spot) or at the time of autopsy can be comprehensively and inexpensively tested by tandem mass spectrometry to establish these diagnoses (see ▶ Chap. 34, "Pediatric Metabolic Diseases").

Miscellaneous

Other causes of sudden infant death (discussed elsewhere in this text) include, but are not limited to, congenital malformations, especially obstructive lesions of the left side of the heart, as well as cardiac neoplasms, myocarditis, sepsis, abusive head trauma, and accidental or inflicted suffocation (Krous et al. 2005b).

Sudden Unexplained Death in Childhood (SUDC)

We have defined SUDC as "the sudden death of a child *older than one year of age* which remains *unexplained* after a thorough case investigation, including review of the clinical history and circumstances of death, and performance of a complete autopsy with appropriate ancillary testing" (Krous et al. 2005a).

Our initial analysis of 36 cases (Krous et al. 2005a) suggested a tentative SUDC profile: 1–3-year-old toddlers who are predominantly male and born at term as singletons and have an occasional history of recent minor head trauma. A family history of SIDS or SUDC is occasionally obtained. Death is apparently associated with sleep. Most are found prone, often with their face straight down into the sleep surface. Minor findings are commonly seen at postmortem examination, but they do not explain their deaths.

Remarkably, a personal and/or family history of seizures may be associated with a fever and hippocampal abnormalities; a linkage that has been confirmed in our subsequent analyses (Kinney et al. 2007, 2009b). In our first report of this association, all five SUDC cases died unexpectedly during the night, apparently during sleep; within 48 h before death, two toddlers had fever, three had a minor upper respiratory tract infection, and three sustained minor head trauma without loss of consciousness (Kinney et al. 2007). Two (40 %) had a history of febrile seizures and two (40 %) had a family history of febrile seizures. Their hippocampal findings included external asymmetry and two or more microdysgenetic features, the latter consisting of marked hyperconvolution and/or focal duplication of the dentate gyrus, granular nodular heterotopia, hamartia in the

hippocampus proper, residual subventricular neuroblasts, abnormal subicular folding, columnar ("fetal-like") cortex in the adjacent temporal lobe gyri, and excessive interstitial neurons. Miscellaneous findings included focal clustering of pyramidal neurons in Ammon's horn and disorganized islands of Calleja. Based on these findings, we proposed that there is a potential subset of SUDC cases whose sudden death is caused by an unwitnessed seizure arising during sleep in the anomalous hippocampus and producing cardiopulmonary arrest. Precipitating factors may be fever, infection, and/or minor head trauma. Suggested risk factors are a personal and/or family history of febrile seizures. We subsequently reported 64 children aged 1.0–5.9 years (median 1.7 years) who were divided into groups based upon a history of febrile or nonfebrile seizures, familial febrile seizures, and autopsy classification of cause of death (Kinney et al. 2009b). Forty-nine (77 %) were classified as SUDC, of whom 40 % had a personal and family history of febrile seizures. Of the 26 SUDC cases with available hippocampal sections, 19 (62 %) had hippocampal and temporal lobe anomalies, including 82 % (9 of 11) cases with a personal and/or family history of febrile seizures. Cases with these anomalies were all found dead during a sleep period, and 87 % were in the prone position. The mechanism of death appears analogous to sudden death in (temporal-lobe) epilepsy, with a putative unwitnessed seizure during sleep leading to airway occlusion and death.

Given these findings, postmortem evaluation must include determination of a personal and/or family history of seizures that may be associated with a fever as well as careful bilateral hippocampal examination for asymmetry and microdysgenesis.

Insufficient information exists at this time to provide definitive general recommendations to the public that might reduce the overall incidence of SUDC. However, available data do suggest the importance of careful evaluation and consideration of prescription of antipyretics to toddlers with a fever and who have a personal and/or family history of febrile seizures.

Disorders Mimicking SUDC

There are a variety of disorders and conditions that can cause sudden unexpected death in childhood. Two thirds of 50 cases of sudden unexpected death in childhood initially reported from the San Diego SIDS/SUDC Research Project database comprised SUDC; the remainder had explained causes of death including, but not limited to, accidental asphyxia, sepsis, lymphocytic myocarditis, eosinophilic myocarditis, probable fatty-acid oxidation disorder, disseminated intravascular coagulation complicating an infectious febrile illness, arrhythmogenic right ventricular dysplasia, and brainstem encephalitis (Krous et al. 2005a). Benign and malignant neoplasms, parainfluenza virus-1-induced laryngotracheitis, viral meningitis, and meningioangiomatosis are other documented causes of sudden unexpected death in childhood. Aspirated foreign objects and abusive head trauma can also be lethal to toddlers.

Manner of Death

The manner of death in cases of sudden unexplained death in infancy and childhood varies among certifiers. If unexplained after review of all of the available information, then "undetermined" is the most defensible despite a tendency for some to use "natural" in cases of SIDS and SUDC.

Conclusion

Sudden unexpected death occurs in infants and young children alike. In both age groups, establishing the cause and manner of death often presents a difficult but important challenge. If the cause of death is not established after comprehensive postmortem evaluation, then it generally defaults to SIDS in infants and SUDC in children beyond the first birthday. In recent years, improved death scene investigations have led to a justifiable diagnostic shift in cases of sudden unexpected infant death away from SIDS toward undetermined or positional asphyxia (suffocation); these improved death scene reconstructions illuminated the possibility of asphyxia contributing to or causing death. The triple-risk model hypothesizes that SIDS results when a sleeping infant at a critical stage of development rendered vulnerable by an underlying abnormality, such as those now documented in the medullary serotonergic system, experiences a risk factor that typically is asphyxial in nature. Large-scale education campaigns, such as the Back to Sleep campaign in the USA, have succeeded in dramatic reductions in SIDS rates as a result of altering infant-care practices such that dangerous sleeping conditions are avoided.

That a diagnostic shift has occurred in cases of sudden unexpected infant death is appropriate given recent improvements in death scene investigation and reconstruction. Nevertheless, it is important to remember that only a very small percentage of infants sleeping in a potentially unsafe environment actually die. The evidence now strongly points toward the necessity of an underlying infant vulnerability, the most important being abnormalities in the medullary serotonergic system, coupled with a coexistent critical stage of development, sleep, and presence of risk factor(s) in order for SIDS to occur. SIDS is not simply the lethal consequence of an unsafe sleep environment leading to asphyxia but rather all elements in the triple-risk model must be met. Absent the critical state of development, sleep state, and underlying vulnerability, positional asphyxia can become the cause of death provided the scene substantiates the lethality of the sleep site.

Sudden *unexplained* death in childhood (SUDC) appears to be the most common cause of sudden *unexpected* death in toddlers. In contrast to the developmental stage and pathophysiology associated with SIDS, evidence is mounting that a significant proportion of SUDC cases represent a potentially new entity defined by sleep-related death in the prone position, personal and/or family history of seizures that are often febrile, and hippocampal and temporal-lobe abnormalities.

Accurate determination of the cause and manner of sudden unexpected death of infants and toddlers alike requires comprehensive review of the medical and family history, reconstruction of the death scene with evaluation of the circumstances of death, and thorough autopsy examination with extensive ancillary studies. The latter are particularly important when a cause of death is not apparent from the scene and/or the gross autopsy examination. Understanding of and adherence to widely accepted definitions in the certification of sudden infant and childhood death are important as well as advancing collection of accurate vital statistics, grief counseling, and research.

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Pediatric Asphyxial Deaths

9

Andrew M. Baker

Contents

Abstract

Investigating possible asphyxial death in infants and young children poses numerous challenges. Although the very young can die from almost any type of asphyxial death, some asphyxial deaths are unique to this age group. In many infant and young-children asphyxial deaths, the proper recognition of the cause of death will rest heavily on the history and scene investigation, since autopsy findings may be minimal and nonspecific. Although presumably rare, intentional asphyxiation of infants in most cases remains almost impossible to distinguish from "SIDS", sudden unexplained infant death (SUID), or accidental asphyxiation.

Introduction

Asphyxia, most broadly defined, is the inability of the body or brain to obtain oxygen or the inability of cells to utilize oxygen. As such, asphyxia represents the final common pathway of a variety of causes of death ranging from suffocation

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and strangulation to chemical asphyxia. Though infants and small children can die from almost any type of asphyxia, the small size and developmental immaturity of infants results in some types of death (overlaying, wedging) that are unique to this age group. Compounding the difficulty of such cases is the absence or nonspecificity of autopsy findings in most instances. Accurate determination of the cause and manner of death for asphyxial deaths in children, and particularly infants, requires a clear understanding of the scene and investigative findings. Death investigators and law enforcement officers evaluating such deaths must understand that the autopsy alone is unlikely to prove or disprove asphyxia in most cases. A great deal of overlap exists in "gray zone" cases that appear to be potentially, though not conclusively, asphyxial in nature. The reader is referred to other chapters in this text for a discussion of such cases. In instances where a child's asphyxial death is brought about by an aspirated object or a mechanically defective device, it is incumbent upon the pathologist to ensure the case is further investigated by the appropriate regulatory or investigative authorities.

Asphyxia

Asphyxia is defined as inadequate oxygenation of the tissue. It is the common endpoint in a variety of deaths in which the cells either fail to receive or are unable to utilize oxygen. Because of the innumerable pathways that can lead to an asphyxial death, the classification of asphyxia may be broad and varied. Many deaths will not fit neatly into any of the categories described below, as more than one asphyxial mechanism may come into play. The brain, although it accounts for only about 2 % of the (adult) body weight, utilizes approximately 20 % of the body's oxygen supply and is therefore particularly susceptible to asphyxia. Even after respiratory arrest has occurred and the brain is irreversibly injured, the healthy heart may continue beating for many minutes.

Each year in the United States (USA), approximately 873 children less than 14 years old die from suffocation or choking. The majority of these victims are less than 4 years old (National Center for Health Statistics 2007).

In a review of 369 cases of fatal childhood accidents, asphyxial deaths (16 %) ranked well below motor vehicle accidents (51 %) and slightly below drowning (17 %), but they were substantially more common than more "dramatic" deaths such as fires, poisoning, electrocutions, and falls (Byard 2000).

Classifying Asphyxia

Suffocation: deprivation of oxygen in the environment or blockage of the external or internal air passages

- Environmental
- Smothering
- Choking
- Mechanical
- Positional

Strangulation: Pressure on the neck

- Hanging
- Ligature
- Manual

Chemical: Prevention of transport or utilization of oxygen at the cellular level

- Carbon monoxide
- Hydrogen cyanide
- Hydrogen sulfide

Signs of Asphyxia

Petechiae are caused by an acute rise in venous pressure, resulting in the breaking of small venules (Ely and Hirsch 2000). They are most often seen externally in the conjunctivae, oral mucosa, and facial skin. Petechiae are nonspecific and can be seen in many circumstances; conversely, many obviously hypoxic deaths lack them. Petechiae can also develop in dependent areas of the body after death. Though petechiae are frequently encountered in a variety of adult deaths, they are distinctly uncommon in most infant and small-child asphyxial deaths. Congestion and edema, cyanosis, and "engorgement of the right heart and fluidity of the blood" are all nonspecific. Taken together with petechiae, these have been referred to as the obsolete pentad of asphyxia (Adelson 1974). With the exception of specific toxins (e.g., carbon monoxide), there is no laboratory test that will diagnose asphyxia.

Suffocation

Environmental asphyxia occurs due to inadequate oxygen in the environment. In children, nearly all such cases are accidental. Examples include a sudden drop in partial pressure of oxygen (such as cabin failure in an aircraft), displacement of oxygen by another gas (such as by carbon dioxide in the base of a silo or well), or being trapped in a restrictive environment (such as an older refrigerator). The autopsy in such cases would usually be negative, and so the diagnosis is made by evaluating the circumstances, scene investigation, and exclusion of other causes.

Smothering refers to external mechanical obstruction of the nose and mouth. In young children, most cases will be accidental (plastic bags are notorious in this regard in infants). Homicidal asphyxiation via smothering, such as with a hand or pillow, is discussed at the end of this chapter. In young children who are smothered

Fig. 9.1 (Doll reenactment) This infant was suffocated with a plastic bag. A breeze from an open window picked the bag up from the other side of the bed and onto the child's face. The caretaker had only left the room for a few minutes to tend to some laundry

(accidentally or otherwise), there are often no findings at autopsy. Many deaths that have a smothering component, such as *wedging* and *overlaying*, are discussed in more detail later in this chapter (Fig. 9.1).

Choking refers to blocking of the internal airways. In young children, nearly all cases will be accidental due to foreign bodies or food. When a child has choked on a foreign body, every effort should be made to ascertain where that foreign body came from so that further deaths can be prevented. This is particularly true for consumer items. Defective items that result in injury or death should be promptly reported to the Consumer Products Safety Commission (CPSC) for further investigation. Nonfood items implicated in published series of chokings include pacifiers, rattles, hardware, balls, balloons, and coins (Baker and Fisher 1980; Byard 2000) (Figs. 9.2–9.5).

Food bolus asphyxia in adults nearly always occurs in the setting of acute intoxication or neurological (sometimes psychiatric) diseases that interfere with normal eating and swallowing. Such is not the case in infants and toddlers. In cases of food bolus asphyxia, it is not uncommon for the obstructing bolus to be removed by first responders. Medical examiners and coroners should encourage their emergency response colleagues to save these food boluses so that they can be examined by the pathologist and appropriately documented.

Agonal aspiration of food into the upper airways, as part of the dying process or resuscitative efforts, is commonly encountered in adults. Experienced forensic pathologists recognize this as an artifact and not as a cause of death. Such agonal aspiration in children is generally less common and less dramatic but nonetheless should not be misinterpreted as true food bolus asphyxia.

Unlike most other forms of asphyxia, some instances of choking, because they are the result of a natural disease, may in fact be natural in manner. Epiglottitis is the most common of these, though other conditions such as Ludwig angina (a rapidly expanding bacterial infection of the submandibular and sublingual spaces), anaphylaxis with laryngeal edema, and diphtheria can also present as choking.

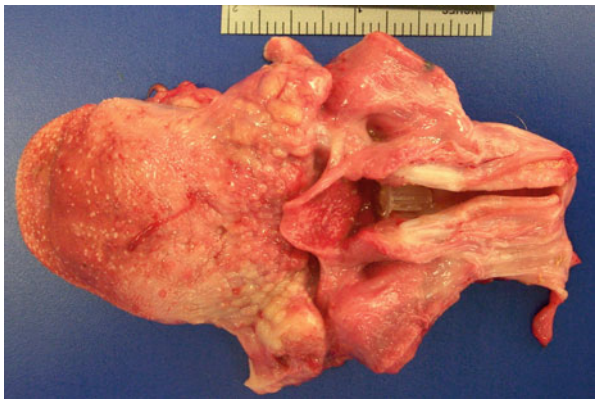

Fig. 9.2 Airway of an 18-month-old boy who choked on a plastic flange from hardware on a kitchen drawer. The item is lodged in the vocal cords and trachea

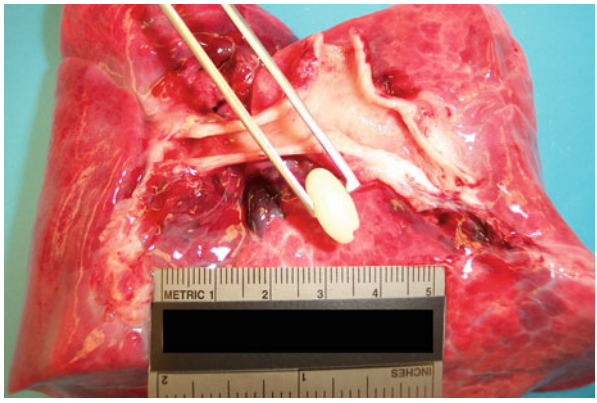

Fig. 9.3 Trachea and mainstem bronchi opened to show the bean a child choked on

Mechanical asphyxia, also known as **traumatic asphyxia**, is due to pressure on the chest and/or abdomen that restricts breathing. Though adult and older child cases often have marked congestion of the face and neck, with petechiae, findings in the very young are often minimal and nonspecific. Other types of infant asphyxia, particularly overlaying and wedging, have a component of mechanical asphyxia in the death. When the definition of mechanical asphyxia is applied narrowly, this type of asphyxia is quite rare in young children. The few published studies on this type of death in children suggest a male predilection (Byard et al. 2003). The injuries seen, which are dependent on the circumstances, vary with the offending agent. The ages of these children are typically older than the infants who die in an unsafe sleep environment or toddlers who aspirate food or toy parts and likely reflect the increased strength and mobility of this older group. Reported scenarios have included furniture (dresser) tip-overs, overturned tables, pinning between wooden pallets and an adjacent fence, and vehicular mishaps (Byard et al. 2003; Campbell-Hewson et al. 1997) (Figs. 9.6 and 9.7).

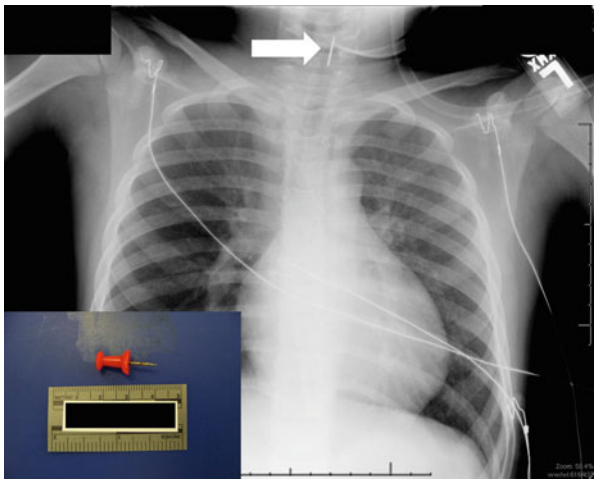

Fig. 9.4 This chest radiograph of a child that choked demonstrates a foreign body in the airway (*arrow*). The *inset* shows the plastic pushpin the child aspirated

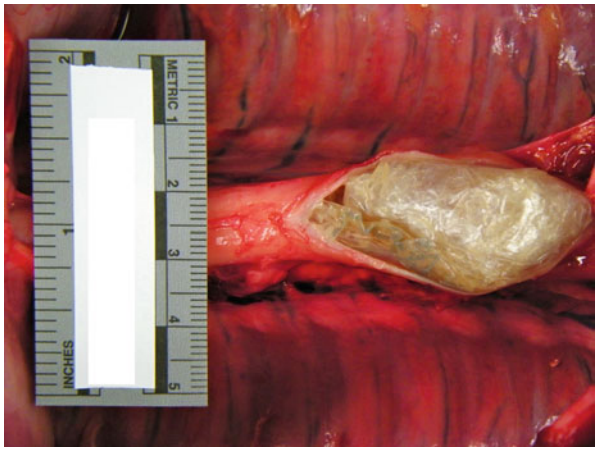

Fig. 9.5 A wad of swallowed cellophane wrap occludes the esophagus of a toddler, resulting in tracheal compression and choking

Positional asphyxia occurs when the victim is trapped or pinned in such a way that the neck is constricted, or breathing is impaired, by anatomy and/or gravity. Most cases in adults involve victims not responding to their abnormal position due to alcohol or other intoxicants or to an inability to extricate themselves due to neurological disease. Infant victims of positional asphyxia generally succumb due to their age and relative immobility (Fig. 9.8).

Strangulation

Hanging occurs when the weight of the body tightens a noose on the neck. Complete suspension is not required, as the weight of the head alone may be sufficient for internal jugular vein, and possibly carotid artery, occlusion. Thus, hangings can and do occur in kneeling, sitting, or even lying-down positions. The primary autopsy feature is the presence of a ligature furrow on the neck, with an

Fig. 9.6 Scene photograph of a bedroom where a toddler tumbled a top-heavy dresser over, compressing himself underneath it

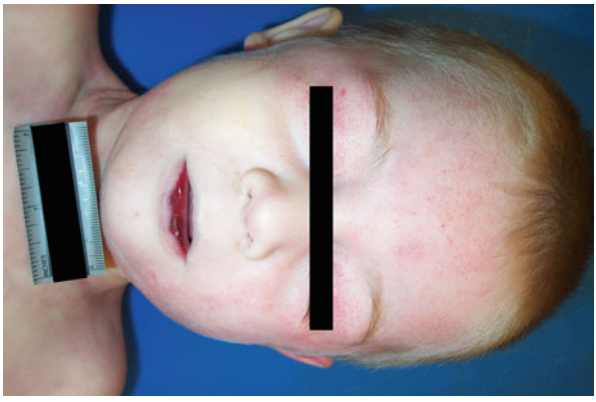

Fig. 9.7 Autopsy photograph of the child from Fig. 9.6. Note the florid forehead and periorbital petechiae

inverted "V" configuration with its apex at the point of suspension. Facial petechiae and congestion may be present, particularly with partial suspension.

Hanging deaths in young children are rare, and, even when children up to 13 years of age are included, pediatric hanging deaths will likely account for fewer than 1–6 % of all hangings seen (Cooke et al. 1989).

Fatal hangings in the very young children are often different from in adults, as the mechanism of hanging may not be a classical ligature intentionally looped around the neck. The very young can be hanged by defective cribs or cribs held together with ropes (Sturner et al. 1976), pacifier strings and ribbons (DiMaio 1973), window blind cords (Rauchschwalbe and Mann 1997), or clothing that gets caught on crib parts of furniture. In one large study of hangings and strangulations in children of all ages, 28 % of the deaths occurred in cribs; the average age in this group was 11 months (Feldman and Simms 1980). Moore and Byard (1993), comparing fatal hanging to wedgings in the very young, found the average age in the former group to be somewhat older at 18.5 months (Figs. 9.9–9.11).

Ligature strangulation occurs when the ligature on the neck is tightened by force, rather than by body weight. Autopsy features are often a congested face with

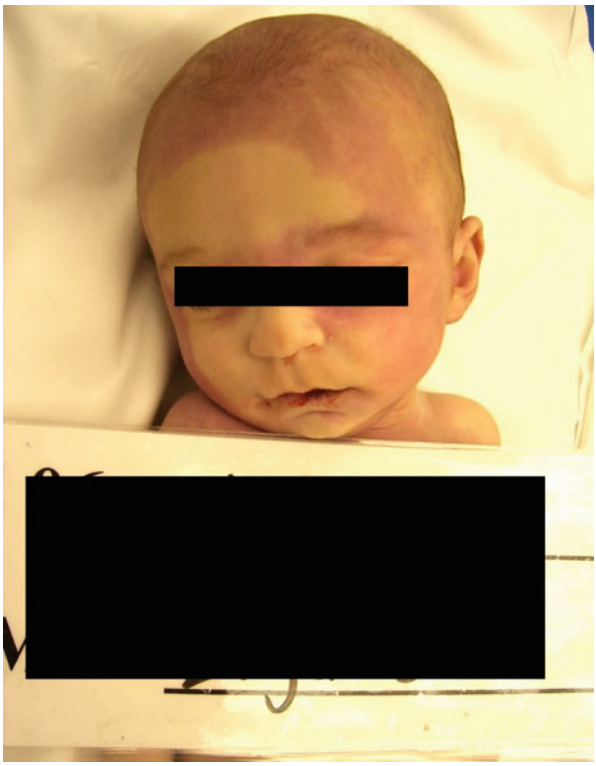

Fig. 9.8 Scene photograph of a deceased infant showing a clear lividity pattern. Such documentation is very helpful in assessing positional asphyxia

Fig. 9.9 A toddler was hanged by a shoelace his older siblings had used as a stirrup to get into a bunk bed

scleral and conjunctival petechiae and a ligature mark on the neck that is relatively horizontal. True ligature strangulations, when using the definition as applied to adults, would be very rare in infancy and young childhood, although many

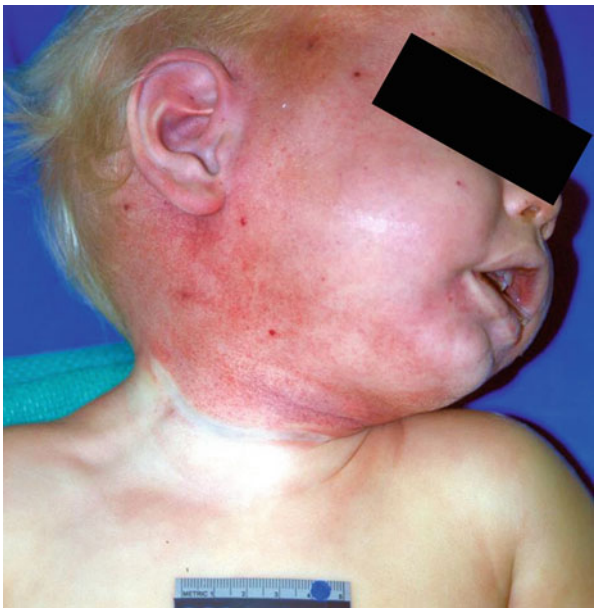

Fig. 9.10 The autopsy findings perfectly mimic an adult hanging: a ligature furrow, facial plethora, and florid petechiae

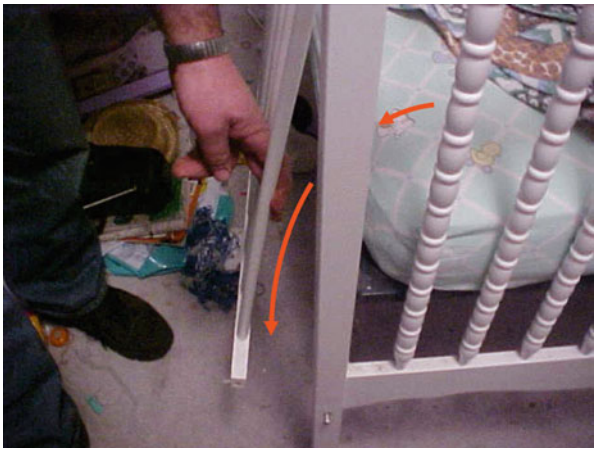

Fig. 9.11 Scene photograph of a crib in which a toddler was fatally hanged. Broken hardware on the bottom of the crib allowed the child to slip between the mattress and end of the crib (*arrow*), compressing his neck against the mattress

asphyxial deaths in this age group will have some of the mechanistic features of ligature strangulation (Fig. 9.12).

Manual strangulation refers to a hand or forearm occluding the neck vessels or airway. Virtually all cases are homicides. Findings typically seen in adult victims include a congested face with scleral and conjunctival petechiae, abrasions and contusions of the neck and chin skin, strap muscle hemorrhage in the neck, and

Fig. 9.12 Scene photographs (doll reenactment) demonstrating how an 11-month-old was fatally strangled in his crib. The bolt holding the corner of the crib together was missing

hyoid bone or thyroid cartilage fractures. Manual strangulation in infants and young children is extremely rare.

Chemical

Carbon monoxide (CO) poisoning occurs when a victim is exposed to the incomplete combustion of carbon-containing fuel. CO competes with oxygen (O_2) for binding by hemoglobin (hemoglobin has 250–300 times more affinity for CO than for O_2). Autopsy findings include "cherry red" lividity and bright red coloration of the fingernail beds, blood, muscles, and viscera. In fire deaths, soot may be seen in the trachea, bronchi, esophagus, and stomach. CO is not produced by decomposition and is not appreciably absorbed after death. Confirmation of the diagnosis can therefore be made by laboratory measurement of hemoglobin–CO saturation.

Much rarer in children are cases of hydrogen sulfide inhalation or cyanide ingestion/inhalation. The former has been described as exhibiting green discoloration of lividity and the internal organs at autopsy in some cases. Scene investigation and air testing may be required, as the thiosulfate in blood or tissues may dissipate with delay in specimen collection or testing. Cyanide can produce bright red lividity similar to that seen in CO deaths and is reported to give off an odor of "bitter almonds" (though not everyone is able to smell it). Elevated blood cyanide levels can be confirmed with appropriate laboratory testing (Figs. 9.13 and 9.14).

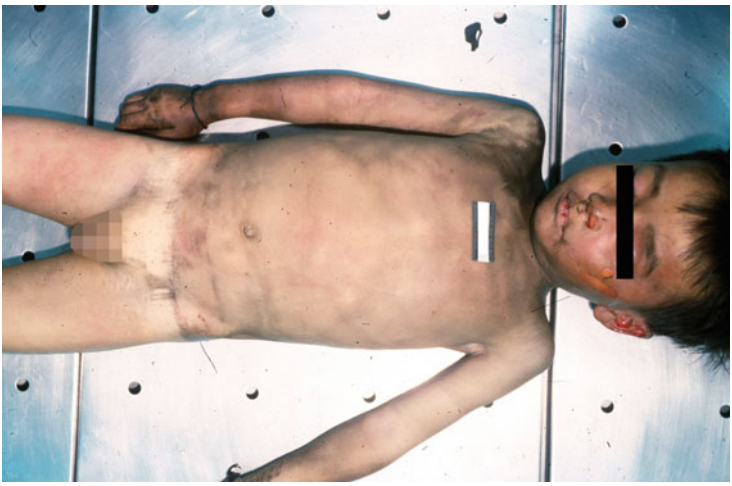

Fig. 9.13 Autopsy photograph of a boy who died from smoke inhalation in a residential fire. Soot is present on many body surfaces as well as on the lips and in the nares

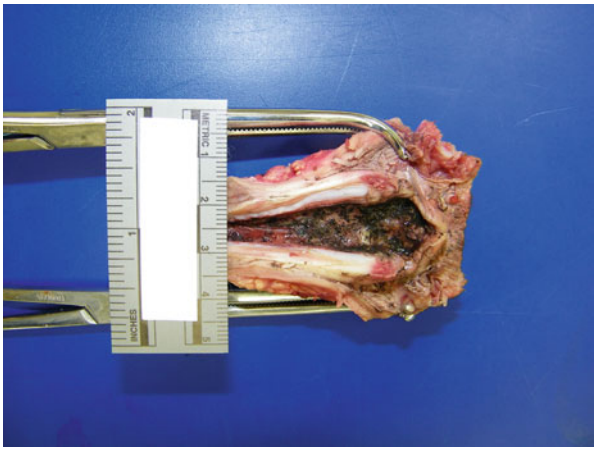

Fig. 9.14 Photograph of the larynx and trachea of a toddler who died in a house fire. Abundant soot coats the mucosa

Unsafe Sleep Environments

As in adults, young children can suffer death by nearly any asphyxial mechanism. In reality, however, there are certain types of asphyxia (choking, smothering, strangulation) to which young children are especially prone due to their small size and/or developmental level. Some types of asphyxia, such as *wedging* or *overlaying*, are virtually unique to the small child and occur in the sleeping environment.

Fig. 9.15 Scene photograph (doll reenactment) demonstrating how a mother recalled taking her infant to bed with her. She awoke later with the child underneath her. Such reenactments are critical in investigating infant deaths where overlaying, SIDS, and SUID are being considered

Fig. 9.16 Scene photograph (doll reenactment) demonstrating how a father recalled taking his infant to sleep with him on the couch. He awoke later with the child underneath his arm, face firmly planted in the cushions of the couch

Overlaying occurs when a larger individual is sleeping on an infant. It represents a complex form of asphyxia that includes airway obstruction, thoracic and abdominal compression, and impairment of neck circulation (Collins 2001). In most instances, autopsy findings will be minimal. Nonspecific findings may include indentations or "pressure marks" on the skin related to bedding or clothing. Because the autopsy is usually negative, it is difficult to separate overlaying from other forms of suffocation (including intentional suffocation). History and scene investigation are therefore critical (Figs. 9.15 and 9.16).

Wedging occurs when the infant (or, more rarely, an older child) is trapped or caught between two objects, such as a mattress and side rails of a crib; between the slats of a crib; or between a mattress and an adjacent wall. Although injuries such as abrasions

Fig. 9.17 Scene photograph (doll reenactment) and autopsy photograph demonstrating how an infant who was cosleeping with her adolescent siblings became wedged in the gap between mattress and the wall

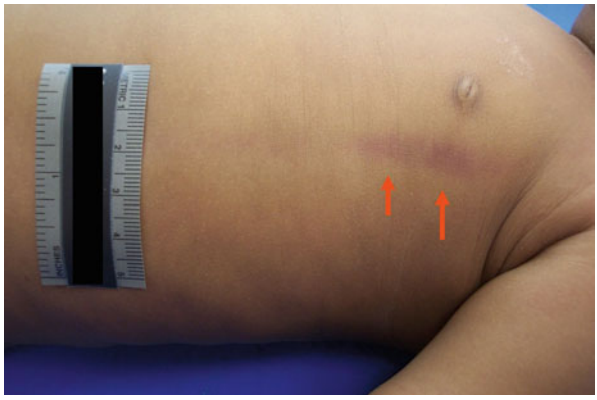

Fig. 9.18 The only finding at autopsy was a nonspecific red mark on the chest (*arrows*)

or contusions may occur from the agents causing the wedging (such as patterned imprints or impressions from furniture fabric, or indentations corresponding to edges and corners of cribs or mattresses), autopsy findings are usually nonspecific. Lividity pattern, if well documented, may offer a clue as to position. As with all pediatric asphyxial deaths, scene investigation is of paramount importance (Figs. 9.17–9.29).

Fig. 9.19 Scene photograph (doll reenactment) demonstrating how an infant who was cosleeping with his parents became wedged in the gap between mattress and the wall

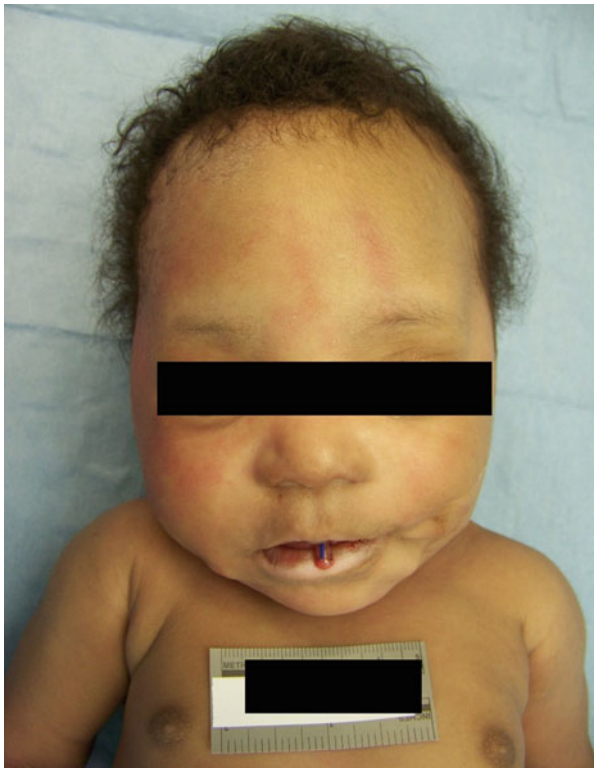

Fig. 9.20 The only findings at autopsy were nonspecific red marks on the forehead

Fig. 9.21 Unsafe sleep environment (doll reenactment) in which this infant slid off the pillow intended for her comfort, resulting in airway occlusion

Fig. 9.22 Unsafe sleep environment (doll reenactment) in which the infant was cosleeping with his parents and rolled or was pushed out of bed in the night, asphyxiating in the pile of plastic bags and other refuse

Fig. 9.23 Unsafe sleep environment in which an infant was cosleeping with her mother. The mother woke up on top of the deceased child. Note the large stain of "purge fluid" on the bedding

Fig. 9.24 Additional scene photograph from the preceding case. Note that a bassinet was available, but clearly not used for infant sleep

Fig. 9.25 Unsafe sleep environment (doll reenactment) in which the infant was left to sleep alone on a couch and rolled into the space where the seat and back cushions meet

Fig. 9.26 Unsafe sleep environment (doll reenactment) in which the infant was placed prone on soft bedding between two pillows

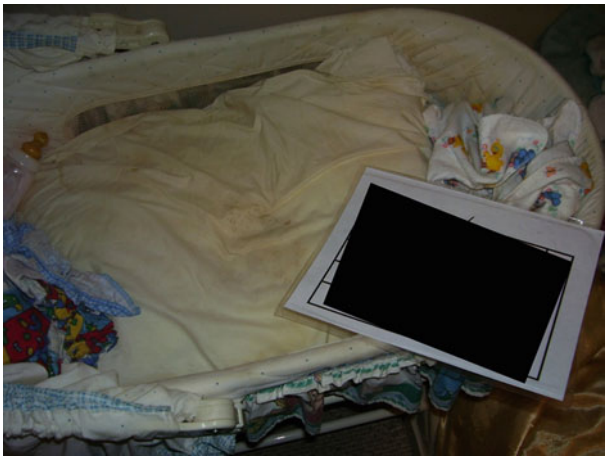

Fig. 9.27 Unsafe sleep environment in which the parents placed an adult pillow into the infant's bassinet. The deceased child was found prone with her face occluded by the pillow

Fig. 9.28 Unsafe sleep environment (doll reenactment) in which the infant was cosleeping with her parents and either rolled off, or was pushed off, the bed onto the quilt wedged into the gap between the bed and the wall

Fig. 9.29 Scene photograph (doll reenactment) in which twin infants were sleeping on an inflatable mattress that was known to leak. As the mattress collapsed, one of the twins rolled into the collapsed area and asphyxiated

Homicidal Pediatric Asphyxia

In most homicidal pediatric asphyxiation deaths, the victims are very young, the child is smothered, and autopsy findings are minimal or absent. The smothering agent may be a pillow, blanket, hand, sheet of plastic wrap, or innumerable other items. The incidence of actual infanticide cases mistakenly designated as sudden infant death syndrome (SIDS) or similar terminology is presumed to be quite low, but estimates vary (American Academy of Pediatrics et al. 2006).

Many cases come to light only after a confession or when multiple children die in the care of the same caretaker. In the investigation of a homicidal asphyxiation of a child, if it is even recognized, three questions often loom:

- How long does it take to suffocate an infant?
- Are the autopsy findings consistent with the confession?
- Do infants and small children "put up a fight"?

How Long Does It Take to Suffocate an Infant?

Obviously, there is no ethical way to study this. Confessions often contain a time estimate, but the accuracy and truthfulness of these must be interpreted with a great deal of caution. However, early work on infants suspected of having imposed airway obstruction (Munchausen syndrome by proxy, or MSBP) offers some insight when physiological monitoring is correlated with the onset of apnea.

A 4-month-old girl reportedly had nearly daily episodes of cardiopulmonary arrest, requiring resuscitation by her mother. An extensive medical work-up and trials of numerous medications were fruitless. At 7 months of age, the child underwent reevaluation with extensive physiological monitoring. Electroencephalogram (EEG) and electrocardiogram (ECG) artifact showed the infant was actively moving for 90 s after the onset of respiratory obstruction. Bradycardia ensued 30 s into the event, and the EEG slowed and then flattened after 90 s. The child was limp and apneic, requiring resuscitation. The episode was captured by covert video surveillance (CVS). The 4-year-old brother of this infant had suffered similar previous episodes since infancy and was cured when his mother was no longer allowed to be alone with him (Rosen et al. 1983).

Two children were described in whom video and electrophysiological monitoring documented the changes that occur with intentional smothering. The first was a 20-month-old who had suffered weekly cyanotic episodes since the age of 4 months. Gross movements stopped at 70 s, the EEG flatlined just after 70 s, and gasping breaths began. A second episode showed similar features, with gasping at 72 s. Covert video surveillance showed that the mother smothered the sleeping child with a T-shirt; the child "awoke immediately and struggled violently." In the second case, a 5-month-old had a similar pattern of physiological changes emerge after 71 s, and the videotape showed a struggle when the smothering of the previously sleeping infant began (Southall et al. 1987).

Is the Autopsy Consistent with the Confession?

As with many accidental asphyxiations, the autopsy alone may offer few (if any) clues as to the cause of death. Petechiae are uncommon. Meadow (1990) reviewed the cases of 27 children (18 living, 9 dead), from 27 different families, who had been suffocated. Five of the children had facial petechiae and two had bruises on the neck, while at least 14 had no external findings related to suffocation. In these 27 families, 18 of the 33 siblings born before the index case was identified had died. Thirteen of these 18 had been certified as SIDS or similar terminology.

Southall et al. (1997) reported 39 cases referred to a children's hospital after exhaustive medical evaluations for apparent life-threatening events. Using constantly monitored CVS, the authors documented abuse in 33 of the 39 cases. In 30 of the 39 cases, the abuse was intentional suffocation. Only 4 of the 30 suffocated

children had petechiae. Nasal/oral bleeding was seen in only 11 of the abused children (compared to zero instances of nasal/oral bleeding among 46 normal controls). Of 41 siblings born before the index cases, 12 had died suddenly and unexpectedly. After CVS, the parents confessed to having suffocated 8 of the 12. A number of valuable lessons emerge from these studies regarding the care and diagnostic evaluation of living children. For the pathologist charged with the postmortem examination of a dead infant, one lesson is clear: more often than not, even in a child known to have been smothered, the autopsy will not demonstrate specific physical injuries referable to intentional asphyxia.

Do Infants and Small Children "Put Up a Fight"?

Some texts, in classifying infant homicides, use the term "gentle" to describe the intentional smothering of infants. Those who have captured on film and/or witnessed such events have written:

> *Smothering has been labeled 'gentle' battering. We reject this. The video and physiological recordings showed that both children struggled violently until they lost consciousness. Considerable force was used to obstruct their airways.* (Southall et al. 1987)

> *Covert video . . . reveals the violence that smothering entails. Infants and young children struggle hard when their airways are blocked: the mothers have to lean on them with force.* (Meadow 1999)

Conclusion

In accidental asphyxiation of the small child:

- Many forms of pediatric asphyxia, particularly infant deaths from wedging, overlaying, and smothering, will, more often than not, have negative autopsies or autopsies with nonspecific findings.
- In most cases, the autopsy findings in a suffocation death of an infant (accidental or intentional) will not differ from the findings in "SIDS." Therefore, the death investigation (scene, medical history, witnesses) is of paramount importance.
- Death investigators, law enforcement officials, coroners, medical examiners, and other physicians reviewing childhood deaths should not assume that a negative autopsy alone is sufficient for a determination of "SIDS."
- The likelihood of petechiae is highly dependent on the particular type of asphyxia involved. In general, external petechiae (facial, conjunctival) are more rare in the very young child than the older child or adult.
- Childhood asphyxial deaths, particularly those that occur in the sleep environment, are largely preventable. Parents should receive instruction from their healthcare providers regarding appropriate sleep environments and sleep positioning. Both the CPSC and the American Academy of Pediatrics have specific recommendations.

- Do not dismiss pediatric asphyxias as "merely another example of one of the inevitable risks of early life. The pathologist is in an excellent position to identify these hazards and can recommend [assessment by] product safety experts" (Byard 2000).

In homicidal asphyxiation of the small child:

- Smothering of infants is the most common type of homicidal asphyxia in children, but other types do occur.
- In most cases, the autopsy findings in the intentional suffocation death of an infant will not differ from the findings in SIDS, overlaying, wedgings, and other non homicidal infant deaths. Significant nasal or oral bleeding may suggest inflicted airway obstruction but would be expected only in a minority of cases. The intentionally smothered infant may show no signs at all to even experienced forensic pathologists or clinicians (Meadow 1989).
- Physiological data and covert video surveillance from MSBP studies may help to answer some of the relevant questions in known fatal infant smotherings.

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Factitious Illness by Proxy in Children

10

Roger W. Byard

Contents

Abstract

Factitious illness by proxy in the pediatric setting refers to a situation where an adult carer, who is usually the mother, either causes or falsifies illness or injury in a child to gain medical attention and to initiate extensive investigations. It is uncommon in pediatric forensic practice. Although originally called "Munchausen syndrome by proxy," this term has been criticized, as the same apparent diagnostic term was being applied to two quite different individuals. The issue that arose concerned who was actually suffering from the syndrome: was it the individual responsible for the deception (the Munchausen component) or the victim (the proxy)? As our understanding has evolved, it has become obvious that no one really suffers from "Munchausen by proxy," as it refers to a particular set of circumstances rather than to a diagnostic entity. This is not to say that the term has

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not been extremely useful in focusing attention on certain parents who have repeatedly hurt their children to gain medical attention. However, the term should not imply that those circumstances, in themselves, constitute a specific psychological process with clearly defined, fixed criteria. The characteristic features are summarized in the following chapter in which the terms Munchausen by proxy, Munchausen syndrome by proxy, and factitious illness by proxy will be used interchangeably, given that these terms have all been used in publications.

Introduction

A number of years ago, an unusual type of abuse was recognized where a parent or carer had clandestinely either caused or simulated illness or injury in a child (Meadow 1977). The purpose of this activity was believed to be to focus medical attention on the child and family and to initiate extensive clinical investigations (Brown and Tierney 2009; Byard and Beal 1993; Mitchell et al. 1993; Schreier 2002). Initially known as Munchausen syndrome by proxy, it has had quite a contentious history subsequently, with cases being challenged in courts as to the validity of the "syndrome" as a diagnosis (*R vs. LM* 2004). Questions were asked about the nature of the condition and who actually suffers from Munchausen syndrome by proxy – the individual creating the subterfuge or the victim? (Byard 2009).

History

Asher in 1951 was the first to use the name "Munchausen" in the medical literature when he used the term Munchausen's syndrome to describe patients who regularly attended hospital emergency departments and clinics with complex, but falsified, histories of illness (Asher 1951). Their presenting symptoms were often quite convincing, and the aim of the exercise was to achieve hospital admission and treatment. The syndrome represents one manifestation of the "deception syndromes" which are characterized by simulation of illness, pathological lying (pseudologia fantastica), and wandering from place to place (peregrination) (Green et al. 1999). The name was taken from Baron Hieronymus von Munchhausen [sic], an eighteenth-century German soldier who was known to be a famous raconteur with a wide repertoire of colorful stories, many of which were clearly not true. The complicated stories told to medical staff by hospital-addicted patients with the syndrome that now bears his name were thought to mirror his "embellished" travels (Turner and Reid 2002). Unfortunately, the medical profession is often not well equipped to deal with falsified symptoms, and so the result has often been numerous unnecessary investigations and surgical procedures for the sufferer – all of which are associated with a certain level of morbidity.

Twenty-six years later, in 1977, a far more disturbing disorder was reported by Meadow which involved an adult guardian or parent putting a child forward as a proxy to initiate extensive medical investigations and treatment (Meadow 1977).

Money and Werlwas had actually reported two cases of psychosocial dwarfism that fulfilled these criteria in the previous year (Money and Werlwas 1976).

Confusion regarding terminology has occurred from the earliest days of the syndrome, with the term Polle syndrome being initially coined to refer to cases of Munchausen by proxy inflicted by a parent who was themselves suffering from Munchausen syndrome (Verity et al. 1979). Later this was modified and used synonymously with the term "Munchausen by proxy" (Clark et al. 1984) and then as the confusing "child abuse variant of Munchausen by proxy" (Liston et al. 1983). The name derived from a mistaken belief that Baron von Munchhausen had a son called Polle who died at an early age (Burman and Stevens 1977). Subsequent investigations have, however, revealed that the Baron did not have a son and that the name "Polle" instead derives from the town where his second wife had lived (Meadow and Lennert 1984). Given the changes that have occurred in our understanding of factitious illness by proxy, and the essential inaccuracy of the term Polle syndrome, there appears to be little justification to support its continued use.

Characteristics

The essential features of Munchausen syndrome by proxy were summarized by Rosenberg in 1987. These involve the fabrication of an illness, or the induction of a genuine illness, in a child by a carer (usually the mother). Illness is used in this context to refer to chronicity in the behavior and not to just a single episode in isolation. Cases are characterized by repetitive attendance at medical facilities for examinations, investigations, and treatment. Other features that are typical are the complete absence of symptoms and signs, or a dramatic improvement in the illness, if the offending carer or parent is absent, and a complete denial by the perpetrator of any involvement in the child's ill health when confronted. There has also been a significant mortality rate reported in the literature (Rosenberg 1987).

Possible Presentations

The range of possible presentations of factitious illness by proxy is extremely varied as the symptoms and signs may be entirely falsified or they may result from clandestine activity/injury, both designed to initiate extensive and often invasive medical investigations (Galvin et al. 2005). In 75 % of published cases, the illness has actually been created (Meadow 1985; Rosenberg 1987). Parental activity has included falsifying sweat tests and stool fat analyses; adding human or animal blood or protein to urine or fecal samples; injecting saliva, vaginal secretions, or feces; injecting insulin or petroleum distillates; poisoning or administering psychotropic drugs, laxatives, or warfarin; scratching or pricking the skin; exsanguinating; and manual suffocation (Galvin et al. 2005; Halsey et al. 1983; Hvizdala and Gellady 1978; Kohl et al. 1978; Lee 1979; Malatack et al. 1985;

Orenstein and Wasserman 1986; Samuels and Southall 1992; Saulsbury et al. 1984; Shnaps et al. 1981; White et al. 1985). Parents may falsely claim that their child suffers from allergies, reflux, or epilepsy, or has been the victim of sexual abuse (Barber and Davis 2002; Meadow 1993). Hospital staff may also become unwitting participants in the process if extensive testing is undertaken because factitious illness by proxy has not been suspected (Donald and Jureidini 1996; Jureidini et al. 2003; Zitelli et al. 1987; Squires and Squires 2010).

Perpetrator

Almost all reported cases have shown the perpetrator to be the child victim's mother (Meadow 1984b, 1990). Although only a small number of cases have involved fathers (Makar and Squier 1990; Meadow 1998; Morris 1985; Samuels et al. 1992), it is likely that some collusion may exist between the parents. In cases where the child has been hospitalized, the mother typically gets on well with staff and may have some medical knowledge.

One of the difficulties that has been raised in the use of terminology is that there appears to be no consistent or definable psychiatric disturbances identifiable in the mothers. There is general agreement that psychosis is usually not present; however, the literature is contradictory and incomplete in terms of other diagnoses (Emery 1986). For example, while some studies have documented a low incidence of personality disorders among the perpetrators (Rosenberg 1987), others have found this to be a feature in all cases (Samuels et al. 1992). Part of the difficulty may be the basis and criteria that were used to define what was meant by the term "personality disorder." Others have described depression, emotional disturbances, and drug addiction (Souid et al. 1998).

The psychosocial and medical background of the perpetrators has also yielded variable features. For example, although emotional, physical, or sexual abuse was found in the perpetrators in 11 of 14 cases of imposed upper-airway obstruction in one series (Samuels et al. 1992), a history of abuse in the mother may not always be found (Rosenberg 1987). Whether this reflects the problems inherent in the retrospective evaluation of medical notes is not certain. Although up to 50 % of cases have had some elements of Munchausen syndrome or abnormal illness behavior present, many cases do not (Meadow 2002).

Victim

One of the difficulties that arises, particularly in case of induced asphyxia, is in differentiating this from sudden infant death syndrome (SIDS). Generally victims of factitious illness by proxy tend to be older than infants who succumb to SIDS, with the average age at diagnosis being a little over 3 years. This compares to the majority of SIDS cases who are aged less than 9 months. Although victims of

inflicted suffocation tend to be a little younger than other cases, there is still a significant difference in the average age at death. Infants with spurious apneas usually have the first episode between 1 and 3 months of age and survive for 6–12 months after this (Meadow 1990).

The spectrum of factitious illness by proxy has expanded, with cases detected in a number of countries (Feldman and Brown 2002). The victims have included fetuses, older children, and adults in care, and a similar behavior has also been described in pet owners who repeatedly create illness and injury in their animals to obtain veterinary attention (Awadallah et al. 2005; Munro and Thrusfield 2001a, b).

Motivation

The exact motivation for this type of behavior is poorly understood, and this is probably a reflection of the very eclectic nature of cases that are grouped under this umbrella (Brink and Thackeray 2012). At one end of the spectrum, there may be an unconfident young mother who fabricates symptoms so that she can have the comfort of medical attention with reassurances that her child is fine. This contrasts with the other end, where perpetrators will not only asphyxiate children in their own family but may also harm the children of relatives and neighbors, and even adopted children. An example of this was a woman who fatally asphyxiated seven infants over a 23-year period (DiMaio and Bernstein 1974). One difficulty arises in identifying parents who may merely be genuinely over-concerned about their child's health; this is sometimes a particular problem if the child has had a significant illness in the past that resulted in intensive medical contact.

Suggestions for the motivation for these types of actions have ranged from an overly simplistic concept that it is merely a type of attention-seeking behavior to more complicated ideas that it represents the manifestation of an encapsulated behavioral disturbance akin to a "perversion" or that it is simply a form of serial killing. While diagnoses of factitious illness behavior (Munchausen syndrome) have been made in some mothers (Kucuker et al. 2010), this does not apply to the majority of the perpetrators, who usually do not have any diagnosable psychiatric illness. This suggests that the basis for the diagnosis has been established on similarities in behavior rather than in psychopathology – behavior that has been undertaken in an effort to obtain that "curious sense of purpose and safety in the midst of the disasters which they themselves have created" (Meadow 1985; Rosenberg 1987).

It is sometimes unclear whether there was a genuine intention to murder an infant or whether the lethal event occurred due to a miscalculation when the mother was attempting to increase the severity of the symptoms. Certainly this may be plausible with the first infant death, but it becomes less tenable as the death toll rises. Ambivalence in maternal feelings toward victims also suggests that there is a very complicated sequence of psychopathological processes contributing to the overall behavior other than simple secondary gain (Meadow 1995).

Pathological Presentations/Diagnosis

Both hospital and forensic pathologists may be involved in the assessment of cases. In hospitals, pathologists may be asked to examine biopsy material from particularly puzzling cases or to perform autopsies on cases where the lethal mechanism is unclear (Byard 2010). Tissues taken from patients may include liver biopsies to exclude rare metabolic disorders or skin biopsies from unusual rashes. Characteristics of such cases often include the large number of clinical services that have been consulted, the range of the differential diagnosis, the number of inconclusive tests, and the lack of agreement on the possible etiology of the presenting features. Unfortunately, the failure of treating pediatricians to recognize inflicted injury/disease means that there may have been active, albeit inadvertent, participation by the medical profession in the process, with perpetuation of the situation (Jureidini et al. 2003).

Forensic pathologists may encounter infants who have allegedly been found dead in their cribs, sometimes with a history of recurrent apneas or apparent life-threatening events (ALTEs). In these circumstances, establishing the diagnosis based purely on the autopsy findings will usually not be possible, as acute asphyxia has no pathognomonic markers (Byard 2011; Byard and Jensen 2007; Byard and Tsokos 2005). This is also true even when an infant has been repeatedly rendered hypoxic to produce significant apneic episodes (Light and Sheridan 1990; Mitchell et al. 1993).

If an infant has been suffocated without undue force, for example, under a pillow or into a soft surface such as a mattress, the autopsy findings will be indistinguishable from SIDS, with no evidence of injury, and petechial hemorrhages limited to the thoracic cavity (Mitchell et al. 2002; Moore and Byard 1993; Valdes-Dapena 1982). This absence of autopsy findings may have resulted in incorrect diagnoses of SIDS being made in a number of cases where infants were suffocated by their parents. For example, the diagnosis of SIDS in five infants in a single family must raise the likelihood of either an inherited cardiac or metabolic condition or inflicted asphyxia, particularly given that two of the children were aged 13 months and 2 years, respectively (Diamond 1986). On occasion, police investigations will uncover Internet usage by a parent who has accessed numerous websites for information on ways to murder an infant or child without leaving signs. Smothering is usually mentioned. For this reason it may be useful to have police check home and work computers in suspicious cases.

The assertion that multiple deaths in a single family are most likely due to natural causes (Carpenter et al. 2005) has been challenged, with a reanalysis of the data in the series reducing the number of "natural deaths" from 87 % to 43 % (Bacon and Hey 2007). These authors also warned that "it is misleading to classify every unexplained death as natural if no unnatural cause has been established." While it is agreed that the diagnosis of SIDS has sometimes been made too readily in the past (Emery et al. 1988), it would seem unlikely that up to 10 % (or more) of infants whose deaths were attributed to SIDS were smothered by their mothers (Meadow 1989). In the author's experience, these cases are uncommon but are less likely to be overlooked if there has been a careful interview of the parents by trained personnel, formal death scene investigation, and performance of the autopsy

according to standard protocols by a pathologist, preferably with pediatric forensic experience (American Academy of Pediatrics 2001; Byard and Krous 1999; Smialek and Lambros 1988). Despite the best investigations and intentions, however, there will always be a certain number of cases that will remain unproven or undetected.

Another form of lethal inflicted injury that usually leaves no pathological findings is poisoning. For this reason, the standard pediatric autopsy requires the taking, toxicological testing, and storing of body fluids such as blood and vitreous humor and tissues such as liver. Biochemical analysis of serum, vitreous humor, and gastric content electrolytes may also be informative in cases of lethal salt poisoning (Coe 1993; Su et al. 2010). Medications prescribed for the parents or present in the homes may guide toxicological screening and testing, and poisoning has occurred from a wide variety of drugs including phenothiazines, insulin, warfarin, antidepressants, barbiturates, laxatives, and antidiarrheal agents. Unfortunately, further issues in interpretation arise in the very young as central blood samples from the heart may not be appropriate for analysis due to postmortem redistribution, and toxic and/or lethal levels for many drugs in infants have often not been established, with standard ranges based on adult data (Byard and Butzbach 2012).

Diagnosis

The diagnosis of factitious illness by proxy is often difficult, and even when confronted with incontrovertible evidence, the response of the perpetrator is often complete denial (see "Case Report" below). The major issue with establishing the diagnosis is to ensure the safety of the victim and other children in the household. A somewhat controversial technique that has been used is in-hospital covert video surveillance which consists of setting up a hidden camera to film the interaction of the parent with the child (Hall et al. 2000). Although it has been claimed that this technique will exonerate the innocent, and while it has been used successfully to identify a number of cases of factitious illness by proxy, there has been considerable debate as to its ethical status (Anonymous 1994; Byard and Burnell 1994; Epstein et al. 1987; Foreman and Farsides 1993; Rosen et al. 1983; Shabde and Craft 1999; Shinebourne 1996; Southall et al. 1987, 1997; Williams and Bevan 1988). While observation in hospital is not guaranteed to either detect or prevent the behavior (Berger 1979), it has been estimated that in 95 % of cases events have been recorded. Criteria for the implementation of covert surveillance have been reported (Samuels et al. 1992), in addition to guidelines for the forensic evaluation of possible cases (Sanders and Bursch 2002). Potential medical liability on the part of hospitals undertaking covert surveillance in the event of an adverse outcome has also considerably limited its use in recent years. Multichannel monitoring of infants who are being smothered may be an alternative technique which typically shows evidence of obstructive apnea with considerable body movement artifact, thus dispelling any ideas that this may be considered "gentle battering."

Case Report

The following case study provides details of a family where two infants had died and the mother was filmed by covert video surveillance attempting to suffocate a third infant (Byard and Burnell 1994).

Case 1: A previously well 10-week-old girl had been found by her mother in her crib, pale and not breathing. She had been bottle-fed an hour and a half previously. Her mother initiated cardiopulmonary resuscitation resulting in shallow breathing recommencing. The infant was taken to a local hospital by ambulance where clinical examination, laboratory testing, electroencephalography, and cranial ultrasound revealed no significant abnormalities. No further episodes occurred during 2 days of in-hospital monitoring on an apnea mattress. Three days after discharge, a similar episode occurred at home resulting in readmission to the hospital where she was found to be slightly drowsy, hypotonic, and tachypneic. Tests, including toxicology, blood and urine cultures, serum electrolyte measurements, an electrocardiogram, a chest X-ray, a scintiscan for gastroesophageal reflux, and measurements of urinary amino acid and organic acid levels, were normal. She was monitored for 5 days in hospital with no further episodes and was discharged with an apnea mattress alarm.

The day after discharge she was again found by her mother apneic and pulseless after the apnea alarm had sounded. Despite attempts at resuscitation she remained ventilator dependent, with death occurring six and a half hours after her discovery at home.

At autopsy there was no evidence of injury or underlying disease that could have caused or contributed to death. Death was attributed to diffuse hypoxic-ischemic encephalopathy complicating a resuscitated apparent life-threatening event (ALTE) in a case of SIDS.

Case 2: A little over a year later, a second sibling, a previously well 8-week-old girl, was found by her mother to be pale and apneic in her stroller following a long walk. Resuscitation was not successful. At autopsy there was no evidence of injury or underlying disease that could have caused or contributed to death, and so death was attributed to SIDS.

Case 3: A year later, a third sibling, a previously well 6-week-old girl, was found pale and apneic by her mother. She was investigated in a peripheral hospital with no abnormalities being found. Two weeks after discharge, she was again seen at the hospital following a further apneic episode but was removed from the hospital by her parents the same day, only to be readmitted the following morning after yet another apneic event had occurred. Given that she remained pale and hypotonic for a number of hours, she was transferred to a pediatric hospital for investigation.

Review of all three cases revealed that every apneic episode had occurred in the presence of the mother alone. As physical examinations, laboratory tests, and autopsies when undertaken had not demonstrated any underlying organic cause

for the apneic events, the possibility of factitious illness by proxy (or Munchausen syndrome by proxy, as it was then known) was raised. Covert video surveillance was set up but was initially restricted to visiting hours only. A decision was then taken to admit the mother to hospital with the child and to film continuously. The next day the mother was filmed turning off the apnea alarm, placing a folded towel on her shoulder, and forcing the infant's face into the soft fabric. After several minutes the mother put the unconscious infant back in the crib and then turned the alarm back on.

When confronted by the police who had been watching the video, the mother denied that the event had occurred. Eventually she pleaded guilty to manslaughter of the first infant (case 1) and to causing grievous bodily harm to the third infant (case 3) and was sentenced to 3 years imprisonment with a non-parole period of 12 months. Charges in the second infant (case 2) were not pursued. Following the court case and sentencing, the surviving infant was placed in foster care and did not experience any further apneic episodes.

Prognosis

As can be seen from the above cases, factitious illness by proxy is not a benign entity and may be associated with significant morbidity and mortality (Stirling 2007). In one study of 117 victims, 9 suffered some form of permanent disability and 10 died (Rosenberg 1987). The most common symptoms prior to death were decreased conscious state, seizure, apnea, bleeding, and diarrhea. Major causes of death were poisoning in five (three due to salt poisoning) and suffocation in four (Rosenberg 1987). Brain damage may occur in survivors from repeated hypoxic episodes or from drugs or poisons, and unfortunately there may be considerable morbidity associated with unnecessary medications, investigations, and operations (Meadow 1984a). As many as 20 % of children who have died had been identified correctly in one series as being victims of Munchausen by proxy, but had been discharged from the hospital to the care of their parents (Rosenberg 1987).

Meadow had a mortality rate of 33 % in his series of 27 infants who were repetitively suffocated by their mothers, with further investigations revealing 18 previous deaths in the 33 older siblings of these infants (a mortality rate of 55 %) (Meadow 1990). In another series, the sibling mortality rate was 11 %, with 39 % also having had illnesses fabricated by their mothers (Bools et al. 1992). When the deaths of siblings were subsequently examined, a number of the fatalities had been attributed to SIDS, which in retrospect must be viewed with skepticism. For example, the two fatal cases described by Steinschneider that linked repetitive apneic episodes with SIDS (Steinschneider 1972) were in reality homicides occurring in a family in which three other sibling deaths had occurred in children under the age of 28 months (DiMaio 1988; Firstman and Talan 1997; Little and Brooks 1994; Hick 1973).

Conclusion

The concept of "Munchausen syndrome by proxy" has undoubtedly been an extremely useful one which has enabled the identification of situations where serial deaths have occurred in some families due to inflicted injury. It has also enabled the early detection of this situation in other families enabling protection of the victim and siblings. However, problems do exist, as the use of a specific name may have created undue certainty in the minds of investigators who may assume that there must be clear diagnostic criteria with a defined victim and an identifiable perpetrator. It must be remembered that a syndrome in medicine is *not* necessarily a diagnosis (Byard 2009). The lack of defining features in Munchausen by proxy has led many to avoid using the term and also has resulted in certain courts declaring that it cannot be regarded as a recognized psychiatric disorder or mental illness. Instead it is "merely a name for a type of behavior" (*R vs. LM* 2004). In an attempt to address this issue, it has been suggested that the term should be dropped in favor of diagnoses that are more specific to individual cases (Fisher and Mitchell 1995; Morley 1995). Other terms such as "pediatric condition falsification" (PCF) and "factitious disorder by proxy" (FDP) have been proposed (Ayoub et al. 2002; Craft and Hall 2004; Schreier 2002). The advantage of the latter terms is that they enable the situation to be flagged without attempting to link it to possible motives and psychological profiles of the alleged perpetrator; that is, the most important part of the equation, the abused child, has been identified without being lost within the semantic jungle of medical terminology.

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Cutaneous Findings in Children

11

Peter Ellis

Contents

Abstract

The abuse of children can take many forms, although physical and sexual abuses are the forms that are most likely to result in cutaneous abnormalities. In order to effectively and reliably document changes in the skin, the examination must be carefully planned and should be conducted under optimum conditions. Such an examination may include photography as well as the detection of trace evidence by swabbing. This chapter describes these examination methods.

The most commonly observed cutaneous injuries are bruises, but these may have various features that allow the investigator to distinguish between abusive and non abusive causes. Such features may include location, pattern, number, appearance, and variations in apparent age. Occasionally natural medical conditions may cause or contribute to bruising, and these must be recognized as such to allow reliable identification of those unnatural situations. Bite marks are

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specific injuries that may carry serious connotations of abuse, and they are discussed in some detail especially in respect of the ability to classify them and to apply the examination to the identification of a perpetrator.

Burns and scalds represent a common form of child abuse, and these injuries should necessarily be recognized and adequately recorded and interpreted. They are discussed in detail especially in respect of their value in the investigation of mistreatment. The recognition of scarring as evidence of injury is also described. Finally, it is necessary to recognize the many natural and non abusive conditions and situations that may mimic or be misinterpreted as representing non accidental injury. These are described and documented.

Introduction

The abuse of children can take many forms (Ellis 1997). Of these, physical and sexual abuse and even neglect can all be reflected in changes appearing in some form in the skin. While emotional abuse does not directly cause cutaneous injury, the secondary effects may be manifested by abnormalities that can be observed in the skin. For example, trichotillomania, possibly associated with emotional abuse, can produce areas of alopecia that may be misinterpreted as abusive hair pulling (Scales et al. 1999). Physical abuse can take many forms and can result in bruising, burns and scalds, patchy alopecia, and ultimately scarring and deformity if prolonged. These will be discussed in detail below. Sexual abuse will be described elsewhere in this text (see ► Chap. 23, "Pediatric Sexual Abuse") but can be associated with cutaneous changes around the genitalia as well as bite marks which should be carefully identified and recorded. Neglect, by virtue of increasing the opportunity for skin infections and causing reduced cutaneous integrity, may also produce changes in the skin that need to be recognized for what they are. Severe dermatitis or cutaneous scaly rashes caused by nutritional deficiencies may occasionally represent forms of abuse, although this may not be readily recognized (Swerdlin et al. 2007).

Examination of the Skin

It is self-evident that the examination of the skin must be thorough and reproducible before attempting to attribute any cutaneous appearances to non accidental or unnatural causes. While the examination of the live child presents its own challenges, including medicolegal issues of consent as well as the general health and nutritional and even social settings of the child and its family grouping, the circumstantial data that is available to the forensic pathologist may be limited. It is, therefore, imperative that the examining pathologist be acquainted with as much information surrounding the child's situation as is available. It is likewise essential that the examination is conducted under optimum conditions so as to maximize the value of any observations

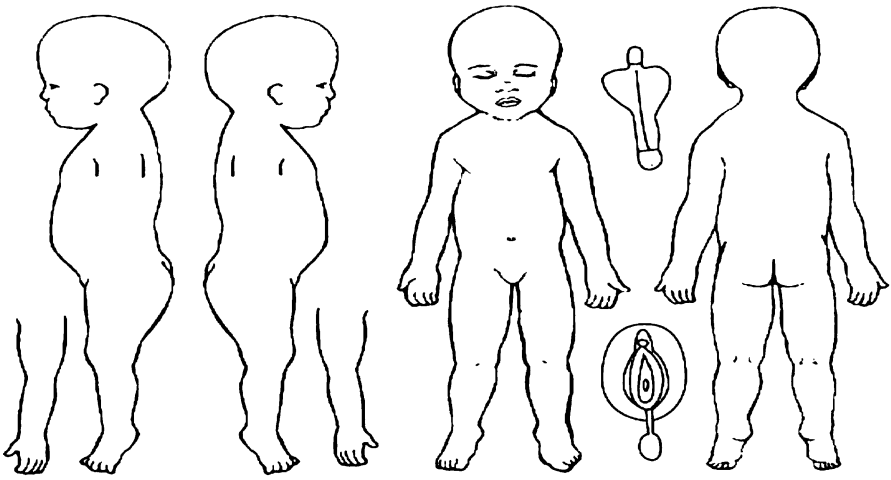

Fig. 11.1 Infant body outline (From http://www.afmes.mil/assets/docs/SUIDIform.pdf)

that are made. There is little point in attempting to interpret a detailed description of external pathological findings if the lighting is poor, all surfaces have not been cleaned and visualized, or the presence or availability of relevant physical evidence, such as wounding objects, has not been recognized. As injury of the skin can be the result of many different physical agents, it is appropriate to be familiar with possible injuring agents, such as belts, straps, and heated objects such as irons, cigarettes, hot plates, and scalding water (see below).

The examination of the skin requires recognition of all the various possible abnormalities that can be seen including bruises, bite marks, abrasions, lacerations, sharp injuries, burns and scalds, scars, and keloids, as well as natural conditions that may be misinterpreted as injuries. These include Mongolian spots, various congenital hemangiomata, as well as a number of rashes and erythemata. These are discussed in more detail below. If abnormalities are identified, it is appropriate that they should be photographed and possibly also recorded on a body outline (see Fig. 11.1). In this way, it is possible to relate a pattern of abnormalities that may of itself impart more information than is available just from consideration of the isolated skin mark.

Photography of injuries and other abnormalities should not be undertaken without consideration of all the technological issues that can maximize the value of this essential procedure (Oliver 2011). When recording injuries, correct lighting is essential. This lighting must ensure that the injury is evenly illuminated and clearly visible even if it is located on a curved or protected part of the body surface. Photographing injuries in body crevices or folds may present significant challenges. It is often appropriate to consider the use of both color and black-and-white photography as these may highlight different features. It has been considered that the variation of color within any individual injury (especially bruises) may provide information relating to the age of that injury. While that is the subject of further discussion elsewhere in this text, it is important to recognize that if it is intended

that the color of an injury is to be used to aid in its interpretation, then it is appropriate that color scales are also used in the photograph. Of course, in any photograph that may be used in a forensic setting, an accurate scale must be incorporated into the image to facilitate the assessment of size and dimension.

Different lighting techniques can be utilized to illustrate different aspects of an injury especially in association with digital technology (Tetley 2005). Simple light photography using the visible spectrum is widely available and will provide an accurate and convenient method of recording injuries. Photography using specific wavelengths especially those that are red free may facilitate observation of areas that are normally predominantly red. Infrared photography may demonstrate tissues beneath the epidermis particularly in areas that have differential absorption characteristics. It is said to be useful in detecting early bruising. Ultraviolet photography can be useful in observing old lesions, scars, bruises, and bite marks as there is good surface detailing (Tetley 2005). The application of alternative light sources to outline skin lesions is well known in forensic pathology, and the use of a Wood's lamp may be considered in the documentation of both new and healing bruises (Vogeley et al. 2002).

Special procedures may need to be undertaken when there are suspected bite marks on the skin surface. As these marks are made by the dentition and it is recognized that this area may have some unique identifying characteristics (see below), it is necessary to ensure that any examination can capture those features that may allow identification of a perpetrator. Therefore, the physical examination must be especially thorough including breasts, genitalia, thighs, arms, and the back. Bite marks are often multiple so it is necessary to record these separately as well as jointly. The very fact that the marks may show evidence of differing ages (insofar as that is possible to determine) is in itself a positive observation that supports an abusive origin. Photography is an essential adjunct to the recording of bite marks, and it must be undertaken using special L-shaped rulers that allow the reliable comparison of sizes and shapes. The camera must be positioned at 90° angle to the bite to minimize any perspective effect that may render comparison unreliable (Bell 2000; Oliver 2011). It is advisable to take an initial localizing photograph to record the position of the bite and then to record a close-up with a properly aligned and orientated scale. It may be appropriate to take a black-and-white photograph as the better contrast may enhance study of the dimensions, although current digital technology allows for image manipulation to facilitate that process.

Finally, DNA evidence should be obtained by swabbing of the wound and its surrounding skin. The exact technique used will vary according to the procedures adopted by the local forensic laboratory, although it is often recommended that a double-swab ("wet and dry") technique be used (Sweet et al. 1997). In this method, the initial swab is taken by wiping the area with a swab that has been moistened with sterile water. This loosens the surface epithelial cells which will then adhere to the second, dry swab that is wiped across the wound. This technique of swabbing the skin to retrieve nuclear material can be applied to any skin wound and is useful in detecting the presence of an assailant's DNA. Another method that can be used to recover DNA on human skin is minitaping, in which adhesive

Table 11.1 Characteristics of bruising that are suspicious of abuse (Data modified from Maguire et al. (2005))

Bruising occurring in infants (less than 6–9 months)
Bruising occurring in children who are not independently mobile
Bruising occurring on non-bony areas
Bruising on the face, back, abdomen, buttocks, arms, hands, soles of feet, and ears
Multiple bruises of similar shape
Multiple bruises of apparently different ages
Multiple bruises in groups or clusters especially on different surfaces
Bruises that form a pattern or suggest the imprint of an implement

tape is applied to lift foreign DNA that has been transferred from the assailant (Kenna et al. 2011). When using both of these techniques, it is appropriate that a control sample be taken from an uninvolved location on the body of the victim. Given that assailants in child abuse are often close contacts of the victim (and therefore likely to have deposited DNA on the skin anyway), this testing has limited value in the examination of much pediatric blunt trauma, but since bite marks are infrequently part of natural activity, this may be a useful adjunct to the forensic examination of the skin.

Bruises

Given that any application of external blunt force can cause bruising, it is obvious that the examination, description, and recording of bruises are an important part of the forensic examination of children. Bruises characteristically occur without surface damage. Of course they may be found in conjunction with other more disruptive injuries of the surface such as abrasions or lacerations, but these are then regarded as compound injuries. As up to 90 % of victims of child physical abuse show skin injuries, it is incumbent on the forensic examiner to attempt to identify those bruises and bruise patterns that are likely to be non accidental (Stephenson 1995). They are documented in Table 11.1.

A bruise follows damage to cutaneous blood vessels and the escape of blood into the surrounding connective tissue. The ensuing appearance is then the result of a number of factors. These include the extent of vessel injury leading to differing quantities of free blood as well as the density of connective tissue in the surrounding support structures and the presence of nearby hard tissue such as bone that may increase the likelihood that trauma applied to small capillaries results in damage to the wall and leakage of red cells. As a corollary, the presence of soft tissue such as fat beneath the skin may have the reverse effect. In that situation, a given degree of trauma may not distort the cutaneous capillaries sufficiently to result in damage and leakage of blood. The effect of this differential support offered by hard versus soft tissues is ably illustrated by the ease with which blunt force trauma applied to the skin of the head produces bruising (due to the hard bone beneath the skin), whereas

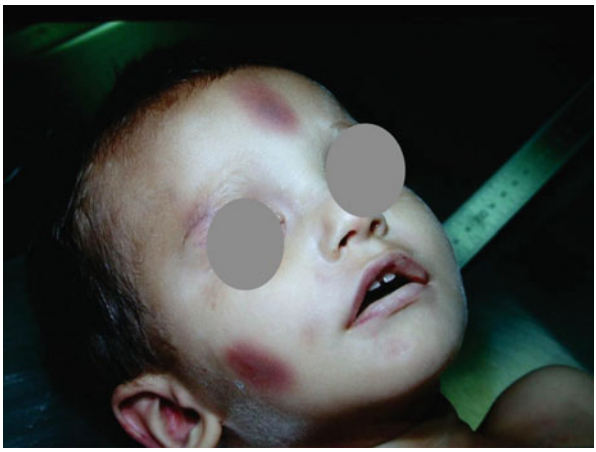

Fig. 11.2 Facial bruising probably caused by an object with a rounded edge

even strong trauma applied to the front of the abdominal wall in a child may cause catastrophic internal damage leading to fatal gastrointestinal injury and hemorrhage but leave little or no evidence of bruising in the skin of the front of the abdomen.

The presence of diseases or medical therapies that affect the coagulation of blood or the integrity of blood vessels may significantly alter the propensity of a child to bruise and by inference the size and extent of bruising in a child exposed to any type of trauma. As mentioned elsewhere, diseases such as Henoch-Schönlein purpura, idiopathic thrombocytopenic purpura, or other coagulopathies may cause a child to appear well but to have unexplained bruising (Stephenson 1995).

Of more importance is the fact that bruises are more common among children as they become more mobile. Skin injuries are a normal feature of growing up and increasing mobility, and this pattern must be recognized by the forensic examiner in the assessment of a child who has bruises (Labbe and Caouette 2001; Sugar et al. 1999). The majority of children who are becoming mobile (greater than 9 months old) have one or more bruises. Alternatively, if a child is not mobile, then the presence of bruising should at least raise the specter of a non accidental cause (Maguire et al. 2005). There is an oft-quoted aphorism that states "children who don't cruise rarely bruise" (Sugar et al. 1999). The pattern of bruising seen in mobile infants and young children reflects the increased exposure of the body to blunt force contact especially during times of increased mobility (such as during warmer weather in temperate regions) (Labbe and Caouette 2001). Accidental bruises are observed on bony surfaces such as the anterior aspects of the lower limbs or the dorsal surfaces of the forearms. Bruises on the forehead may be accidental. Bruises caused by abuse are much more common on other parts of the head, the neck and face, the anterior chest, as well as the back and buttocks (Dunstan et al. 2002) (Fig. 11.2). Other characteristics that are suggestive of physical abuse include multiple bruises in clusters, multiple bruises of uniform size or shape, and bruises that have a defined pattern or that suggest the imprint of a used implement.

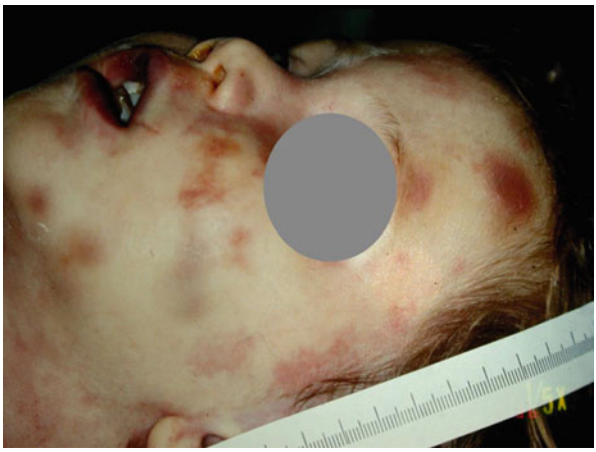

Fig. 11.3 Bruises caused by fingertips or knuckles

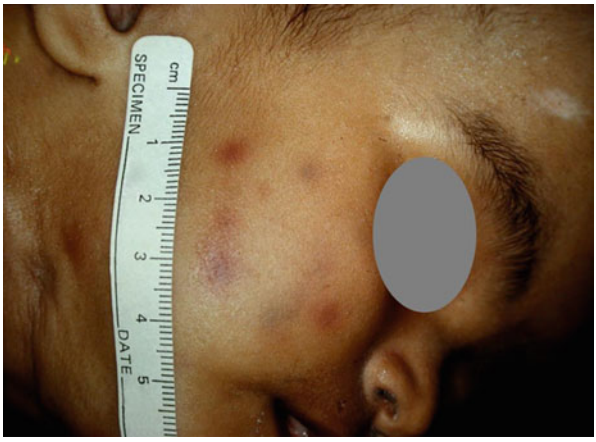

Fig. 11.4 Bruises caused by fingertips or knuckles

Among the patterns of bruising commonly seen in abuse is the grouping of small round or oval bruises that raise the suspicion of contact with the fingertips of the striker (Figs. 11.3 and 11.4). This pattern may be seen over the face where it suggests that a hand has been placed firmly over the mouth to quieten a cry. This proposed scenario carries the implication that fingers have been placed with sufficient force to cause bruising. It is tempting to try to match the bruises to a hand pattern, but this should not be over-interpreted. The use of the hand to slap the face hard may also leave fingertip bruises as it is those parts of the hand that are most likely to impact the skin with the greatest force. However, this may also produce multiple parallel bruises reflecting contact with several fingers (Figs. 11.5 and 11.6). The pattern of fingertip bruising may also be seen on the upper arms or legs where the abuser is gripping the limbs either as enforced restraint or while holding the child during the act of throwing the body around or against a surface.

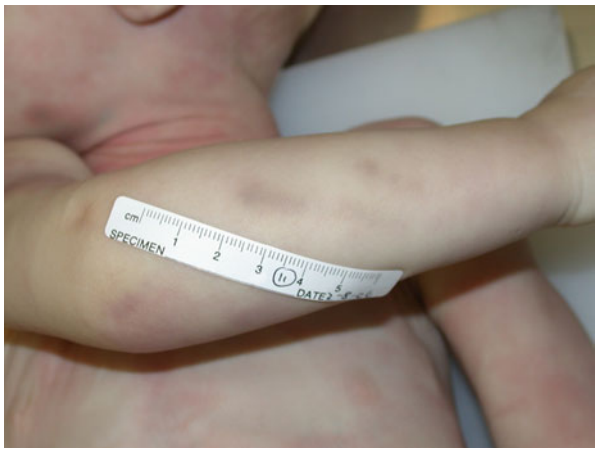

Fig. 11.5 Parallel bruises suggestive of gripping by fingers

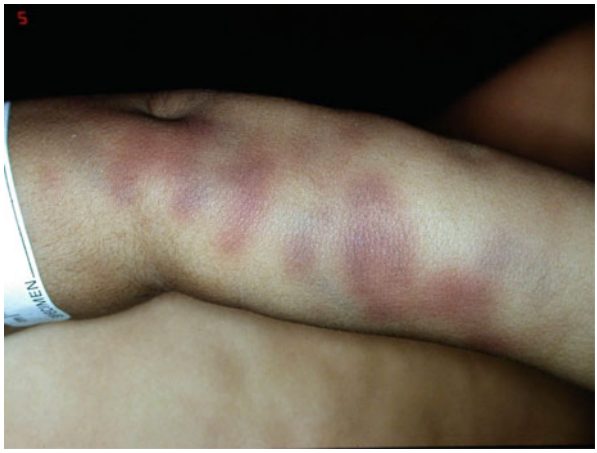

Fig. 11.6 Parallel bruises suggestive of gripping by fingers

In this situation, the bruises are often seen on the inner surfaces of the limbs, and this is highly suggestive of non accidental injury. Additionally, repeated blows with a closed fist may produce multiple bruises that each carry rounded features suggestive of fingertips or knuckles (Fig. 11.7).

The forcible application of an object may produce a bruise that carries the pattern of that object. Commonly seen are marks made by belts and belt buckles, various hard articles such as bats and wooden paddles, wide flat surfaces such as books, and narrow cylindrical articles such as cords, canes, branches, and other rods. Tubular structures characteristically produce bruises that carry a "tram track" configuration of two parallel lines often separated by a pale or non bruised strip (Fig. 11.8).

While bruises are the most common external signs of physical abuse, they are rarely severe enough to be fatal of themselves. However, occasionally bleeding in

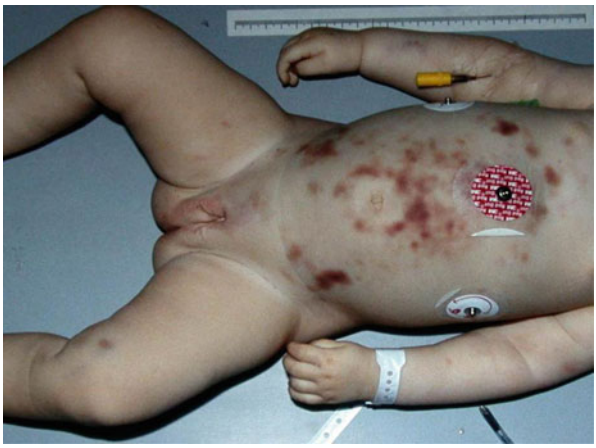

Fig. 11.7 Bruises caused by fingertips or knuckles

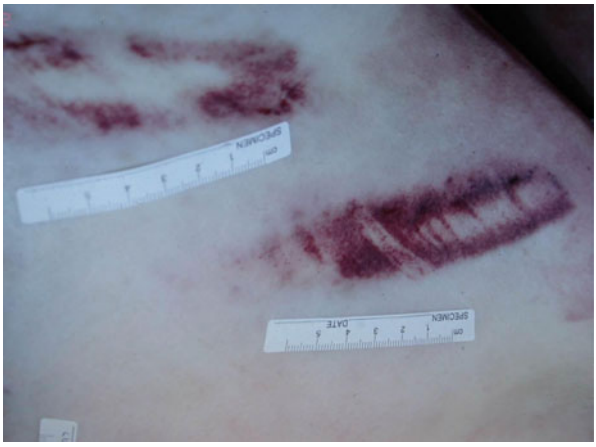

Fig. 11.8 Tramtrack bruises caused by a rod

the skin is so extensive that there may be major clinical consequences such as anemia or even death. Unless there is a coexisting coagulation defect, this extensive bruising should be considered to be abusive until proved otherwise (Fig. 11.9).

As indicated above, one of the cardinal signs of abusive bruising is the presence of multiple injuries especially when those injuries have been inflicted over a prolonged period. To make such an observation implies the ability to distinguish differing ages of observed bruises. The combination of recent and older bruises especially in areas not prone to accidental trauma is highly suggestive of inflicted injury. This implies an ability to determine the age of individual bruises with sufficient accuracy to allow the distinction of different times of infliction. The subject of the aging of injuries in children is discussed in detail elsewhere in this

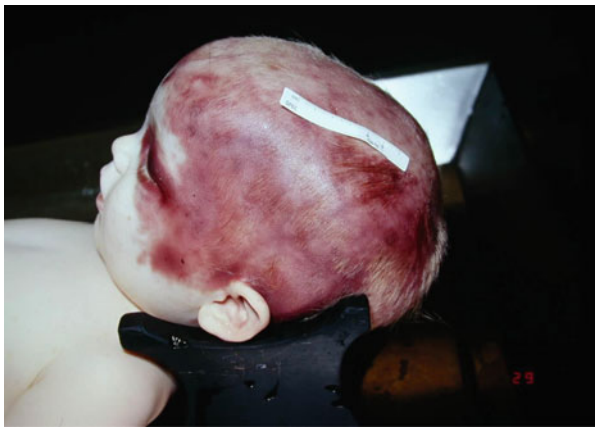

Fig. 11.9 Bruising occupying the whole scalp

Table 11.2 Factors affecting the color of bruising (Data modified from Stephenson (1997))

Amount of blood extravasated
Depth of the bruise in the skin
Force used to inflict injury
Vascularity of underlying tissue (related to location on body)
Age of child
Color of child's skin
Medical conditions and drugs affecting bruise resolution

text, but in any examination of the bruised child, consideration of whether multiple lesions were inflicted at the same or different times should be part of the process. It has been traditional to consider the differences in the coloring of various injuries as reflective of different ages, but there are many reasons why bruises have varying colors (Table 11.2).

The aging of bruises may involve more than the assessment of the color. The histological examination to assess any inflammatory and repair response may be part of the formal forensic examination of abusive bruising, although it should not be over-interpreted as there have been few reliable studies to support its efficacy (Langlois 2007).

Bite Marks

A bite mark is a mark made in a substrate by teeth, although the structures responsible may also involve other oral or perioral structures. The first phase in examination of a bite mark is the determination that the mark has indeed been caused by biting.

Table 11.3 Class characteristics of bite marks

Evidence of injuries from two dental arches – an upper arch and a lower arch
Individual marks resulting from individual teeth
Possible movement of teeth during bites or multiple bites
If the arches of teeth have moved during biting and the causative teeth remain in contact with the tissue, then the patterns of contact also move in the same direction for a similar distance
Bruising or laceration or a combination of both

Table 11.4 Individual characteristics of bite marks

Specific patterns of marks that comprise the whole injury
Size and patterns of dental arch curvatures. Some individuals have sharply curved dental arches whereas other have individual teeth out of the line of the arch and so on
Drag marks may be seen. These may be associated with the spaces between individual teeth when the dental arch is dragged across the tissue surface

As skin and subcutaneous tissue are elastic, they may be movable and may not record impressions reliably. They may stretch or compress according to the position of the body, and therefore distortions may be introduced. Bruising may occur or frank laceration may be present. This complicates the determination of tissue injury caused by teeth. It is necessary to consider other objects that may cause skin injury that resembles bite marks. For example, shoe heels, some belt buckles, and even the corners of a hot iron may inflict injuries that look similar to bites.

Assuming that a determination has been made that the tissue injury is consistent with a bite, it is necessary to determine whether it is an animal or human bite and if human, whether it is caused by a juvenile or by an adult mouth. Initially *class characteristics* should be determined (Table 11.3). These are the characteristics that determine if an injury is likely to be a bite mark or not. There may also be *individual characteristics* that may facilitate specific identification (Table 11.4) (Fig. 11.10).

Problems may arise when attempting to relate bite mark injuries to individual perpetrators using only anatomical or topographical evidence. It is inappropriate to use bite marks to identify offenders purely on the basis of the physical appearance of the injuries. There are too many uncontrolled variables. For example, as mentioned above, tissue is elastic and may stretch, and this is compounded by the fact that not all teeth will necessarily impact the bitten surface at the same time. So there may already be some distortion by the time that later teeth impact the surface (Sheasby and MacDonald 2001). Additionally, the child may pull away from the biter and this may introduce further distortions. Multiple bites may be inflicted in a small area, making it difficult to separate all the components of each individual bite. Therefore, in the absence of forensic biological analysis and DNA matching (see above), it is appropriate to confine anatomical bite mark analysis to being an exclusionary technique. Notwithstanding that rider, it may be possible to state that "a particular individual cannot be excluded as the perpetrator of this bite mark."

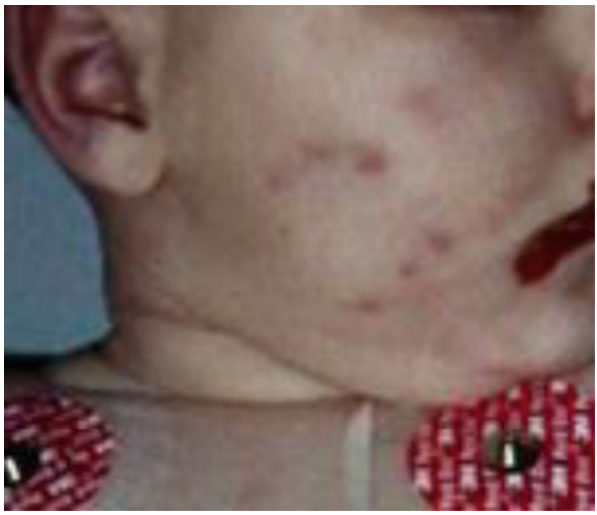

Fig. 11.10 Pattern of bruising indicative of bite marks

In considering the resulting skin injury, it is worth describing how a bite mark is inflicted. The most common scenario has the mouth fairly wide open when the bite is begun. The lower anterior teeth impact the skin being bitten with the incisal edges holding that material steady (rather like the spikes on a meat tray holding the meat still for carving). These teeth are fairly small and narrow and tend not to move a great deal. They therefore leave similar small well-defined marks. The upper teeth tend to have a larger profile. When they first hit the skin, it is the inside, or palatal, surfaces of the teeth that contact the area being bitten, and as the jaws move closer together and the mouth closes, a wave of tissue (skin and subcutaneous soft tissues) is pushed up against the palatal surfaces. If the dental arches close together to a greater degree, then the upper teeth drag more than the lower teeth because of the greater surface area and lesser friction. In a bruised injury, this means that the mark left by upper teeth will generally be more diffuse than that left by lower teeth. This dragging may leave distinctive marks that have been compared to a "bar code." It is not sure how distinctive this is for a given set of teeth. Not all teeth will touch the skin being bitten at the same time, either because there is a relative difference in heights of individual teeth relative to the bite plane or because there may be an angle between the bite plane and the skin surface being bitten.

Certain elements in a bite mark case are susceptible to comparison (Table 11.5). This is properly the field of the forensic odontologist, and such expertise should be sought when a bite mark injury is suspected.

There is probably no good relationship between the estimated force applied by individual teeth and the extent of resulting bruising. Therefore, examination of bite marks on the skin of a child tends to be an exercise in pattern matching, and the proper use of swabbing for DNA detection becomes an essential part of the forensic examination (Liston et al. 2001; Pretty and Hall 2002).

Table 11.5 Characteristics of bite marks amenable to comparison

Size and shape of dental arches
Patterns due to the positions of individual teeth
Diffuse as opposed to sharper, more distinctive elements in a bite injury (upper vs lower teeth)
Drag marks ("bar code")
3-D comparison of teeth to injury to account for missing marks

Burns and Scalds

Child abuse by burning constitutes from 6 % to 20 % of child abuse cases (Peck and Priolo-Kapel 2002). It is therefore essential that forensic investigators can recognize those lesions that have been caused by the application of heat and also that they can recognize those situations that may be confused with thermal injury. Burns occur when the skin and the subcutaneous tissues are damaged by thermal energy. For this to occur, a number of criteria must be satisfied, and the injury that results will depend on which of those criteria occur and for how long that injury is inflicted. These criteria include the temperature that is applied to the skin, whether the skin is wet or dry, whether the heat is wet or dry, the thickness of the keratin covering the area over which that heat is maintained, and the duration of that contact. These can be summarized in considering the coefficient of thermal conductivity. The resulting skin lesion and any systemic sequelae are dependent on the summation of these different components (Faller-Marquardt et al. 2008).

Young children constitute a high proportion of burn victims, and up to 25 % of pediatric burns may have had an abusive cause (McLoughlin and McGuire 1990).

Dry burning results when the heat that is absorbed by the skin results in local tissue damage. If this damage is extensive enough, it may be associated with systemic responses which may be fatal if severe or untreated. Similar results may follow scalding, and given that liquids may, by their very nature, spread this contact effect over extensive areas of skin, scalding is a more common cause for hospital admission than injury inflicted by dry heat. The damage that occurs after thermal contact will initially be observed as reddening of the surface as cutaneous erythema occurs. If the temperature is high enough, the contact long enough, or the heat transfer deep enough, there will be damage to the dermal and subcutaneous tissues resulting in blistering and even ulceration. It is possible in extreme cases to have charring of the skin if the heat is so high that the organic material combusts, such as when fireworks explode (Al-Qattan and Al-Tamimi 2009) or cigarette ends are applied to the skin for a prolonged time (Faller-Marquardt et al. 2008).

Thermal damage is traditionally classified according to whether the injury is inflicted by dry heat (burning) or by hot liquids (scalding), although the principles of damage are the same and it is not necessarily helpful to maintain this distinction. There are patterns of burn injury that are suggestive of an abusive origin. Many of these relate to the depth of the wound. Second- or third-degree burns, especially if they are multiple or symmetrical, should raise the index of suspicion. Skin is an

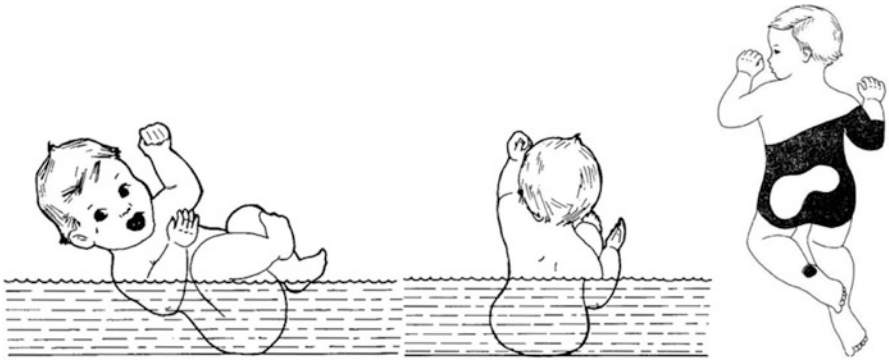

Fig. 11.11 Typical dipping immersion pattern of scalding (From Lenoski and Hunter 1977)

effective insulator of heat, and most damage is confined to the epidermis due to the usually brief duration of contact. It is a normal reflex to rapidly withdraw an exposed area from applied heat, and if the damage is observed to be deep, then it implies that the time of contact may have been prolonged. This is strongly supportive of a non accidental cause. Burn injury patterns have been variously categorized, but one of the most useful classifications depends on the method of heat application rather than the resulting appearance. In this classification (Lenoski and Hunter 1977), burns are associated with splash, immersion, and contact. A flexion pattern may also be seen as a subset of immersion burns.

Splash burns result when the scalding liquid is thrown or poured onto the skin. This is more likely to be the result of an accidental event in children, and the burns that are produced may have a very heterogeneous range of appearances (Drago 2005; Fracasso et al. 2009; Shoufani and Golan 2003; Wallis et al. 2008). The liquid may drip or flow after contact and therefore the heat damage may spread locally. However, the temperature of the liquid may also fall rapidly after contact so the duration of the damaging heat may be short-lived and the injury is limited. If the hot liquid flows after impact, the burn may be directional in a way that demonstrates the position of the child when the liquid struck the skin. There is nothing in splash burns that is probative for abuse, although accidental splashes are frequently seen on the front and upper half of the body and face. The typical "spill" burn occurs on the anterior surfaces of the face, lower neck (the upper neck is often protected by the chin), chest, shoulders, and extended arms. Splash burns occurring in other areas should be regarded as suspicious for a non accidental origin.

Immersion burns are more frequently abusive than splash burns. They tend to be of even depth and have a uniform distribution over those areas in contact with the hot liquid. They are caused when the child is dropped or dipped into a hot liquid. A typical situation is bath water that is either accidentally or deliberately too hot for safety. The injuries tend to have a sharp line of demarcation between burnt and normal skin and are often of uniform depth. If an area of skin contacts the container, it may be protected from the heat, and this results in an

uninjured zone in the middle of the large burn (Fig. 11.11). This "target" effect is typically seen on the buttocks. If the immersion burn is the result of accidental contact, it may be complicated by the presence of drip or splash marks as the child has the ability to move and to attempt to withdraw the affected body part from the hot liquid. Such an ability is often lacking in abuse, and such irregularities of the edge are less common.

Flexion sparing is seen when limbs are held in flexed positions during immersion. This results in the skin within creases being spared burn injury. These shielded areas include the hip flexion creases, the anterior elbow creases, and the posterior knee popliteal fossae. Shielded skin creases may also be seen on the anterior lower abdomen if the lower trunk is forced into flexion during immersion with the child in a seated position.

Distinguishing intentional from unintentional scalds may be difficult, but intentional injuries are often immersive, involving the extremities and buttocks or both. Additionally they are frequently symmetrical with clear upper margins (Maguire et al. 2008). Unintentional scalds are more commonly due to splash or spill and tend to affect the upper body with irregular margins and depth. Additionally, accidental scalds, burns, or splashes are more frequently referred for immediate medical attention.

Contact burns are usually caused by dry objects and characteristically reflect the size and shape of the applied burning object. These may be accidental or abusive. However, burns caused by contact with certain objects, such as those not normally associated with children, are more likely to be non accidental. Of course, contact with some heated household objects may be accidental, especially if the child is newly mobile and explorative. These injuries usually occur on the hands and are unilateral and shallow, being restricted by the rapid withdrawal of the burnt hand on contact with the hot surface (Wilson Jones et al. 2008). Prolonged contact or repeated contact with one object is probably abusive (Faller-Marquardt et al. 2008).

Cigarette burns are common findings in physical child abuse and present a characteristic appearance. They are of a similar size to the tip of a cigarette and are usually rounded and clearly defined. It is important to note that there may be some variation in the shape of wounds created by contact with a lighted cigarette as the nature of that contact is so variable. The contact may be intentional and well defined, in which case the wound is often discrete and rounded (Fig. 11.12). This is a feature of non accidental injury. If however there is a glancing touch, then the shape of the wound may be oval or poorly defined. Cigarette burns are frequently multiple, and their significant depth often produces scars that are easily recognized. However, as with most burns, the depth varies and the appearance depends on the degree of penetration (Faller-Marquardt et al. 2008). First-degree burns tend to be erythematous and may show local edema. As they may heal with no sequelae or just with mild hyperpigmentation, they may be difficult to identify forensically. Second-degree burns involving the superficial dermis may blister, and this should be recognizable by the forensic examiner. The full-thickness third-degree burn may show necrosis, blistering, or even a dry leathery appearance due to local thermal coagulation. It is these deeper wounds that readily scar.

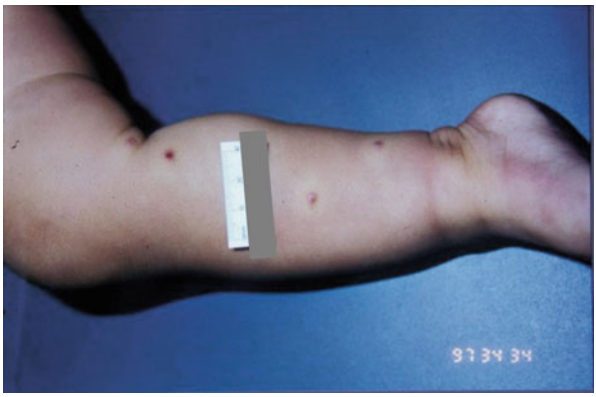

Fig. 11.12 Discrete rounded injuries caused by contact with heated cigarette ends

Other forms of contact burn are not infrequent, and some may strongly suggest an abusive origin. Burns from contact or close proximity to household objects such as hair dryers and other cosmetic appliances may frequently be accidental (Prescott 1990; Wilson Jones et al. 2008). In this case, they are usually isolated, and any multiplicity of such injuries should raise the specter of a deliberate abusive origin. In some communities, electric water heaters may present a dangerous hot surface and can cause localized burning if the child places his/her hand onto the outside surface (Chuang et al. 2003; Drago 2005). Of course this pattern of injury whereby the child's hand is deliberately held against a hot surface is a fairly frequent form of abuse. The most commonly available surface is a cooking hotplate/stove top and if burns of the palms of the hands or feet are seen, and especially if they are large, deep, or bilateral (implying prolonged or repeated application), then non accidental injury should be considered likely. Burns following the application of an object such as a hot iron are not uncommon and must be considered to be abusive until proved otherwise. As the surface is fairly broad, the resulting injury is naturally fairly large.

Microwave ovens are occasionally a source of childhood burns. While accidental injuries occur after contact with fluids or other food heated in such devices, abusive injuries have been reported following the placement of the child within the ovens (Alexander et al. 1987). Sharply defined burns have appeared in areas closest to the microwave-emitting devices, although there is nothing specific about the burns that indicate microwave radiation as the causative agent. The penetration depth of microwaves is small, and the heating takes place near the surface at the skin (Ozen et al. 2011). The temperature cannot be accurately predicted as there are so many variables (e.g., strength of radiation, duration of exposure, and moisture content of surface tissues), but temperatures of over 100 °C can be achieved in foods placed in microwave ovens.

Scarring

If an injury is deep or severe enough and if the child survives long enough, then a scar may form at the site of the original injury. Whether a scar forms depends

on a number of factors including the size of the original injury, the age of the victim, the depth of the injury, and the tissues damaged by the original trauma. Infection at the site of the original injury or the presence of foreign material may predispose to scar development. Pediatric burns may develop into hypertrophic scars if they are particularly deep and if the healing time is prolonged (Cubison et al. 2006). The use of electrical cords to inflict injuries can lead to characteristic curved scars (Showers and Bandman 1986). Additionally some racial groups are more prone to develop post-injury scars, and some of those scars can be very prominent. Keloids are hypertrophic scars that are more common in persons of African ancestry.

Scars and keloids may therefore be a useful indicator of a history of injury. If such lesions are numerous or are observed in areas not normally susceptible to accidental trauma, then the very presence of scarring may support a suspicion of abusive trauma. In some groups, this scarring may be symbolic and can reflect local customs (Johnson 1994).

Skin Lesions That Mimic Child Abuse

As cutaneous lesions are recognized as the most common manifestation of child abuse, it must be remembered that there are some abnormalities of the skin that may be misinterpreted as evidence of mistreatment. This misreading of physical signs can have serious consequences for the child, the family, caregivers, the falsely accused, and even for investigators so the range of conditions that may give rise to misdiagnosis should be familiar to forensic examiners.

The first step in ensuring that observed abnormalities are definitely representative of abuse, both physical and sexual, is a full and accurate medical history of the child. This may include knowledge of the social and racial circumstances of the family. In this way, changes that may represent certain ethnic and cultural practices can be recognized for what they are. Of course, when those practices result in physical changes in the skin, some authorities may still interpret that as evidence of abuse. That is a matter for legal opinion and is outside the scope of this chapter. It merely needs to be recognized that some "folk remedies" may result in physical damage to the skin. Additionally, the knowledge of the racial background of the child may alert the examiner to recognize that some cutaneous abnormalities may be more common in certain racial groups. A history of congenital onset obviously excludes an abusive origin even in a lesion that otherwise may be interpreted as an injury. There are several reviews that outline the most common lesions that have the potential for misinterpretation as abuse (AlJasser and Al-Khenaizan 2008; Hansen 1998; Mudd and Findlay 2004; Scales et al. 1999).

Folk Remedies

Folk remedies and cultural practices present a significant potential source of misunderstanding with child abuse (Mudd and Findlay 2004). There are several

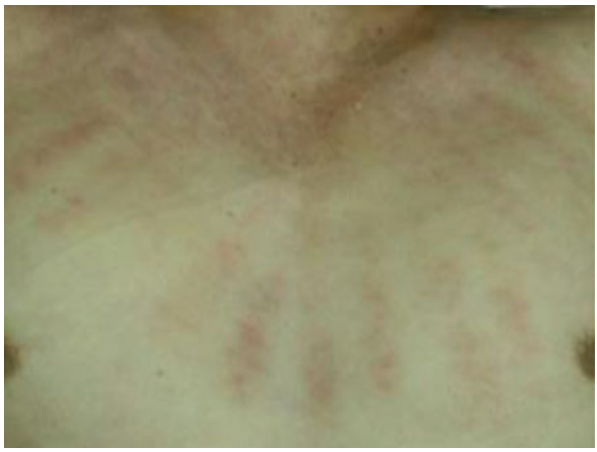

Fig. 11.13 Parallel bruising caused by coin rubbing

practices that can result in hyperpigmentation and unusual bruises. The remedies known as coin rubbing (Vietnamese) or spoon rubbing (Chinese) can result in quite dramatic marks in the skin that mimic abuse. In coin rubbing, or *cao gio* ("scratch the wind"), the skin is rubbed with a coin, often after the application of medicated oil or ointment. This rubbing occurs along the spine, neck, or down intercostal spaces until petechiae or bruises appear. The Chinese variant termed spoon rubbing, or *quat sha*, is similar except that the back or side of a spoon is used. This process is believed to rid the body of "bad winds" that can cause many symptoms. However, it appears as one or more often parallel lines of reddening or bruising. These may even be bilateral and symmetrical (Fig. 11.13). Indeed this symmetry is a useful clue to the nature and origin of the lesion. If the rubbing was performed sometime before the examination, there may be hyperpigmentation following the same pattern. Occasionally, the skin may be pinched at the same time, and this can complicate the observations.

Cupping, dry or wet is an ancient remedy that is still seen in many cultures, including Russian immigrant families and Asian groupings (Hansen 1998). In the former, a vacuum must be created in the cup for it to be effective. This can be done in a number of ways, but most commonly a cotton wool ball soaked in alcohol is burnt to consume oxygen and thereby reduce pressure. On removing the ball, the cup is placed on the skin and the reduced pressure draws the skin upward. This produces a red circular mark with varying bruising in the center. Wet cupping differs in that small cuts are made on the skin surface prior to the application of the cup. This causes local bleeding. Both forms of cupping leave erythema, bruising, and sometimes burns. They may be confused with child abuse although, as mentioned above, it may itself be regarded as an abusive procedure.

Other "burns" can be produced by the practice of moxibustion, in which a piece of moxa herb (mugwort) or yarn is rolled into a ball, placed onto the body surface, and then ignited. This produces circular burns that will scar and may be confused with intentional abuse, especially by cigarette burns. Occasionally this may be

Table 11.6 Lesions that may be confused with inflicted traumatic bruises

Postmortem lividity
Cutaneous pigmentation, esp Mongolian spot
Hemangiomas
Henoch-Schönlein purpura
Cutaneous hypersensitivity reaction
Eluted clothing dye
Bruising in the context of bleeding diathesis

combined with acupuncture, and it is a practice that is observed in several Asian countries including China, Japan, Cambodia, and Laos (Faller-Marquardt et al. 2008). Small deep burns can also result from some therapeutic cautery seen in some Arabic cultures ("maquas") and some parts of Africa (Feldman 1984, 1995). Even the therapeutic use of garlic may produce burns after prolonged contact with the skin, and the use of common rue, an evergreen shrub found in the Mediterranean region and applied to treat various ailments, may cause phytophotodermatitis (Risser and Mazur 1995). This may also occur after the application of plants such as lemons, limes, celery, and many herbs (Scales et al. 1999).

Conditions Confused with Bruising

As indicated above, there are a number of appearances and conditions that may be mistaken for bruises (Table 11.6). In the forensic examination of a deceased child, the most common source of confusion is the misinterpretation of postmortem lividity as cutaneous bruising. All pathologists will be familiar with the great variation in the distribution of lividity. Characteristically, the pattern reflects the position in which the body has been lying in the period since circulation ceased (death). Therefore, the most dependent parts of the body contain cutaneous blood vessels that are suffused with blood, imparting a darker color than those skin areas either less dependent or under some compression due to contact with a surface or some other object, such as clothing. This dependent congestion may be very patchy, and not infrequently there may be areas of cutaneous darkening that are easy to misinterpret as bruising. It is not always clear why there are irregular areas of lividity on less-dependent parts of the body. What is important during the forensic examination is that each suspect area is examined carefully for the presence of extravasated blood. Fortunately this is usually quite straightforward as a small incision into the discolored area will quickly demonstrate the presence of extravascular red cells if there is genuine bruising. In the event of confusion or doubt, histological examination will establish the presence or absence of bruising in a suspect area. The performance of iron stains will identify those areas in which the presence of hemosiderin confirms earlier bleeding.

Bruises may be real but they are not necessarily the result of abuse. This is discussed above in the section on bruising. Several medical conditions produce cutaneous changes that either may be confused with bruising or may produce hemorrhage in the skin that is not abusive in origin.

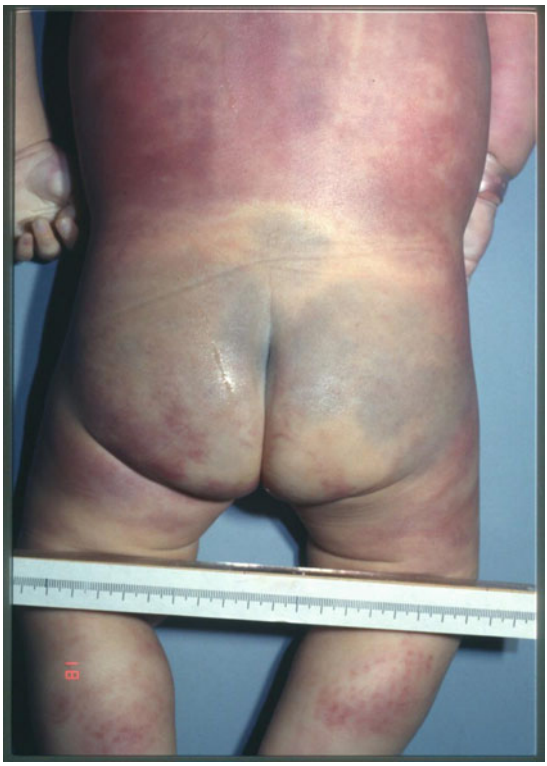

Fig. 11.14 Mongolian spot

Mongolian spots are variable patches or macules of blue/gray cutaneous pigmentation. They are usually present at birth and often fade gradually over weeks or months, although occasionally they may persist (Fig. 11.14). As the name suggests, they are more common in children of East Asian origin although they can be seen in many ethnic groups. Mongolian spots are most frequently observed over the lower back, above the natal cleft, but can be found in many other parts of the body including the shoulders and the extremities. In those situations, they can be easily mistaken for bruises, and their atypical location (including sites not normally associated with normal activity-based pediatric bruising) may compound this misinterpretation. Unlike bruises, their color does not change (although they usually fade over time), and the presence of several marks of varying colors such as blue, gray, green, and yellow strongly supports a diagnosis of bruising and mitigates against Mongolian spots. Histologically, there is an increase in pigmented melanocytes in the deep dermis with no extravasation of red cells.

Hemangiomas are congenital lesions that are commonly found in childhood. If they are deep lesions, they may be blue and may be misinterpreted as deep bruises. If superficial, especially in vascular areas such as the perineal area or in perioral tissues, they may be mistaken for injuries. Other lesions that may mislead include Henoch-Schönlein purpura, various hypersensitivity reactions (such as erythema

Table 11.7 Lesions that may be confused with burns

Bullous impetigo
Staphylococcal scalded skin syndrome
Fixed drug eruptions
Epidermolysis bullosa
Dermatitis herpetiformis
Urticarial pigmentosa
Laxative-induced dermatitis
Severe diaper rash

multiforme and erythema nodosum), phytophotodermatitis, Ehlers-Danlos syndrome, and some lymphangiomas. Even the dyes that can elute from some clothing may color the skin in such a way as to confuse. Knowledge of the history, including the familial story and the circumstantial situation, should allow these conditions to be recognized (Scales et al. 1999).

Diagnostic errors may occur in children who have a bleeding disorder as well as bruising, and it is imperative that this situation is considered in the forensic examination. While it is relatively simple to perform coagulation studies and other laboratory investigations in the living child, this may be problematic after death. Retrieving a thorough clinical and family history is essential. The absence of any history that suggests a bleeding diathesis may support a diagnosis of inflicted injury, although the presence of such a history does not necessarily exclude it. Children with bleeding disorders do get abused (Lee 2008).

Conditions Confused with Burns

Many of the folk remedies mentioned above may produce lesions that are burns but are considered to be non abusive because of the circumstances. There may also be lesions that physically resemble burns but are in fact natural conditions, such as bullous impetigo or staphylococcal scalded skin syndrome (Table 11.7) (Porzionato and Aprile 2007). The latter may be so extensive that it is mistaken for extensive scalding. There are other disorders that resemble burns including epidermolysis bullosa, dermatitis herpetiformis, urticarial pigmentosa, and fixed drug eruptions (AlJasser and Al-Khenaizan 2008). Even severe nappy rash may be misread as scalding affecting the perianal area, and the possibility of burns caused by dipping the child in hot water needs to be considered. Laxative-induced dermatitis has been incorrectly diagnosed as abusive burns (Leventhal et al. 2001).

Lesions that can be confused with cigarette burns are many and include acne vulgaris, insect bites, focal pyoderma, healed infected chicken pox, and even smallpox vaccination scars. Indeed any irritated lesion, especially if scratched, could potentially be misinterpreted as a burn. Burns with other hot objects with similar profiles may be mistaken for cigarette burns (Faller-Marquardt et al. 2008).

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Skin Conditions Mimicking Pediatric Inflicted Injury

12

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Contents

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Abstract

The skin is the site of most accidental trauma in childhood and the site where a number of medical conditions may manifest. An incorrect diagnosis of skin lesions, the most common manifestation of child abuse, may result in a decision to return a child to an abusive environment. Alternatively, failure to recognize mimickers of child abuse may result in delayed treatment and accusations against the child's caregivers. This chapter aims to provide information to assist with the identification of skin and medical conditions that may mimic child abuse, to differentiate abusive/inflicted injuries to the skin from medical conditions, and finally to identify cultural practices that may be confused with findings found in child abuse.

Introduction

Skin lesions are the most common manifestation of child abuse. The skin is also the site of most accidental trauma in childhood and the site where a number of

medical conditions may manifest. Further, the visibility of the skin means that lay individuals may observe a skin lesion, assume it represents trauma, and notify child protection authorities. Clinicians and pathologists need to be aware of such medical conditions and, in particular, be able to differentiate them from accidentally or non accidentally induced trauma.

An incorrect diagnosis of skin lesions may result in a decision to return a child to an abusive environment, an outcome with the potential for significant morbidity and mortality. Alternatively, failure to recognize mimickers of child abuse may result in delayed treatment and accusations against the child's caregivers.

The diagnosis of any skin lesion must be underpinned by a thorough history and a comprehensive physical examination. A number of investigations or referrals may also be indicated as part of the diagnostic process or to refine the differential diagnosis. Generally, these conditions will be diagnosed prior to the involvement of a pathologist performing an examination. Hence the obvious importance of accessing the child's medical records in each case.

Dermatologic Conditions

Contact Dermatitis

These are hypersensitivity-cutaneous reactions resulting from exposure to allergens (allergic contact dermatitis) or irritants (irritant contact dermatitis). Contact dermatitis (in the groin region) may be caused from the child's own urine and feces, especially when there is diarrhea or if there has been prolonged contact with these substances, so-called diaper dermatitis. Differentiating contact dermatitis from cutaneous signs of child abuse is usually reasonably easy, assisted by a history that confirms exposure and the finding of lesions that are generally well demarcated (and often itchy) and are typically limited to sites of contact.

Eczema

Eczema is a generic term for inflammation of the epidermis. It is a skin eruption characterized by inflammation, weeping, lichenification, and itch (Kliegman 2011). If there are punctate lesions, then these may be mistaken for cigarette burns, and hyperpigmented marks (from scratching) can be mistaken for inflicted injuries (Reece and Christian 2009a). Pruritus associated with eczema may result in self-inflicted scratch marks; in the anogenital region this may be mistaken for abusive trauma.

Differentiation from other etiologies may be assisted by a personal or family history of atopy, a response to moisturizers or topical steroids, the distribution of the lesions (typically in the flexures), and an association with dry skin on the rest of the body.

Striae/Stretch Marks

Striae are a frequent finding, occurring in up to 35 % of children going through puberty (Reece and Christian 2009a). There is also a strong association with obesity and steroid use. They initially appear as depressed, reddish–purplish linear markings which gradually change to a lighter flesh color. They may be manifest as multiple parallel lines.

While they can appear anywhere on the trunk and limbs, they are most likely to appear in places where larger amounts of fat are stored (e.g., abdomen, breasts, thighs, and buttocks). Their appearance, location, and the fact that they persist (when signs of inflicted trauma resolve) are useful diagnostic features.

Inflammatory Linear Verrucous Epidermal Nevus (ILVEN)

ILVEN is characterized by papular lesions that tend to group together into a linear pattern (http://www.dermnetnz.org/lesions/ilven.html). The lesions are red, inflamed, and itchy, and the surface of the affected skin may look like eczema or psoriasis (red and scaly). The rash appears before 5 years of age in the majority of cases and occurs more frequently in females. The rash most commonly involves the extremities but can also exist on the trunk and is usually unilateral (AlJasser and Al-Khenaizan 2008).

Because of its linear distribution and the possible presence of linear abrasions or scars (from scratching), ILVEN can be mistaken for inflicted trauma. Differentiation may be assisted by a history of pruritus, the location and features of the rash, and the distinct keratinous histological appearance.

Urticaria Pigmentosa

Urticaria pigmentosa is caused by abnormal mast cell proliferation (mastocytosis) causing brown papules and plaques on the skin (http://www.dermnetnz.org/colour/urticaria-pigmentosum.html). The first patches usually appear at a few months of age and gradually increase in number until early childhood. They then eventually fade away, and most of the patches would have disappeared by the teenage years. The patches can appear on any part of the body.

When one of the brown patches is rubbed, the rubbed area becomes reddened, swollen, and itchy within minutes, Darier's sign. This confirms the presence of mastocytosis. Lesions may blister and appear like bruises and hence can be misdiagnosed as inflicted injuries.

Differentiating characteristics include a positive Darier's sign, and further confirmation can be made with a biopsy of the lesion.

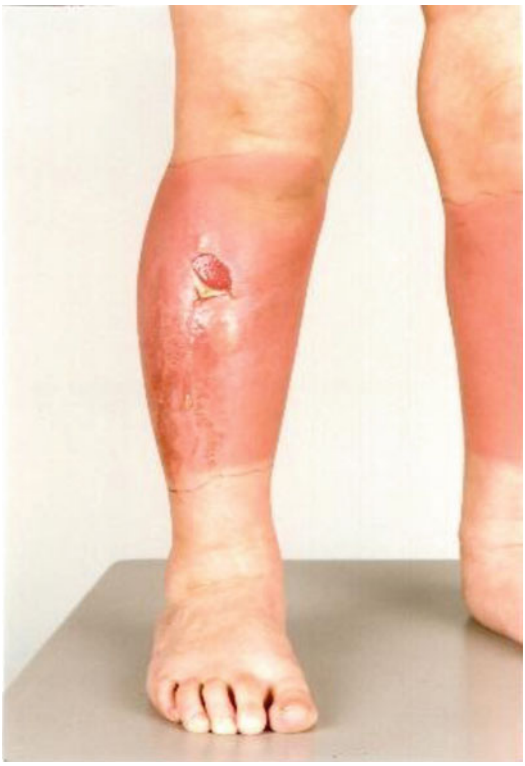

Fig. 12.1
Phytophotodermatitis. Burn-like lesions caused by sunlight interacting with photosensitizing compounds (the irregular linear marks above and below the areas of erythema were added to monitor the margins of the lesion)

Phytophotodermatitis

Phytophotodermatitis is a skin condition that produces burn-like lesions when sunlight interacts with photosensitizing compounds (Fig. 12.1). These compounds (psoralens) are found in certain vegetables or fruits; limes, lemons, and celeries are the most common sources (Bergeson and Weiss 2000). The skin eruptions may appear hours to days after exposure.

The lesions are typically burn-like with hyperpigmentation and areas of erythema and possibly bullae. The lesions are most commonly found around the hands and mouth produced by contact with food products. The lesions may have unusual patterns corresponding to the contact of the food substances, for example, linear streaks from dripping juice or a "handprint shape" from an adult cleaning their child (Endon et al. 2011).

Differentiation from other causes of burns is aided by a history of contact with one of the known food substances and exposure to sunlight, a past history of similar episodes, and the sunburn-like eruptions with unusual configurations and typical locations.

Congenital Conditions

Hemangiomas

Hemangiomas are congenital vascular anomalies that often grow in size before shrinking. Their red–purple discoloration and an appearance of localized tissue swelling may cause them to be mistaken for bruises. If subjected to trauma (e.g., scratched, irritated), they may develop an appearance similar to healing burn.

The differentiation from bruises will be aided by a history (or documentation) of their presence since birth (or in the early months) and the absence of tenderness or color change over proceeding days.

Mongolian Spots

Mongolian spots are congenital hyperpigmented lesions (caused by aggregations of melanocytes) that are blue/purple/gray in color and may be confused with bruising (Fig. 12.2). They are more commonly found in infants of Asian, African–American, and Hispanic descent but may be found in children of all ethnicity. They can vary in shape, size, number, and color, and while they may be found anywhere on the body, they are most commonly located on the lumbosacral region, buttocks, shoulders, and back.

Differentiating characteristics (from bruising) are similar to those described with hemangiomas. A biopsy will reveal the characteristic pigmented intradermal melanocytes rather than the presence of blood or iron deposition.

Port-Wine Stain

Port-wine stains are vascular cutaneous markings consisting of superficial and deep dilated capillaries in the skin and mucous membranes, which produce a red to purple discoloration. They are most commonly located on the face but could exist anywhere on the body. Port-wine stains are present at birth, and the area of affected skin grows in proportion to general growth.

Early stains are usually flat and pink and deepen in color as the child matures. They persist throughout life if no treatment is initiated.

Differentiation from bruising includes the presence of (usually) well-defined edges, blanching if the skin is stretched, and the longevity of the lesion.

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome is an inherited connective tissue disorder characterized by hyperelasticity and fragility of the skin and hypermobility of the joints (Fig. 12.3).

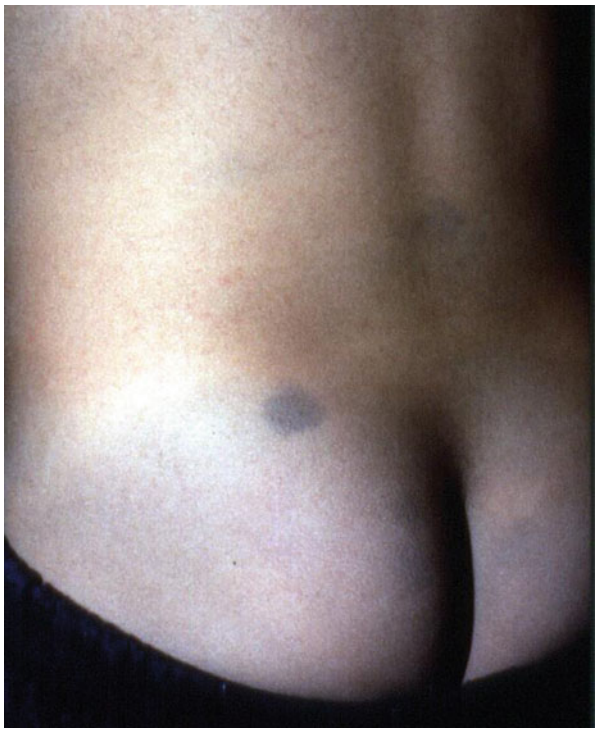

Fig. 12.2 Mongolian blue spot. Caused by collections of melanocytes, these lesions may be mistaken for bruises

Individuals with this condition may have a range of findings including easy bruising, extensive cutaneous injuries from minor trauma, and poor wound healing. These features may raise concerns about assaultive trauma.

Diagnostic assistance may be provided by a possible positive family history for Ehlers-Danlos syndrome or hypermobility of joints and hyperelasticity and fragility of skin and supplemented by genetic investigations.

X-Linked Ichthyosis

X-linked ichthyosis is caused by a steroid sulfatase deficiency resulting from a genetic mutation of the coding gene (STS) (http://emedicine.medscape.com/article/1111398-overview). An X-linked recessive condition, it is relatively common, affecting 1 in 6,000 males. It may manifest at birth or in early infancy and becomes more prominent as the child ages. It begins as mild erythema and generalized peeling of skin with large, translucent scales most pronounced on the face, neck, anterior trunk, and lower limbs. The clinical features (perhaps with histological findings) are diagnostic.

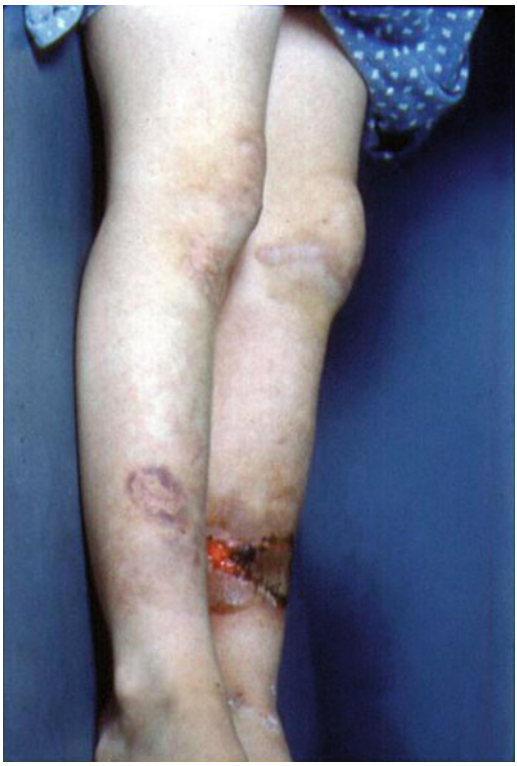

Fig. 12.3 Ehlers-Danlos syndrome. The hyperelasticity and fragility of the skin in this condition may result in minor trauma causing extensive skin injuries

Incontinentia Pigmenti

Incontinentia pigmenti is a rare X-linked genetic disorder that involves the ectodermal, neurological, and ophthalmological systems (Jenny 2011a) (Fig. 12.4). The dermatological findings include vesicular eruptions in a linear configuration with associated erythema and sometimes purpura. These later become linear hyperpigmented lesions along the lines of Blaschko. The erythema, vesicular, and purpuric changes can be mistaken for non accidental injuries.

Differentiating characteristics from cutaneous lesions of child abuse include a positive family history and involvement of neurological, ophthalmological, and other ectodermal tissues; the condition can be confirmed on skin biopsy.

Hypomelanosis of Ito

Also known as incontinentia pigmenti achromians, hypomelanosis of Ito is a non inherited genetic abnormality. The typical cutaneous lesions consist of various patterns of bilateral or unilateral hypopigmentation following the lines of Blaschko and sparing the palms and soles. The skin findings can be accompanied by a wide

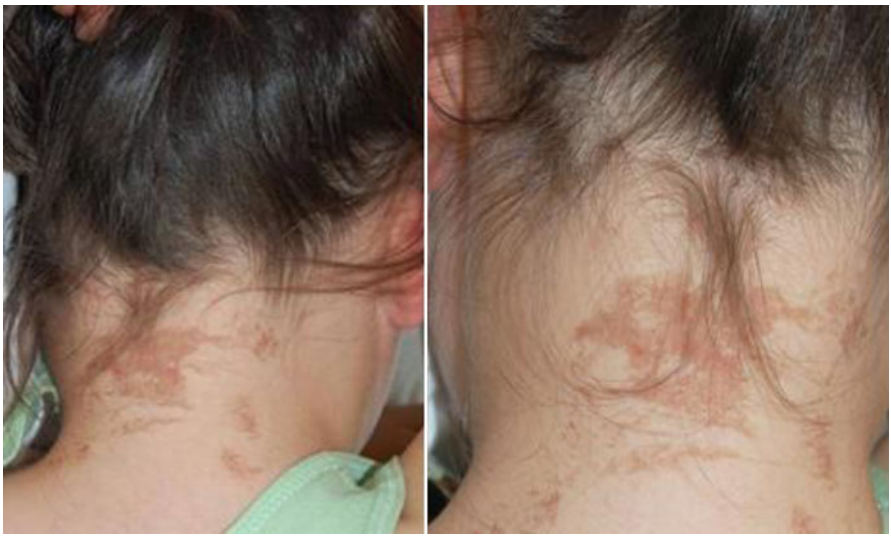

Fig. 12.4 Whorls and dermatome distribution are also seen in incontinentia pigmenti. Such lesions may be mistaken for bruises arising from blunt trauma

range of systemic findings including central nervous system, ocular, and musculoskeletal defects. The hypopigmented lesions mimic healing abrasions.

Diagnosis is assisted by the presence of typical whorl-patterned lesions, the involvement of other systems, and histological findings.

Epidermolysis Bullosa

Epidermolysis bullosa is an inherited connective tissue disease causing blisters in the skin and mucous membranes. While this condition has a wide range of severity, the more severe forms often start at birth. Sufferers of this condition will develop blisters or bullae (from little or no trauma) which may be mistaken for scalds or burns.

Differentiating features include repeated presentations with extensive formation of blisters on the skin and mucous membranes. Diagnosis is confirmed pathologically by a fibroblast culture and genetic testing.

Immune-Mediated Vasculitis

Henoch-Schonlein Purpura (HSP)

Henoch-Schonlein purpura is a small-vessel vasculitis seen in children. The typical presentation is of palpable purpura, petechiae, arthritis/arthralgia, abdominal pain,

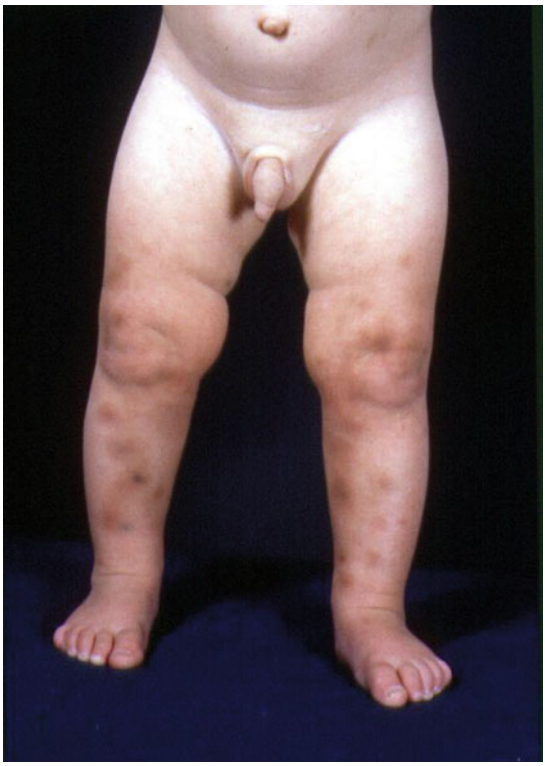

Fig. 12.5 Idiopathic thrombocytopenic purpura. The hyperelasticity and fragility of the skin in this condition may result in minor trauma causing extensive skin injuries

and renal disease. The rash usually begins with small hives or erythematous maculopapular lesions which then progress to palpable purpura and eventually evolve into a more ecchymotic appearance.

The rash might be mistaken for traumatic bruising; however, it is usually symmetrically distributed and located on the lower extremities and buttocks, although some lesions may appear elsewhere on the body.

The presence of other systemic symptoms and the typical symmetrical distribution and location of the rash are useful differentiating factors.

Idiopathic Thrombocytopenic Purpura (ITP)

Idiopathic thrombocytopenic purpura is a condition in children where there is sudden immune-mediated drop in platelet count sometimes following an infection (Fig. 12.5). ITP usually presents as sudden development of generalized bruises and/or bleeding in an otherwise healthy child. Petechiae, purpura, and ecchymoses with or without mucosal bleeding can be found, and in serious cases intracranial hemorrhage may occur. Most of the patients recover completely within several months without any permanent consequences.

Differentiating characteristics from trauma include an otherwise healthy child with thrombocytopenia and an otherwise normal blood count and smear.

Erythema Multiforme

Erythema multiforme is a skin condition mediated by deposition of immune complexes in the superficial microvasculature of the skin and mucous membrane that usually follows an infection (e.g., herpes simplex virus or mycoplasma) or drug exposure (e.g., non steroidal anti-inflammatory drugs, NSAIDs, or sulfur drugs).

The initial presentation of erythema multiforme is of round erythematous papules that can mimic bruises. As the rash progresses, the classic target lesions start to evolve and eventually turn into typical target lesions consisting of a red inflamed central area surrounded by a pale ring of edema and an erythematous halo on the periphery of the lesion. It is usually a self-limiting process.

Differentiating characteristics include a history of recent infections or exposure to drugs commonly known to be associated with erythema multiforme, a usually symmetrically distributed rash, and the evolution of the rash into typical target lesions.

Erythema Nodosum

Erythema nodosum is a delayed hypersensitivity reaction to antigens that causes red–purple painful subcutaneous nodules most commonly seen in the pretibial region and may mimic bruises. The lesions are 1–6 cm in size and generally have a symmetrical distribution. The pathogenesis is largely unclear, though in children, it has associations with streptococcal pharyngitis, inflammatory bowel diseases, and other autoimmune disorders.

A history of recent pharyngitis or the coexistence of other autoimmune disorders and the typical distribution on the anterior surfaces of the legs are useful diagnostic markers.

Panniculitis

Panniculitis refers to a group of skin disorders that involve inflammation of the subcutaneous adipose tissue. It causes tender-skin hard nodules that can resemble bruises. Common causes in children are cold panniculitis following exposure to a cold substance and traumatic panniculitis, also known as fat necrosis, secondary to injuries (Paller and Mancini 2006).

Factors differentiating the condition from other trauma include a history of exposure to cold or trauma and the presence of discrete hard nodules that are extremely tender to touch.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a systemic autoimmune disease that can affect any part of the body including the skin. About 50 % of the patients suffer from the classic malar rash (or butterfly rash) associated with the disease. It is an erythematous rash in a malar distribution over the cheeks and bridge of the nose which could be mistaken for bruising. Other patients may exhibit thick, red, scaly patches on the skin (discoid lupus). Alopecia, mouth, nasal, and vaginal ulcers and lesions on the skin are also possible manifestations.

Thrombocytopenia (a platelet count of less than 150,000/μL) occurs in approximately 50 % of children with SLE. The degree of thrombocytopenia is usually mild and hemorrhage is rare. However, the correlation between the number of platelets and the likelihood of bleeding is poor (Schmugge et al. 2003).

The most common clinical manifestations of thrombocytopenia are petechiae, purpura, and ecchymoses, particularly on the lower arms and legs. Steroids, often used in the management of SLE, may further reduce platelet counts and hence aggravate a bleeding tendency.

Diagnostic assistance is provided by a prior history of SLE, the presence of other systemic autoimmune symptoms, and an abnormal complete blood count.

Infections

Impetigo

Impetigo is a common, highly infectious, superficial skin infection caused by *Staphylococcus aureus* and *Streptococcus pyogenes* (Fig. 12.6). It mainly affects young children, particularly neonates and infants. The condition starts as small vesicles that rapidly enlarge to become bullae which then evolve into erosions with honey-colored crusts.

The differential diagnosis of impetiginous lesions includes cigarette burns. The former condition may be associated with a history of similar findings among siblings or other contacts. The lesions of impetigo vary in size and shape, while cigarette burns tend to be distinct circular or oval shapes. Further, changes in the lesions of impetigo (with or without treatment) further assist in distinguishing the conditions.

Staphylococcal Scalded Skin Syndrome (Ritter Disease)

This condition is caused by *Staphylococcus aureus* though the source of the infection may be unclear. It is usually associated with fever and systemic signs. The toxin-mediated desquamation may be extensive and may simulate burns.

The presence of systemic symptoms, a positive Nikolsky sign (blistering of previously uninvolved skin during stroking), and progressive involvement of previously normal skin help differentiate this condition from burns (Reece and Christian 2009b).

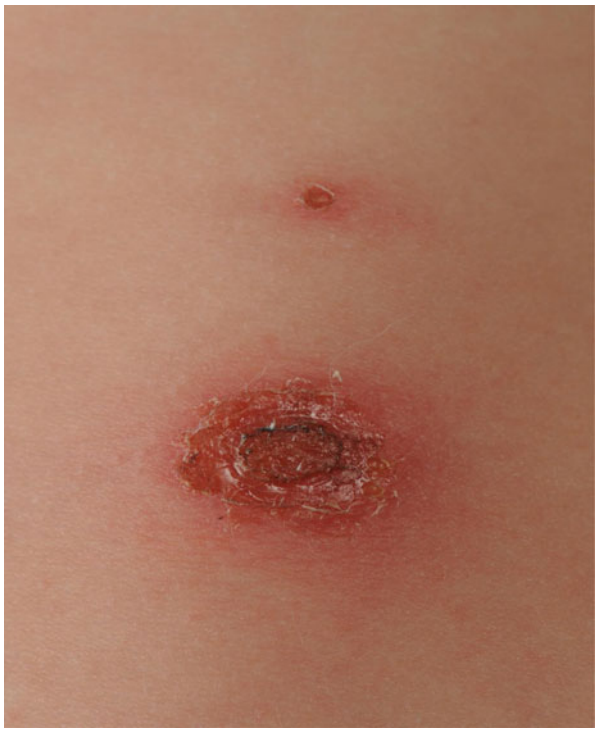

Fig. 12.6 Impetigo. The lesions of impetigo may be mistaken for cigarette burns. Impetiginous lesions, however, vary in size and shape and develop as small vesicles enlarging to become eroded lesions with honey-colored crusts

Fungal Infections

Tinea corporis (also known as ringworm) is a dermatophyte infection. It starts as a scaling red circular or oval patch, and the edges remain slightly raised and red as the center becomes paler in color. The result is a lesion that is ring-shaped. It can be mistaken as burns with scaling, erythema, and well-demarcated edges.

The ring-shaped appearance and the response to antifungal treatment will assist any diagnostic dilemmas.

Meningococcal Septicemia

Meningococcal septicemia is caused by *Neisseria meningitidis* and may be associated with the production of a generalized rash. The rash is initially small, non-blanching, discrete petechiae that can coalesce into larger purpuric and ecchymotic lesions.

Differentiation from bruising secondary to trauma is generally not difficult as further lesions develop over a short period and the child is typically very unwell, especially by the time large purpuric lesions are noted. Pathological diagnosis is achieved by polymerase chain reaction (PCR) and cultures of blood and cerebrospinal fluid (CSF).

Scabies

Scabies is a contagious skin infection that is caused by the mite *Sarcoptes scabiei*, which burrows under the host's skin, causing intense allergic itching ("Scabies". *DermNet NZ*. New Zealand Dermatological Society Incorporated. http://www.dermnetnz.org/arthropods/pdf/scabies-dermnetnz.pdf.). The rash consists of small, red lesions that are often excoriated. Sometimes burrows can be identified.

It would be unusual to confuse scabietic lesions with trauma, but a history of similar symptoms and findings in other family members, an account of intense pruritus (especially at night), and the finding of the lesions at sites such as webs of fingers and toes and around genital–anal area and occasionally on the inner wrists, buttocks, palms, soles, and scalps of infants will help to clarify the diagnosis.

Hematologic Conditions

Bruising is the most common manifestation of blunt trauma occurring in childhood whether occurring in accidental or non accidental circumstances. As mentioned, there are some conditions that may mimic bruising. While the majority of these conditions can be diagnosed clinically, there may be occasions when histologic examination is required. A fundamental element that must be addressed in the assessment of bruising is the possibility that the bruising may be secondary to a hematologic condition. This should occur with the awareness that bleeding disorders and non accidental injuries are not mutually exclusive, and the presence of both conditions may have serious consequences for a child.

In addition to a range of specific disorders, there may be hematologic manifestations caused by a range of systemic disorders, malignancies, and liver or renal diseases. Drug ingestion (therapeutic, accidental, or inappropriately administered) is another potential contributing cause, for instance, anticlotting agents, corticosteroids, and NSAID.

The plethora of inherited hematologic conditions and their relative frequency demand a thorough targeted and consultative process with particular reference to any family or individual history of "easy bleeding," general health, and drug use.

Bleeding/Coagulation Disorders Secondary to Factor Deficiencies

Hemophilia

Hemophilia A and Hemophilia B are common inherited bleeding disorders inherited in an X-linked recessive pattern. Clinical manifestations of hemophilia vary in severity and include excessive bleeding, hemarthrosis, and easy bruising following minor trauma.

A coagulation screen will reveal a prolonged activated partial thromboplastin time (APTT) with a reduced level of Factor VIII (Hemophilia A) or

Factor IX (Hemophilia B). Prothrombin time (PT) will be normal reflecting the normal production of fibrin via the extrinsic pathway and the common final pathway.

Differentiation from non accidental causes of bruising is assisted by a family history of hemophilia, a history of excessive bleeding or easy bruising following minor trauma or procedures, and an abnormal coagulation screen.

Von Willebrand Disease

Von Willebrand disease is the most common inherited bleeding disorder. The symptoms and disease severity can vary widely, and it usually manifests as ready bleeding and bruising especially of the mucous membranes. A coagulation screen may reveal an increased bleeding time and APTT, but these may be normal. Diagnostic tests are von Willebrand factor and activity (ristocetin cofactor assay).

Diagnosis of this condition is made by similar markers to hemophilia albeit with a different abnormality on coagulation screening.

Coagulation Disorders Secondary to Deficiency of Other Clotting Factors

Other inherited bleeding disorders that may present as excessive bleeding/bruising include deficiencies of Factor II, Factor V, Factor VII, Factor X, Factor XI, and Factor XIII (Minford and Richards 2010). Diagnosis is assisted by an abnormal coagulation screen and/or a reduced level of the specific factor(s).

Clotting Disorders Secondary to Platelet Disorders

Platelet disorders can be congenital or acquired and may affect platelet production, destruction, or function. Examples of congenital platelet disorders include Bernard-Soulier syndrome (giant platelets), Wiskott-Aldrich syndrome (X-linked immunodeficiency with platelet dysfunction and thrombocytopenia), and Glanzmann thrombasthenia (an autosomal recessive bleeding disorder characterized by a defect in the platelet glycoprotein IIb/IIIa complex) (George et al. 1990). Examples of acquired platelet disorders include immune thrombocytopenia purpura (ITP), hemolytic uremic syndrome (microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury), and disseminated intravascular coagulation (DIC) (an acquired syndrome characterized by hemorrhage and microvascular thrombosis).

Platelet disorders may present as bruises, petechiae, or purpura, which may occur spontaneously or following minor trauma.

Differentiation from non accidental causes may be assisted by background or family history of platelet disorders and abnormal platelet function tests.

Vitamin K Deficiency

Vitamin K is required for the activation of coagulation Factors II, VII, IX, and X. Deficiency in vitamin K can be associated with a predisposition to bruising and bleeding.

Vitamin K deficiency may occur in a range of clinical settings:

- Antibiotic use. Antibiotics can cause vitamin K deficiency by affecting intestinal bacteria and also through direct effects on vitamin K activation in the liver.
- Vitamin K deficiency in newborns. Newborn infants are at risk of vitamin K deficiency because their immature liver does not efficiently utilize vitamin K. Further, they tend to have low vitamin K stores because of the low vitamin K content of breast milk, a sterile gut, and poor placental transfer of vitamin K (Olson 2000).
- Vitamin K deficiency in children in cystic fibrosis (CF). CF is associated with pancreatic and/or liver diseases and hence children with CF are at risk of fat-soluble vitamin (vitamins A, D, E, and K) deficiencies. Also, chronic use of antibiotics in patients with CF can worsen the vitamin K deficiency through the mechanism mentioned above.

Differentiating bruising from cutaneous signs of child abuse will be assisted by ascertaining the presence of risk factors for vitamin K deficiency (as mentioned above) and the presence of an abnormal coagulation screen.

Malignancy

Neuroblastoma

Neuroblastoma is one of the most common solid tumors of early childhood. It is an embryonal malignancy of the sympathetic nervous system arising from neuroblasts, most commonly from adrenal tissue and the retroperitoneal sympathetic chain (Kliegman 2011).

Clinical presentations vary widely depending on age and the presence or absence of metastasis. The common sites of metastasis are the bone, lymph nodes, bone marrow, and liver. Metastasis to the periorbital bones may cause periorbital ecchymoses (raccoon eyes). This finding could be mistaken as being caused by blunt facial trauma or a fracture of the base of the skull. Imaging, biopsies, and fine-needle aspirates may assist diagnosis, the presence of anemia and cytopenia (bone marrow involvement) will be diagnostic.

Hematologic Malignancies

There are a number of hematologic malignancies that affect the blood, bone marrow, and lymph nodes. These may derive from either of the two major blood

cell lineages: myeloid and lymphoid cell lines. The myeloid cell line normally produces granulocytes, erythrocytes, thrombocytes, macrophages, and mast cells; the lymphoid cell line produces B, T, NK, and plasma cells.

These malignancies may present with pancytopenia and thrombocytopenia and may cause bruising. Differentiating the causes of bruising will be assisted by the presence of other systemic symptoms and signs (e.g., fatigue, fever, hepatosplenomegaly) and the presence of an abnormal complete blood count. Pathological diagnosis will be assisted by histological examination of the spleen and bone marrow.

Cultural Practices

There are a number of traditional or cultural practices whose skin manifestations may be mistaken for non accidental trauma. These practices are performed in good faith (to both children and adults) with no intent of doing harm but rather a genuine belief that the action is treating or curing an intercurrent illness.

There are generally few diagnostic difficulties. The child is likely to be of the ethnic origin of the practice (or have parents or caregivers who are); a history of the "treatment" is also generally forthcoming. The skin changes are usually well circumscribed, and their distribution does not have the randomness associated with an assault. Examples of the more common practices follow.

Cupping

Cupping is a traditional therapy practiced in some Asian, Eastern European, and Central American countries (Jenny 2011b) (Fig. 12.7). Flammable fluid is placed in a cup and ignited. The heated cup is inverted and immediately placed on the skin. A suction force is created by the cooling and contracting of the heated air, and the suction is thought to "draw out" the sickness (Endon et al. 2011). The practice usually produces well-circumscribed circular ecchymoses on the back, chest, and sometimes other locations.

Coining: *Cao Gio*

With coining, the edge of a coin (or other object) is rubbed against oiled skin to get rid of "bad winds" and "heat" in the body that are thought to be causing an illness (Fig. 12.8). It is used in Southeast Asian cultures to treat fever, headache, and chills (Du 1980). Coining produces linear red marks with petechiae or ecchymoses that are usually symmetrically distributed on the back, neck, or anterior chest.

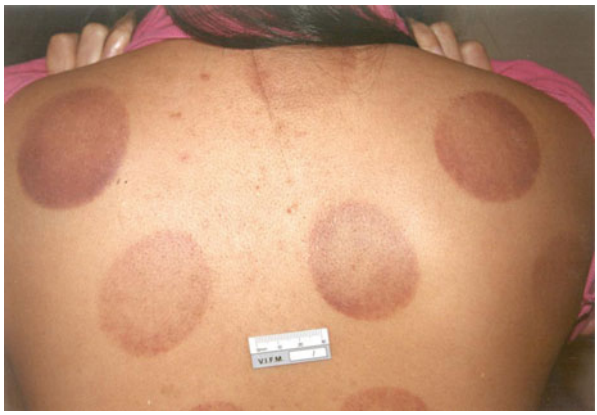

Fig. 12.7 Cupping. A suction force from a heated cup (or similar shaped object) placed on the skin produces well-circumscribed circular ecchymoses

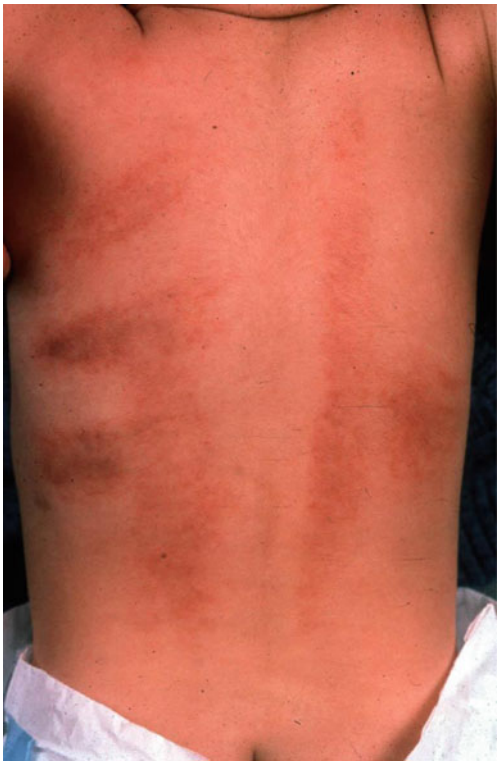

Fig. 12.8 Coining. The symmetrical distribution of erythema or ecchymoses will assist with distinguishing this condition from an abusive trauma

Spooning

Spooning is a Chinese practice similar to that of coining but using a porcelain spoon.

Moxibustion

Moxibustion is another traditional medical practice used in Southeast Asia where mugwort herb (moxa) is burnt on the skin or applied with acupuncture needles. Intended to stimulate circulation, it creates small discrete circular burn marks that could mimic cigarette burns.

Other

Dermatitis Artefacta

Dermatitis artefacta is a factitious disorder characterized by intentional self-inflicted skin injuries. Most commonly seen in adolescent girls, the lesions may be of varying forms, features, shapes, and sizes.

The diagnosis is assisted by the often unusual presentations, an unconvincing account of injury causation, and lesions at usually easily accessible sites (mostly on the dominant side of the body), often bearing geometric patterns or angulated borders that are surrounded by completely healthy skin.

Artifactual Causes

Ink, paint, and dyes from clothing or surfaces that children come into contact with may cause discoloration of the skin that could be mistaken for bruising. These marks are usually easily removed with a cleaning agent and do not change in color, as will occur with bruises.

Anogenital Findings

In addition to the conditions mentioned previously, there are some conditions whose manifestation in the anogenital region may cause confusion with inflicted trauma to the site. Again it is important to acknowledge that these conditions may coexist with sexual abuse.

The diagnosis of these conditions (and their differentiation from sexual abuse) is generally straightforward but may occasionally warrant further investigations. Such conditions include:

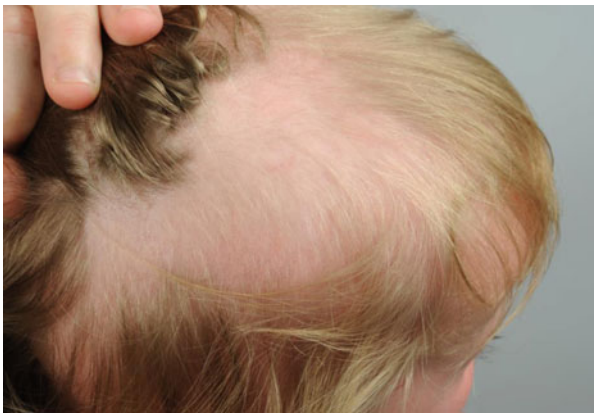

Fig. 12.9 Trichotillomania. The causation of bald spots in children includes self-induced and assaultive hair loss

- Eczema and contact dermatitis (see section "Dermatologic Conditions" above).
- Lichen sclerosus et atrophicus. This chronic inflammatory skin condition is characterized by atrophic skin which is prone to injury after minor trauma.
- Molluscum contagiosum. This viral skin condition may be mistaken for genital warts with the associated implication of sexual contact.
- Perianal streptococcal dermatitis. This infectious condition can produce marked perianal erythema and localized swelling and discomfort.
- Pinworms and their associated pruritus may result in self-inflicted scratches.

Congenital Insensitivity to Pain

Congenital insensitivity to pain may be caused by a hereditary sensory autonomic neuropathy. These are a rare group of disorders of peripheral nerves where the patient does not have sensation of pain and often temperature, whereas all of other sensations (proprioception, light, and deep touch) are intact (Stewart and Rosenberg 1996). The conditions may be inherited in an autosomal dominant or recessive pattern but can also be sporadic (Karmani et al. 2001).

The lack of pain and/or temperature sensation may cause sufferers of this condition to sustain multiple soft and even bony injuries without being aware of them. Secondary bacterial infections of open wounds may also occur without awareness.

Differentiating characteristics from cutaneous signs of child abuse include a positive family history of hereditary sensory autonomic neuropathies, absent sensation to pain and temperature testing, and sensory nerve conduction; velocity tests will be slowed or absent.

Alopecia

Alopecia secondary to trauma is infrequently seen but this might reflect a failure to look rather than a limited incidence (Fig. 12.9). The condition may be more readily

Table 12.1 Postmortem studies that may assist the diagnosis of skin conditions

Diagnostic tests	Examples of conditions
Biopsy/dissection with histologic examination	ILVEN, Mongolian spot, lichen sclerosus
Fine-needle aspiration	Malignancies
Special stains (e.g., iron, immunochemistry)	Bruises, SLE
Cultures (bacterial, fungal, viral)	Meningococcal disease
DNA studies	X-linked ichthyosis, Ehlers-Danlos syndrome
Radiology	Neuroblastoma

Table 12.2 Practical tips for approaching skin conditions when non-accidental trauma is a possible explanation

Consider the possibility of maltreatment coexisting with a medical condition
If in doubt, utilize other specialist opinions (e.g., *dermatological, hematological*)
Seek out any opportunity to view the conditions mentioned in this chapter
Perform investigations if indicated, not only to answer possible questions in court
In living children document (*especially with photography*) *and review the lesions over a period* (*days or weeks*) *to monitor healing or progression*
Ensure that the child is placed in a safe environment, while a definitive diagnosis is being reached

Table 12.3 Issues to be considered for the courtroom

When allegations of child abuse are raised, the final arbitration may occur in the setting of a courtroom. Legal representatives are likely to explore the diagnostic accuracy of any medical evidence. It may be worth considering your responses to the following questions that might be asked of you in court:
Might your findings be explained by a medical condition rather than trauma?
What medical conditions could produce similar findings?
What did you do to exclude an alternative diagnosis? (e.g., *a clotting abnormality*)
Why didn't you do clotting tests/histological examination?
Did you seek an opinion from a hematologist/dermatologist?

evident in children with short hair, while in long-haired children, hair loss may be covered by adjoining strands.

Forceful pulling of the hair may produce a well-demarcated site of alopecia or patchy hair loss. Differential diagnosis includes alopecia areata, tinea capitis, traction alopecia (e.g., in vigorous braiding of the hair), and trichotillomania

(a compulsive urge to pull out one's own hair). Diagnosis of traumatic alopecia (self-induced or abusive) may be assisted by microscopic examination of the remaining shafts and a careful examination of the scalp. A biopsy may reveal traumatized hair follicles with perifollicular hemorrhage, empty follicles, and deformed hair shafts.

Conclusion

All physicians and pathologists working with children should be aware of skin conditions that may mimic non accidental trauma. Reaching a definitive diagnosis requires access to a comprehensive history and physical examination, supplemented on occasions by laboratory investigations or postmortem testing (Table 12.1).

The assessment and management of children in the medicolegal setting carry further obligations for the practitioner, in particular the ongoing safety of the child and other children in the family and the need to convey concerns or a diagnosis to protective, investigatory legal authorities. These further elements require practitioners to turn their minds to specific issues of management and medicolegal processes (Tables 12.2 and 12.3).

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Blunt Abdominal and Thoracic Injuries in Children

13

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Contents

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Abstract

Blunt thoracic and abdominal injuries remain an important cause of morbidity and mortality in children. Motor vehicle collisions account for most blunt chest and abdominal injuries, followed by falls. While mostly seen following accidents, blunt abdominal injuries are, after head injury, the most common cause of homicide in the younger child.

Isolated thoracic or abdominal injuries are less common than combined injuries in both anatomical areas. Thorax injuries have a higher mortality than abdominal injuries. The most common blunt thorax injuries in fatal cases are pneumothorax/hemothorax, lung contusions, and rib fractures. However, mortality is higher where there is cardiac and aortic damage. The most common blunt abdominal injuries are contusions and lacerations to the solid organs, that is, the liver, spleen, and kidneys, and less frequently to the hollow viscera.

The autopsy should not present problems in the identification of injuries, and the circumstances of most cases will not provide any diagnostic problems. However, certain injuries may present concerns, such as posterior rib fractures in young children, where a careful assessment of the history, including a history of resuscitation, needs to be made before an informed opinion on mechanism of injury can be proffered (See ▶ Chap. 21, "Non-Central Nervous System Imaging of Pediatric Inflicted Injury").

Inflicted trauma is an important cause of blunt thoracic and abdominal injury, with abdominal injuries more commonly encountered than thoracic injuries. External injury is often absent. The most common injuries are to the liver and hollow viscera, with injury of the duodenum, ileum, or jejunum. Ruptures may present as peritonitis. Duodenal hematoma may lead to obstruction. Blows may cause the pancreas to be contused, lacerated, or transected and may be complicated by pancreatitis. Thoracic injuries may result from child abuse but are a less a common cause of death than abdominal injuries. Rib fractures are a commonly encountered finding in abuse, but damage to lungs and heart is not common.

Thoracic and abdominal injuries may follow resuscitation, and patterns of injury need to be carefully assessed.

Blast injuries display features similar to blunt trauma and include damage to solid organs and hollow viscera. The circumstances surrounding the infliction of the injury should differentiate these injuries, though blunt trauma may follow bomb blast where the victim is propelled against solid structures or crushed by falling objects.

Introduction and Incidence

Accidents remain the leading manner of death in the pediatric group over 1 year of age in the United States (USA) (Kochanek et al. 2012). The second leading manner of death in children between 1 and 19 years of age is homicide. Traumatic injuries account for over 20,000 deaths annually in the USA in children over 1 year of age (Gaines and Ford 2002). Blunt trauma is more common than penetrating trauma, accounting for 90 % of admissions in a trauma series (Gaines and Ford 2002). Blunt thoracic and abdominal injuries may be seen in both accidents and homicides. In the older child, blunt trauma may be associated with suicide from events such as falls from a height. In a series of blunt trauma cases examined in Denver, Colorado, USA, 7 % of trauma cases were classified as non-accidental (Roaten et al. 2006). After head injury, blunt abdominal injuries are the most common cause of homicide in younger childhood (Pollanen et al. 2002; Phillips and Van Der Heyde 2008).

A number of studies have looked at the incidence of thoracic and abdominal injuries in the pediatric age group, and pediatric trauma registries provide data on the frequency of organ systems involved in trauma. A review of over 25,000 cases reported to the National Pediatric Trauma Registry of the USA occurring between 1985 and 1991 found that 6 % of cases had thoracic injuries and 8 % had abdominal injuries, with 2 % of cases having both thoracic and abdominal injuries. Only 0.2 % had "classic" penetrating thoracoabdominal injuries that traversed the diaphragm (Cooper et al. 1994).

Isolated thoracic and abdominal injuries were half as common as combined injuries. Of 1,553 thoracic injuries, 83 % were due to blunt trauma. Motor vehicle collisions accounted for nearly 75 % of the trauma, with 41 % being vehicular occupants and 33 % pedestrians. Falls (8 %) and bicycle- (7 %) and motorcycle-(3 %)-related injuries were other common causes. Miscellaneous categories accounted for 9 %. While intrathoracic injury accounted for 6 % of injuries, they accounted for 15 % of deaths. The corresponding figures for abdominal injuries were 8 %, but 9 % of all deaths. Thoracic injuries had a higher mortality than head injury, which accounted for 10 % of the fatal cases. The most common penetrating injuries were gunshot wounds (60 %) and stab wounds (33 %).

Incidence of Thoracic Injuries

Of the blunt thoracic injuries recorded, 38 % had a pneumothorax/hemothorax, 49 % had lung contusions with only 1 % lung laceration, 2 % damage to the diaphragm, 35 % rib fractures, and only 1 % had a flail chest (Cooper et al. 1994). Damage to intrathoracic blood vessels accounted for only 1 % of injuries, with the aorta being the most commonly injured vessel. With respect to the heart, 4 % had contusions, but less than 1 % had cardiac lacerations. The larynx, trachea, bronchi, and esophagus were rarely injured (less than 1 % of cases).

An analysis of a series of 195 fatal cases revealed that 50 % had a pneumothorax/hemothorax, 47 % lung contusions, 3 % lung lacerations, 6 % cardiac contusions, and 3 % cardiac lacerations. Twenty-three percent had rib fractures, with 3 % having a flail chest. The aorta was damaged in 3 % of fatal cases (Cooper et al. 1994).

When looking at mortality and injury in blunt thoracic trauma, the incidence of death is 20 % when there is lung damage or a pneumothorax/hemothorax, but rises to 27 % if the diaphragm is involved, 37 % with the heart, and over 50 % if blood vessels are involved. Rib fractures were more common among survivors (35 %) than among those who died (23 %) (Cooper et al. 1994).

Incidence of Abdominal Injuries

In the study by Cooper et al., there were 2,047 abdominal injuries of which 1,754 (86 %) were due to blunt trauma (Cooper et al. 1994). Motor vehicle collisions accounted for nearly 60 % of injuries with occupants representing 32 % and pedestrians 27 %, falls 13 %, bicycle incidents 12 %, and other miscellaneous incidents accounting for 16 %. The overall mortality for blunt abdominal trauma was 9 %. Liver, spleen, and kidney injuries occurred in approximately 30 % of cases, with gastrointestinal injuries accounting for 15 %. Less common were extrarenal genitourinary tract injuries (4 %) and pancreatic injuries (3 %). Vascular injury was present in 3 %, with the celiac and mesenteric arteries and inferior vena cava being the most commonly affected vessels.

In 161 fatal cases of blunt abdominal trauma, the most common damage was to the liver (39 %), with most injuries being lacerations. The spleen was involved in 35 % of cases, the kidneys in 20 %, the gastro intestinal tract in 24 %, with 15 % involving blood vessels, again with the celiac and mesenteric arteries (6 %) and the inferior vena cava (6 %) being the most commonly affected vessels (Cooper et al. 1994).

In examining mortality and intra-abdominal injury from blunt trauma, 13 % of those with liver injury were non-survivors, the figure increasing to 48 % with major lacerations. Similarly with splenic injury, the overall mortality was 11 %, but increased to 28 % with a shattered spleen. Renal injury had an overall mortality of 7 %, increasing to 23 % with laceration and 24 % with disruption. Vascular damage had a 50 % mortality with death in the one case with aortic damage, 82 % with celiac and mesenteric artery damage, and 69 % of children with inferior vena cava damage. The mortality with pancreatic injury was 7 %. Gastrointestinal tract damage had an overall mortality of 15 %: 31 % with injury to the stomach, 5 % with duodenal damage, 12 % with jejunal or ileal damage, and 23 % with colonic or rectal damage (Cooper et al. 1994).

An analysis of 729 falls in the pediatric age group, classified into 393 low-level falls (below 15 ft) and 336 high-level falls (above 15 ft), found that 4 patients had cardiac contusions (0.5 %), 3 of these 4 resulting from a high-level fall; 13 cases had pulmonary contusions, 11 of which were associated with high-level falls. Overall, 12 patients died. All fatal cases sustained a head injury, but 5 of the

12 cases had additional thoracic or abdominal injuries. The mortality with pulmonary contusions was 15 %. Eight patients, all from high-level falls, had a pneumothorax. Seven patients had bowel injuries, 3 from a high-level fall. Eight children had liver injuries, half from a high-level fall. Fifteen patients had a splenic injury, 8 from a high-level fall; 7 cases of renal injury, 3 from a high-level fall (Wang et al. 2001). Trokel et al. reported the three most common causes of abdominal injury were motor vehicle collisions (61.27 %), child abuse (15.75 %), and falls (13.59 %) (Trokel et al. 2004).

The Autopsy in Blunt Thoracic and Abdominal Injury

External Injuries

As with other areas of the body, standard, or usual, injuries caused by blunt trauma may be present. These include abrasions, contusions, and lacerations, depending upon the severity of the trauma (Fig. 13.1). However, even with fatal internal injuries, external injuries may be minimal or absent, especially in the abdomen,

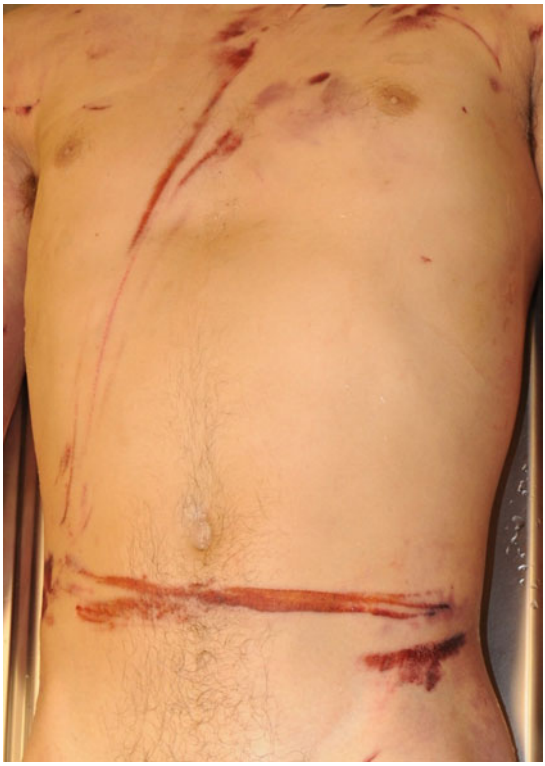

Fig. 13.1 Contusions and abrasions from seatbelt injuries in a teenager

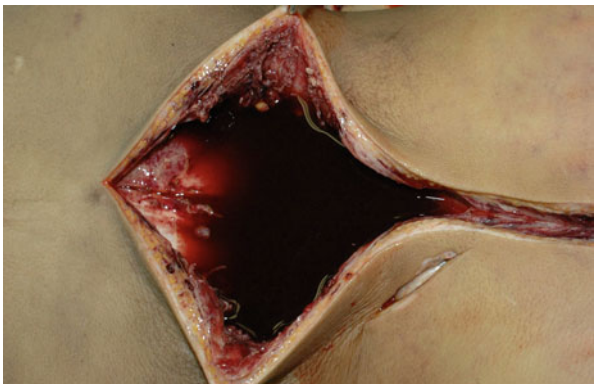

Fig. 13.2 Hemoperitoneum due to blunt force trauma with no external injury

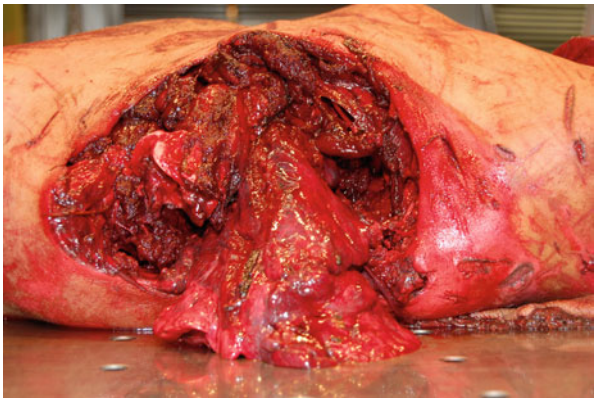

Fig. 13.3 Disruption of the thorax with extrusion of the lung

where the flexibility of the abdominal wall may result in no external injury despite severe inflicted trauma (Fig. 13.2) (Maguire et al. 2013).

Blows to the thorax may result in external injuries that replicate the rib pattern, or the prominences of the spinal processes. Where there has been massive trauma, such as in collisions with large vehicles, there can be extensive disruption of the thoracic and/or abdominal wall, with extrusion of organs (Fig. 13.3).

Injuries to the Thorax

In an analysis of 100 cases of blunt trauma to the thorax from motor vehicle collisions by Roux and Fisher, the most common injuries were pulmonary contusions, present in 73 % of cases (Roux and Fisher 1992). In 38 % of these cases, there was no radiological evidence of rib fracture. Rib fractures were present in 62 % of cases, posttraumatic effusions in 56 %, pneumothorax in 38 %, and pneumatocele in 5 %. Extrathoracic injuries were present in 97 % of cases, most commonly head injuries (80 %).

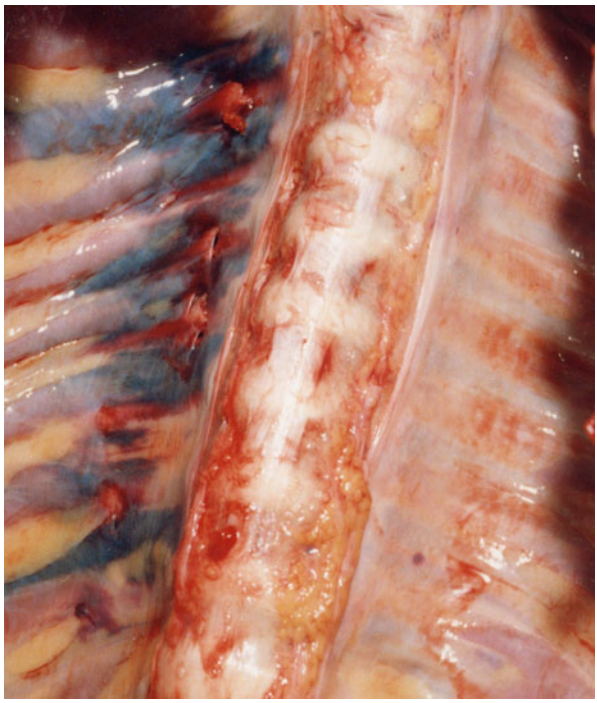

Fig. 13.4 Posterior rib fractures and intercostal hemorrhage

Rib fractures are an important finding in both deliberately inflicted thoracic trauma and in accidents. Rib fractures may be due to birth trauma (Bulloch et al. 2000) (see ▶ Chap. 6, "Birth Trauma"). Ribs are less prone to damage in the young as they are flexible and less likely to fracture. Clinically, flail chest is not common in children and is usually relatively small. In the series by Roux and Fisher, there were only four cases of flail chest (Roux and Fisher 1992). These children had eight or more rib fractures. Sternal fractures are also not common in children (Allen et al. 1997).

Rib fractures in children are reported to be highly associated with non-accidental injury, especially in a child under 3 years of age (Garcia et al. 1990; Barsness et al. 2003). When rib cage fractures are found in children below 3 years of age, there can be a risk of assuming that they are the result of deliberately inflicted trauma. However, before such a conclusion can be drawn, all such findings must be carefully investigated and evaluated. This includes histological analysis. Rib fractures have been reported as a consequence of chest physiotherapy, when they were present both laterally and posteriorly (Chalumeau et al. 2002). In child abuse, rib fractures are commonly seen in the posterior rib cage (Fig. 13.4) (Bulloch et al. 2000). They are also typically seen in various stages of healing (Figs. 13.5 and 13.6), although acute fractures may be present. In cases of reported child abuse, lateral fractures are the second most common location, with anterior rib fractures being less often reported. Posterior rib fractures have been reported in neonates as a consequence of birth trauma (van Rijn et al. 2009). Fractures of the first rib have

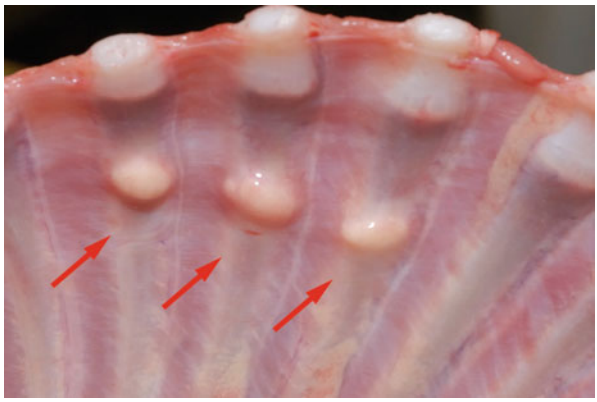

Fig. 13.5 Healing rib fractures (*arrows*)

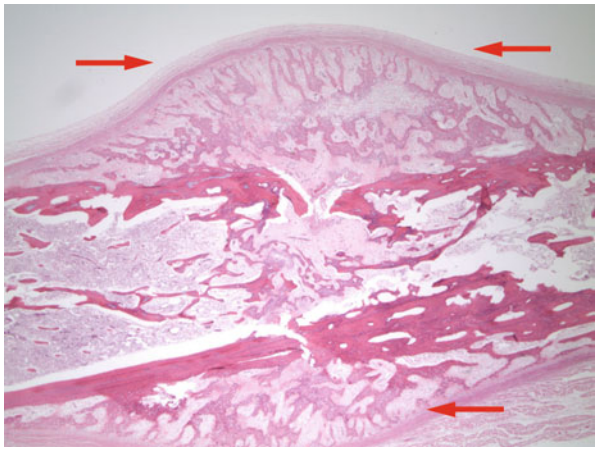

Fig. 13.6 Histologic appearance of healing rib fracture in Fig. 13.5. This image shows callus formation (*arrows*). The estimated age of the fracture is 2–4 weeks. (Hematoxylin and Eosin, H&E ×10)

been stated to be highly specific for child abuse (Melville et al. 2012). Other injuries associated with inflicted trauma need to be carefully sought. Questions that need to be asked in the presence of acute rib fractures are whether cardiopulmonary resuscitation (CPR) has been attempted, by whom, and what technique was used. Rib fractures have been associated with CPR, depending on the age of the child, including posterior rib fractures (Dolinak 2007; Clouse et al. 2008; Weber et al. 2009; Matshes and Lew 2010) (see ▶ Chap. 21, "Non-Central Nervous System Imaging of Pediatric Inflicted Injury"). The recent reports of posterior rib fractures following resuscitation may be due to a change in resuscitation technique. Autopsy studies are likely to have a higher incidence of diagnosed rib fractures if a detailed examination of the rib cage is conducted with removal of the parietal pleura so that the ribs can be examined directly, followed by detailed dissection and histological analysis (Fig. 13.6). The other consideration is whether there is an underlying disorder of bone that accounts for the rib fractures (Carty 1993).

In assessing any case at autopsy where there may be deliberately inflicted injury in a child, it is important that a full skeletal survey is performed, not just

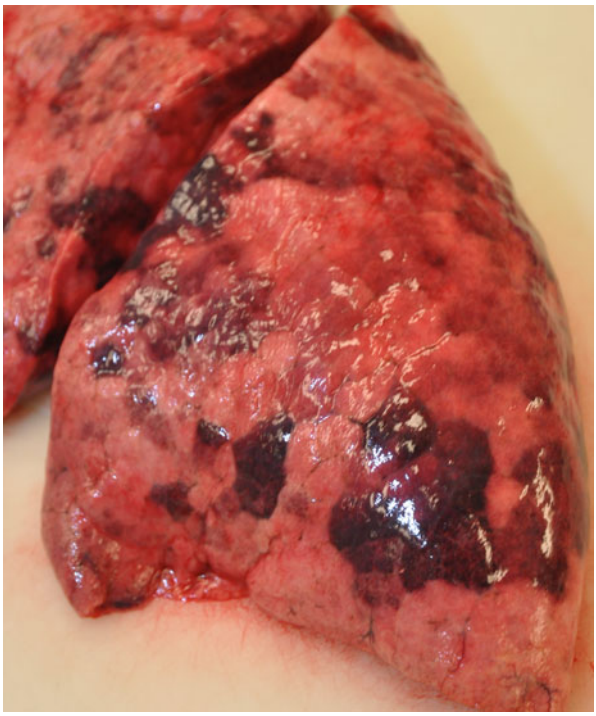

Fig. 13.7 Lung contusions due to blunt trauma

a *babygram*, that the fractures are dissected and submitted for histology along with appropriate normal rib controls, and that other ancillary tests are conducted to exclude metabolic bone diseases.

Pneumothorax can be diagnosed at autopsy by imaging techniques or by opening the chest wall under water and seeing if air comes out when the chest wall is breached. If this technique is not thought of before commencing the dissection, a pneumothorax may be missed, as the lungs normally collapse upon opening the thoracic cavity. The presence of a hemothorax can be identified upon opening the thoracic cavities followed by a search for the cause/source of bleeding. The quantity of blood should be measured. It is advisable to collect this blood for toxicological testing, as other blood may not be easily available in major trauma, though if submitted, the laboratory must be made aware of the site of collection. Where there has also been rupture of the stomach or bowel and disruption of the diaphragm, the blood may have been contaminated with gastrointestinal contents and is less suitable for toxicological analysis.

Injuries to the Lungs and Tracheobronchial Tree

Contusional damage to the lungs is most commonly seen following motor vehicle collisions (Fig. 13.7). Bonadio and Hellmich reviewed 35 cases with pulmonary contusions over a 12-year period. Just over half (19 out of 35) were over 5 years of

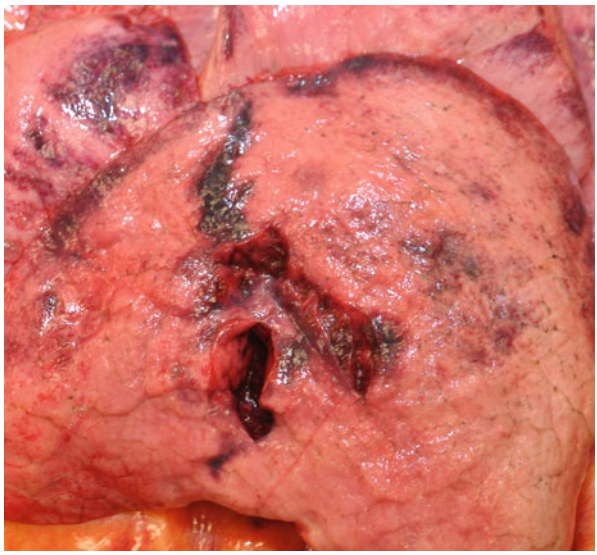

Fig. 13.8 Lung lacerations

age (Bonadio and Hellmich 1989). Extrathoracic injury was present in 29 of the 35 children. Ten patients had rib fracture and 16 had external injury with bruises and abrasions. Clavicular fracture was present in four cases, and a scapula fracture was present in one case. In Cooper's (Cooper et al. 1994) series, mortality associated with contusional damage to the lungs was 15 %. Of note, pulmonary contusions in children may not have as high a mortality rate as in adults (Hamrick et al. 2010).

At autopsy, pulmonary contusions will be seen macroscopically and if necessary by microscopic examination. Lacerations will also be evident on gross examination (Fig. 13.8). Complications of pulmonary contusions include pneumonia and the development of Acute Respiratory Distress Syndrome (ARDS) (Allen et al. 1997). Pulmonary contusions may be a consequence of blast injury and from impact with rubber bullets (Smyth 1979). Rarely there may be rupture of the tracheobronchial tree (Hancock and Wiseman 1991; Wiener et al. 1993; Grant et al. 1998; Ait Ali Slimane et al. 1999). These injuries may occur in the absence of rib fractures.

Injuries to the Heart

The heart may be damaged by blunt trauma including contusions. In an analysis of seven pediatric patients with cardiac contusion(s), all seven involved vehicles: five children as pedestrians, one a passenger, and the seventh being crushed by a car when a jack collapsed. All patients had at least one major organ system injured (Ildstad et al. 1990). An analysis of 499 pediatric deaths in Ontario, Canada, from blunt trauma revealed 41 cases with cardiac injuries. Their mean age

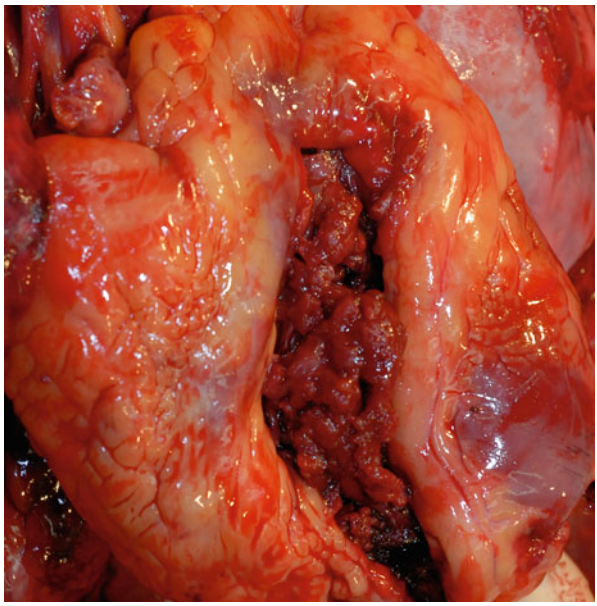

Fig. 13.9 Cardiac laceration secondary to blunt force trauma

was 9.6 years, ranging from 7 months to 16 years. Of these cases, only one was a homicide, the other cases being transport incidents (37 cases) and falls from a height (3 cases). Contusions were seen in 25 cases, most commonly to the left ventricle (12 cases) with rupture of one or more chambers of the heart in 16 cases (Scorpio et al. 1996). Rupture should be easily identified at autopsy (Fig. 13.9). Where the pericardium remains intact, a hemopericardium of varying size will be present (Fig. 13.10).

Injuries to the aorta and other intrathoracic vessels The most common vascular blunt force injury is to the thoracic aorta, which accounts for 95–99 % of all pediatric aortic injuries (Choit et al. 2006). Pediatric thoracic aortic injuries are rare and there is typically injury to other organs (Bliss and Silen 2002). Thoracic aortic injury is most commonly seen in vehicular collisions. Rib fractures may not be present. In the Ontario study of 499 blunt trauma deaths, rupture of the thoracic aorta was in three cases and contusional damage in one case (Scorpio et al. 1996). The typical site of rupture of the thoracic aorta is at the ligamentum arteriosum (Fig. 13.11). External injury may be lacking (Fig. 13.12). It is most commonly seen in the pediatric age group in teenagers (Trachiotis et al. 1996). Pathologists should be familiar with this injury as it is commonly found at autopsy in fatal vehicular collisions. It causes very rapid death.

Esophageal Injuries

Esophageal injuries are rare following blunt trauma. They have been reported following motor vehicle collisions and crush injuries (Sartorelli et al. 1999).

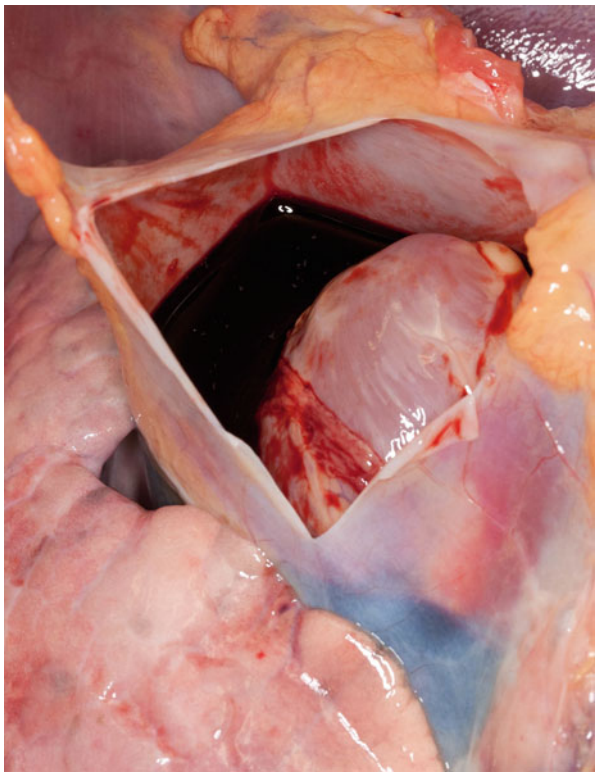

Fig. 13.10 Hemopericardium due to atrial rupture from blunt force trauma

Diaphragm

The diaphragm is rarely injured, reported in less than 1 % of cases of blunt trauma to the abdomen (Barsness et al. 2004). Diaphragmatic injury is commonly associated with other injuries, particularly of the liver and spleen.

Commotio Cordis

An important cause of sudden death in childhood and adolescence following an impact to the chest is commotio cordis. This is a rare event that requires two factors to occur at the same time: an impact over the precordium and at the point in the heart's electric rhythm in the repolarization phase, just 15–30 ms before the T-wave peak in the electrocardiography (ECG) cycle. Children, with their less developed rib cage, are vulnerable. Commotio cordis is usually associated with sporting events, with baseball the most commonly reported activity, though it can occur with any impact over the chest (Maron et al. 1995, 2002, 2007). Chest protectors do not exclude the development of commotio cordis.

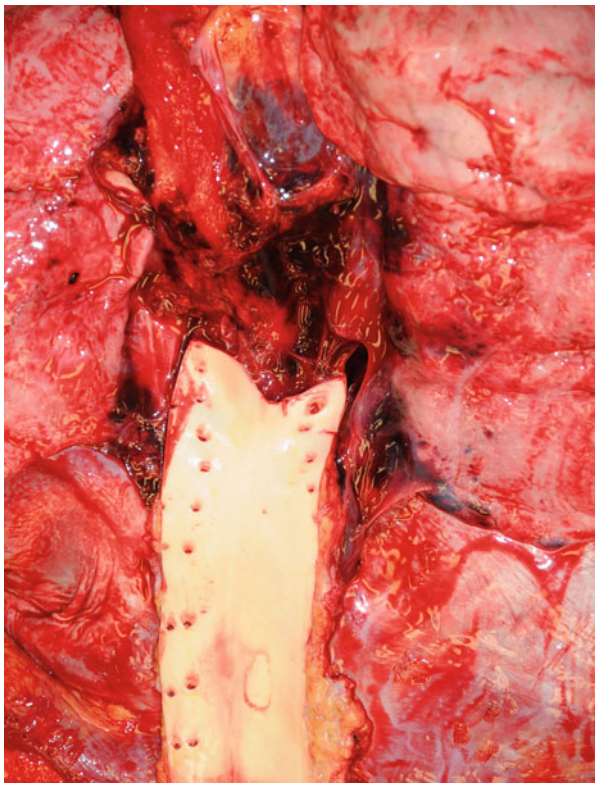

Fig. 13.11 Transection of the thoracic aorta at the ligamentum arteriosum due to blunt trauma from motor vehicle collision

Often the autopsy is negative. The diagnosis is based upon the medicolegal investigation rather than the autopsy findings alone. Homicide by commotio cordis has been reported in the pediatric age group (Boglioli et al. 1998; Baker et al. 2003)

Injuries to the Abdomen

Intra-abdominal injuries from blunt trauma can result in localized organ injury or more generalized effects involving multiple organs, intra-abdominal or retroperitoneal hemorrhage, and subsequent intra-abdominal infection. These sequelae can further result in systemic disorders including shock and generalized septic shock. Injury involving more than one organ is common in blunt trauma. Where there is concern over the age of an injury, histological examination can be undertaken to further determine the age. As with all histological dating, this will allow an expression of a range of possible times, rather than a specific time, for an injury to be identified. If there is hemoperitoneum, the volume should be recorded. Similarly, the volume of the peritonitis fluid should be recorded.

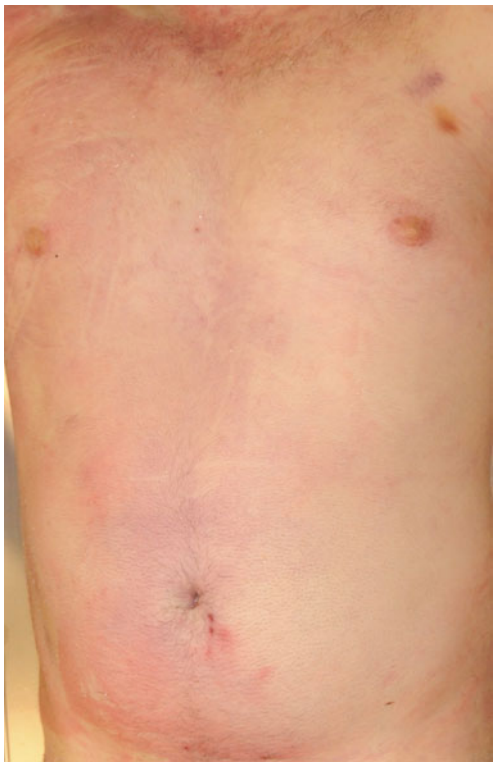

Fig. 13.12 Absence of external injury with underlying transected aorta due to a motor vehicle collision

The Liver

Liver injury is a common sequel of blunt trauma to the abdomen. It may be identified clinically through imaging and a rise in liver enzymes (Oldham et al. 1984). Injury may vary from mild contusions and superficial lacerations, to more severe parenchymal hematoma formation and, in the severest case, hepatic avulsion and "explosive type" parenchymal disruption (Fig. 13.13) (Losty et al. 1997).

The right lobe of the liver is the most frequently damaged. Delayed complications of trauma include rupture of a subcapsular hematoma. Hemorrhage may also result from hepatic vein injury as well as from injuries to intraparenchymal hepatic vessels. Clinically, most patients with liver trauma can be managed conservatively (Cywes et al. 1991).

At autopsy, identification of acute liver trauma should not present problems. Dating may be required and older injury can be present alongside more recent injury, especially in the case of deliberately inflicted trauma. Histological examination of areas of trauma should be undertaken as well as of areas distant from trauma.

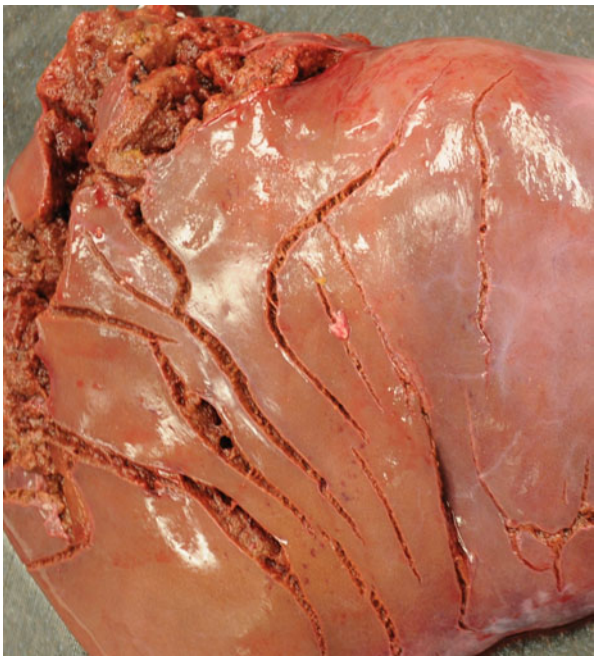

Fig. 13.13 Liver lacerations due to blunt force trauma secondary to a motor vehicle collision

The Spleen

The spleen may show varying degrees of blunt injury with contusional damage, laceration, and, in the severest cases, avulsion (Fig. 13.14). Clinically, many cases of splenic injury are managed conservatively (Sjövall and Hirsch 1997). There may be delayed rupture of a hematoma.

The Stomach

The stomach is less frequently injured in blunt trauma than the small bowel. Gastric intramural hematoma with pneumatosis has been reported in child abuse (Fulcher et al. 1990). The stomach appears to be more vulnerable to gastric perforation from trauma when there has been ingestion of a large meal. Grosfeld and colleagues reported two cases of gastric perforation following trauma, one involving a kick from a horse and the other a child who ran into the bow of a boat, both following ingestion of a large meal (Grosfeld et al. 1989). Another case of a gastric rupture in a child following impact from a cow has been reported (Baeza-Herrera et al. 2003).

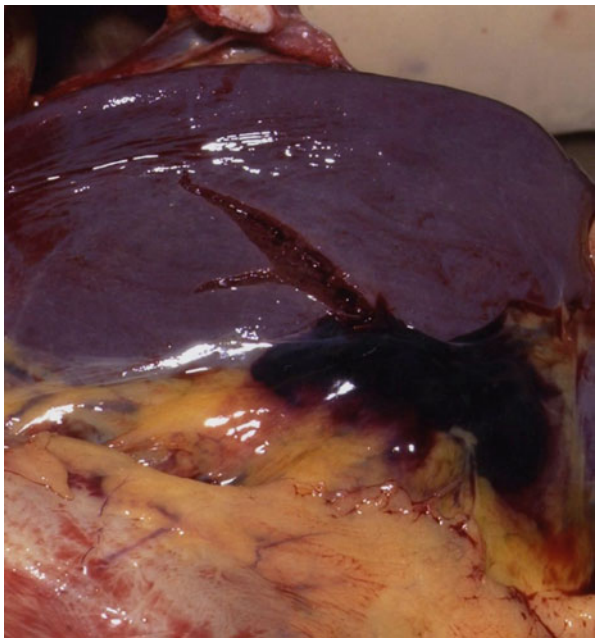

Fig. 13.14 Splenic laceration in a teenager secondary to a fall

The Small Bowel and Mesentery

The most common parts of the bowel damaged with blunt force are the duodenum, jejunum, and ileum. The mechanism of injury in these cases is compression of the bowel against the vertebral column. The duodenum is reported to be injured in 4–6 % of cases of abdominal trauma. The duodenum may be ruptured in its retroperitoneal or peritoneal portion (Pokorny et al. 1986). These injuries may be seen both as a consequence of accidental trauma and following abuse. Duodenal wall hematoma may develop following blunt trauma and present as bowel obstruction (Winthrop et al. 1986). Non-traumatic duodenal hematoma in a case with a bleeding disorder has also been reported (DeRose et al. 1997). Duodenal injuries are often associated with pancreatic injuries (Desai et al. 2003).

The jejunum and ileum are well recognized as structures damaged from blunt abdominal trauma. The jejunum is the most commonly damaged part of the bowel in blunt trauma, especially near the ligament of Treitz (Bruny et al. 2004). The jejunum is typically perforated when the bowel is crushed against the spine. Mesenteric laceration and avulsion commonly accompany small bowel injury. While motor vehicle collisions account for most injuries, falls, kicks by an animal such as a horse, and child abuse also may cause injury (Grosfeld et al. 1989). The presentation may be delayed with peritonitis established by the time the child is assessed medically. This is particularly so

with inflicted injury in the child where the perpetrators are often reluctant to bring the child to medical attention. With abdominal trauma, mesenteric lacerations may occur and represent the primary bleeding source (Ng et al. 1997). At autopsy, there will be obvious laceration to the mesentery with a hemoperitoneum. Mesenteric fibrosis has been reported as a marker of previous blunt abdominal trauma and can be identified on microscopic examination (Byard and Heath 2010).

The Large Bowel

The large bowel is rarely damaged in blunt abdominal trauma, with an incidence of 0.5 % in an analysis of 54,361 cases of patients sustaining blunt trauma (Canty and Brown 1999). Penetrating wounds of the colon are more common (Öztürk et al. 2000).

The Pancreas

When the pancreas is damaged in blunt trauma, the injury may be complicated by pseudocyst formation and pancreatitis. Injuries may vary from superficial contusions to laceration of the head, body, or tail of the pancreas. Blunt trauma is the most common cause of pancreatic injury in a child and involves a number of scenarios including handlebar injuries. These cases can present as an isolated injury. However, pancreatic injury is often associated with duodenal injury. In a study of 1,045 children who sustained blunt trauma and were clinically presumed to have intra-abdominal injury and underwent computed tomography (CT) scanning, pancreatic injury was diagnosed in 18 cases: 10 diagnosed at surgery, 5 at autopsy, and 3 by clinical or imaging follow-up. The injuries consisted of 11 lacerations, 2 transections, 1 contusion, and a tumor with hemorrhage in one case (Sivit et al. 1992a). Three additional children had pancreatitis. Six children had other associated intra-abdominal injury. Raised serum amylase and lipase are common findings in clinical cases (Dahman and Stephens 1981; Bass et al. 1988; Arkovitz et al. 1997; McGahren et al. 1995; Meier et al. 2001).

The Abdominal Aorta

Injury to the abdominal aorta is rare in childhood (Choit et al. 2006). Blunt trauma to the abdomen may cause aortic laceration and transection. Such injury has been reported in motor vehicle collisions in a child wearing a seat belt and also following inflicted injury (Riches et al. 2002). Injury to the abdominal aorta may be seen in association with fractures of the lumbar spine secondary to seat belt use (Choit et al. 2006). Delayed rupture of the abdominal aorta has also been reported (Tracy et al. 1996; Muñiz and Haynes 2004).

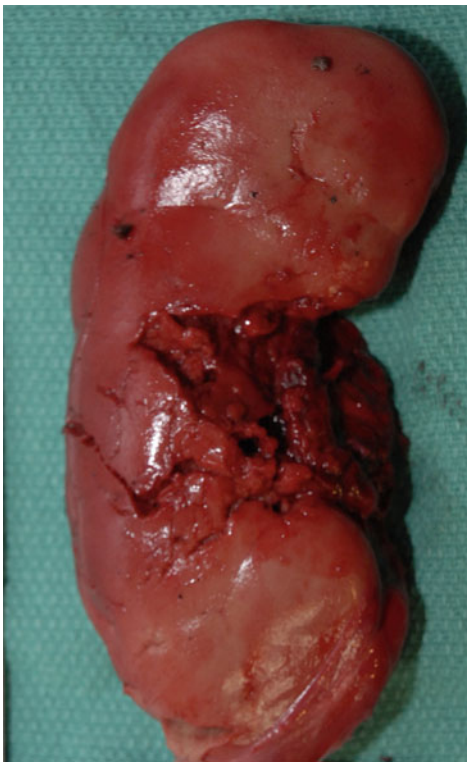

Fig. 13.15 Renal laceration external surface due to a motor vehicle collision

The Kidneys

Blunt trauma injuries to the kidney are rarely isolated as other organs are normally injured as well. Trauma to the kidney may range from contusions and subcapsular hematomas, superficial lacerations, more extensive lacerations, avulsion at the hilum, to extensive rupture of the kidney (Figs. 13.15 and 13.16). Most clinical cases of renal trauma are dealt with conservatively. Blunt trauma accounts for the majority of injuries to the kidneys, which is the most common injury site to the genitourinary tract in blunt trauma. Most cases are caused by motor vehicle collisions, falls, and sports-related injuries (Nguyen and Das 2002). In a series of 333 blunt renal injury cases, only 12 cases (4 %) were classified as severe injury (Buckley and McAninch 2004). Children are more vulnerable to renal trauma than adults because of the relative size of their kidneys; congenitally malformed kidneys are more commonly injured (McAleer et al. 2002). Renovascular injury may occur without there being damage to the parenchyma of the kidney. This represents 1–3 % of all blunt trauma injuries to the kidney and occurs with rapid deceleration injury. Clinically, hematuria may not be seen with this type of injury.

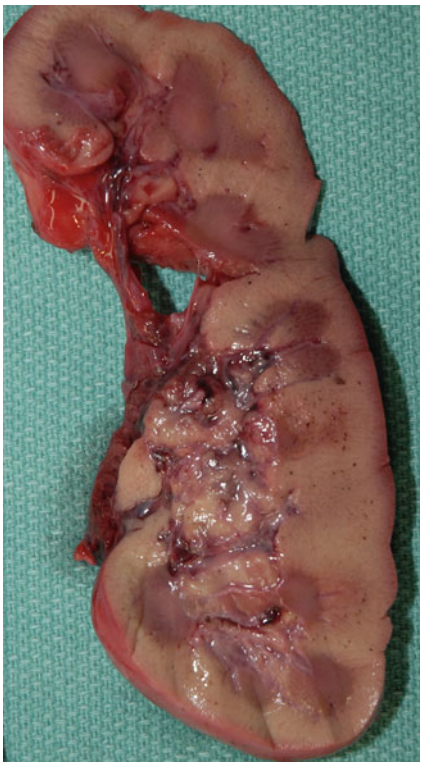

Fig. 13.16 Renal laceration from motor vehicle collision

The Bladder

Blunt trauma is the most common cause of bladder injury in children, most caused by motor vehicle collisions. There are typically other injuries including bony injury to the pelvis, although many pediatric cases do not have fractures (McAleer et al. 1993; Sivit et al. 1995). The trauma may vary from contusional damage to laceration with rupture. Isolated bladder rupture has been reported as a result of deliberately inflicted injury (Lautz et al. 2009).

Retroperitoneal Hematomas

Retroperitoneal hematomas may complicate blunt trauma to the abdomen, including injuries to the duodenum and the genitourinary tract. In a series of 61 falls from a height in children seen in New York, USA, 4 had retroperitoneal hematomas (Barlow et al. 1983). In another series of 64 falls from Montreal, Canada, there was one retroperitoneal hematoma (Lallier et al. 1999). Pelvic fractures are commonly

associated with retroperitoneal hemorrhage. In 120 cases of pelvic fractures, 55 cases had retroperitoneal hemorrhage. Most of these cases were due to motor vehicle collisions (Reichard et al. 1980).

The Adrenal Gland

Adrenal gland hemorrhage may occur following blunt trauma in children. In an analysis of 1,155 cases of blunt trauma to the abdomen in children, there were 34 cases of adrenal hemorrhage indentified on CT scanning (Sivit et al. 1992b). The age range was 2 months to 16 years with a median age of 5 years. The most common mechanism of injury was vehicular collision (25 cases), with 14 pedestrians and 11 passengers. In five cases, the injury occurred following an assault. The other cases involved falls, bicycle injuries, and sled injuries. The adrenal hemorrhage was unilateral in 20 cases and bilateral in 2 cases. In 22 cases, ipsilateral damage was to other organs: the liver in 17 cases, spleen in 6 cases, and the kidney in 5 cases. Ipsilateral thoracic injury was seen in 16 cases, and retroperitoneal hemorrhage in 7 cases. Follow-up CT scans showed that while some cases resolved, in others there was persistent abnormality seen. Similar results were found in a study of 9,199 pediatric cases, with 20 cases of adrenal trauma identified. In 5 cases, adrenal hemorrhage was the only evidence of intra-abdominal trauma. In 4 of these cases, there was extra-abdominal injury. Three patients required blood transfusion for adrenal hemorrhage (Gabal-Shehab and Alagiri 2005).

Deliberately Inflicted Injury to the Thorax and Abdomen

Blunt trauma may be intentionally inflicted to a child and so it is important to understand the potential patterns of injury that may be seen. It should always be remembered that there is a large overlap with injuries caused in accidents and that the pattern of pathology is only one part of the medicolegal investigation (Maguire et al. 2013). Intentionally inflicted injuries to the abdomen are more common than to the thorax. After head injury, abdominal injuries are the leading cause of blunt impact deaths in childhood.

Abdominal Injuries in Child Abuse

Inflicted injuries to the abdomen involve both solid and hollow organs (Hilmes et al. 2011). Blunt abdominal injuries in child abuse have a mortality rate of up to 50 %, and blunt trauma from abuse has a worse prognosis than from accidental trauma (Cooper et al. 1988; Trokel et al. 2004; Cameron et al. 1997).

In a study of 10,000 trauma cases from two hospitals in the USA, 22 were cases of abdominal trauma with a mortality rate of 45 % (Cooper et al. 1988). The average age of the child was 24 months with 14 boys and 8 girls. Delayed presentation was

common. Clinically, there may be disordered liver and pancreatic enzymes which can be used as screening tests in the living for injury (Coant et al. 1992; Kellogg 2007; Lane et al. 2009).

The most common inflicted injuries are to the liver and the hollow viscera (Maguire et al. 2013). External bruising of the abdomen is absent in many cases of abdominal trauma despite there being significant injury to the abdominal organs (Holmes et al. 2002; Wood et al. 2005). The liver is commonly injured by blows to the abdomen. The degree of liver injury will vary. Contusional damage and subcapsular hematomata may be seen. The liver may be completely lacerated so that it is separated into two or more pieces. Older injury may be present, and histological analysis will assist with dating (Figs. 13.17–13.23). In one case seen by the author, separated necrotic liver tissue was present in the peritoneal cavity along with more recent injury, indicating past impact injury to the abdomen (Figs. 13.24 and 13.25). As with accidental blunt trauma, the other solid organs may be injured with lacerations and bruising. The adrenal gland may also show hemorrhage. Laceration of the adrenal gland has been reported in child abuse. More chronic adrenal hemorrhage may be encountered in a previously abused child. Hemorrhage may also represent a stress reaction rather than direct injury (Nimkin et al. 1994).

A common pattern is rupture of the duodenum, jejunum, or ileum (Figs. 13.26 and 13.27). The duodenum is often ruptured at the junction of the third and fourth parts. When the bowel is ruptured, peritonitis will develop if there is no medical intervention, and these children typically present late, or dead, with florid peritonitis. Injury is caused by a heavy blow to the abdomen, either as a punch or kick/stamp. This injury has not been recorded in young children (less than 5 years) as a consequence of a fall (Maguire et al. 2013). The mechanism of the injury is impact to the bowel with crushing against the vertebral column in a “hammer and anvil” manner. Another consequence of a blow to this area is a duodenal hematoma without rupture. These children may present with gastric outlet obstruction. Hemosiderin-laden macrophages may be seen in areas of all traumas in the abdominal organs or supporting tissues, including the wall of the duodenum, indicating a previous impact to these areas (Dye et al. 2008). Mesenteric fibrosis has also been reported as a sign of previous abdominal impact (Byard and Heath 2010). The pancreas is vulnerable to blows that also damage the duodenum (Fig. 13.28). The pancreas may be contused, lacerated, or transected (Figs. 13.29 and 13.30). Complications include pancreatitis, fat necrosis, and pseudocyst formation (Bongiovi and Logosso 1969; Pena and Medovy 1973; Slovis et al. 1975; Ziegler et al. 1988). Osteolytic lesions in bone have been recorded as a complication of pancreatic injury, present in the phalanges, tarsal, and metatarsal bones, as well as in the long bones, and are believed to be related to fat necrosis (Bongiovi and Logosso 1969; Neuer et al. 1977; Cohen et al. 1981).

The stomach is rarely injured, but gastric rupture in abuse has been recorded (Schechner and Ehrlich 1974). In one case where a child was kneed in the abdomen, fatal peritonitis resulted (Case and Nanduri 1983).

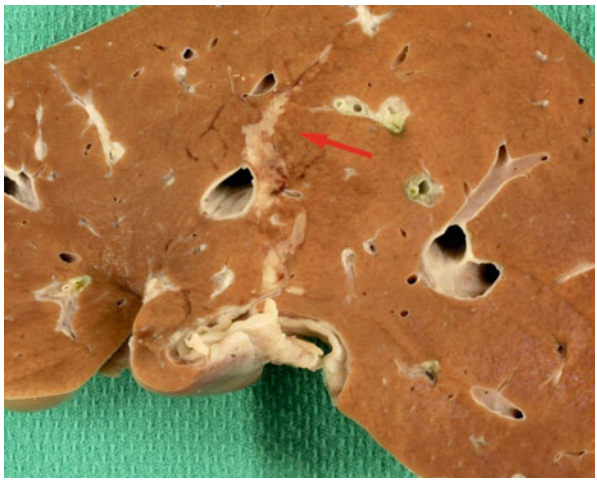

Fig. 13.17 Healing liver laceration found at autopsy, a case of child abuse in a seven-year-old

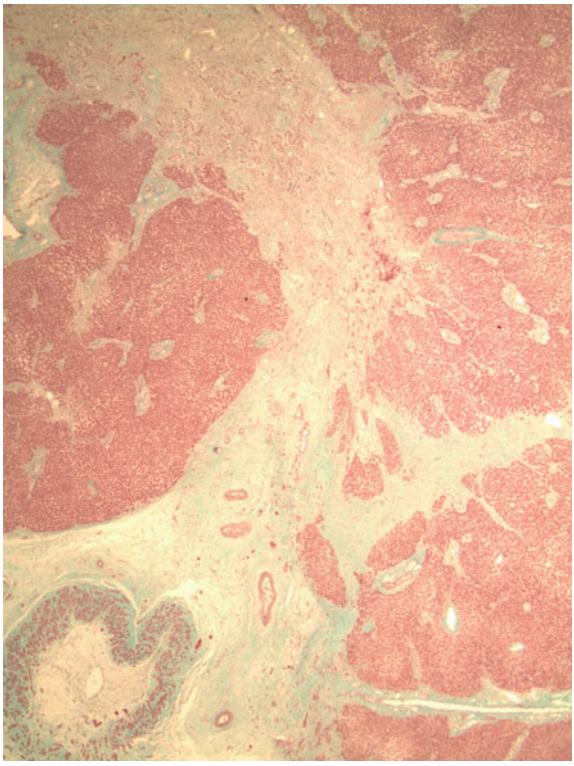

Fig. 13.18 Healing liver laceration with established fibrosis, likely 4–6 weeks old (Trichrome stain × 12.5)

Chylous ascites has been recorded following abuse and as the presenting feature. Other injuries were present in these cases. The mechanism is trauma to the abdomen causing lymphatic damage (Hilfer and Holgersen 1995; Beal et al. 1998).

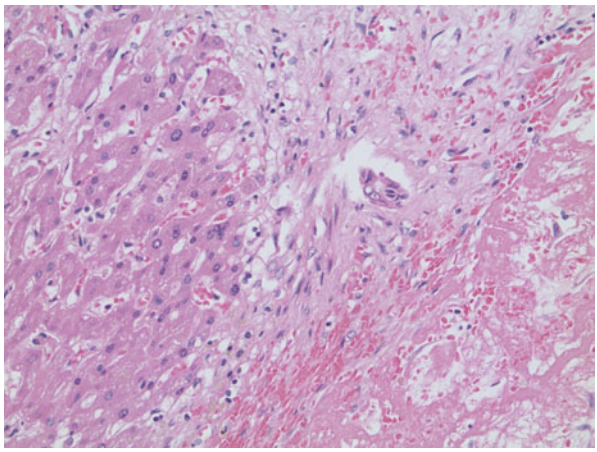

Fig. 13.19 Healing liver laceration in Fig. 13.18 at higher power (Hematoxylin and Eosin, H&E × 200)

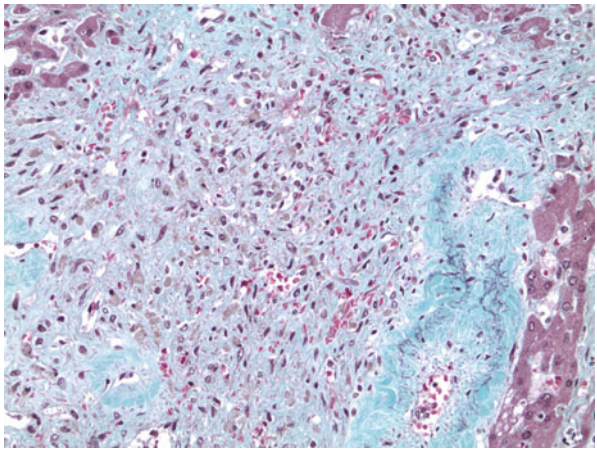

Fig. 13.20 Healing liver laceration in Fig. 13.18 at higher power (Trichrome × 200)

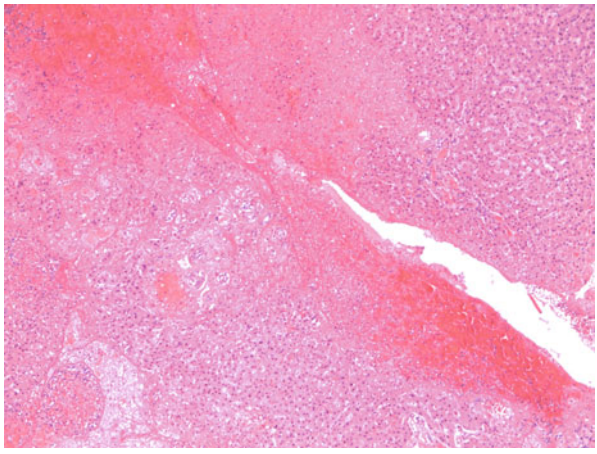

Fig. 13.21 Acute liver laceration with acute hemorrhage (Hematoxylin and Eosin, H&E × 20)

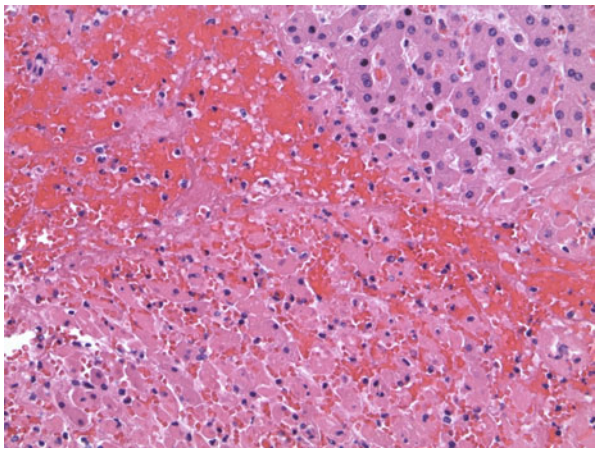

Fig. 13.22 Acute liver laceration with hemorrhage but no significant inflammatory response (Hematoxylin and Eosin, H&E × 200)

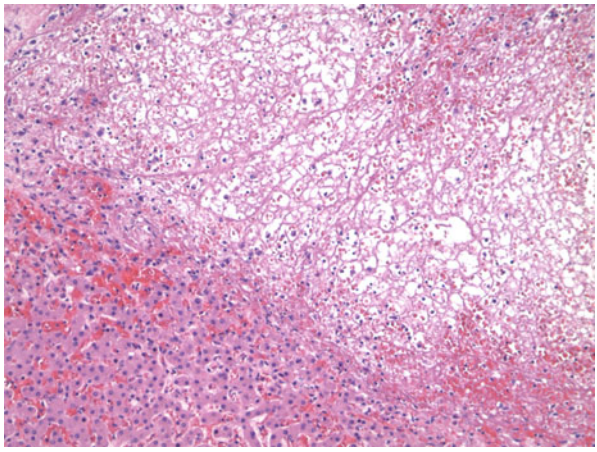

Fig. 13.23 Acute liver laceration less than 48 hours old showing fibrin in the area of laceration (Hematoxylin and Eosin, H&E × 20)

Damage to the aorta is rare in child abuse but has been reported (Fox et al. 1996). Pseudo-aneurysm formation of the aorta has been reported following deliberately inflicted injury (Roche et al. 1995).

Thoracic Injuries in Child Abuse

The thoracic organs are less often injured than abdominal organs in deliberately inflicted injury. In an analysis of 105 children with blunt thoracic injuries from a major trauma center in the USA, 5 were due to abuse, all under the age of 5 years (Nakayama et al. 1989). Rupture of cardiac chambers may occur (Cumberland et al. 1991; Cohle et al. 1995). Cohle and colleagues reported six cases of cardiac injury

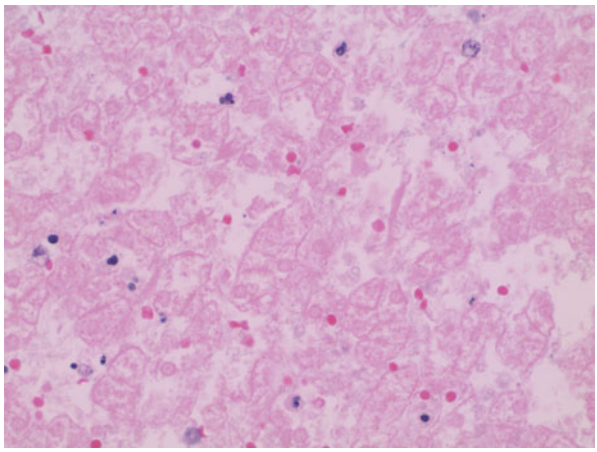

Fig. 13.24 Necrotic liver showing outlines of dead hepatocytes several weeks duration (Hematoxylin and Eosin, H&E × 200)

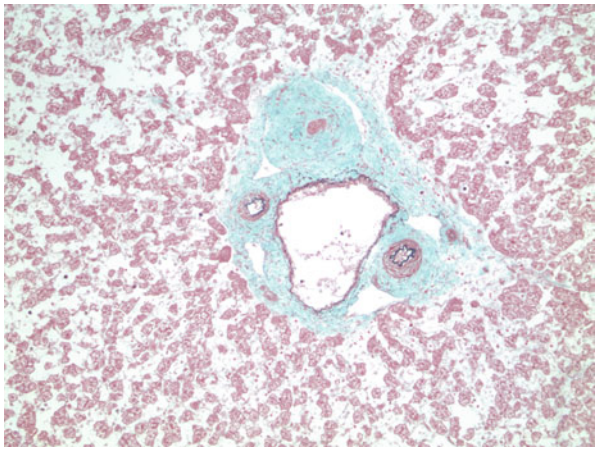

Fig. 13.25 Necrotic liver from Fig. 13.24 showing the hepatic structure (Trichrome × 50)

in homicides (Cohle et al. 1995). The victims were aged between 9 weeks and 2½ years. In five cases, the right atrium was lacerated and in one case, the left ventricle was lacerated (Fig. 13.31). In 2 cases, microscopic examination showed older injuries. In one case, there was interstitial fibrosis, primarily within the interventricular septum. In a second case, there was organized granulation tissue on the visceral pericardium with evidence of a healing contusion in the right atrium at the site of laceration. In 4 of the cases, there were rib fractures. Associated intrathoracic injuries in these cases included pulmonary contusion, thymic contusion, and hemothorax. Injury to the abdominal organs was also present in 5 of the 6 cases, including injury to the liver, spleen, omentum, mesentery, and pancreas. Admitted mechanisms of injury included stomping, kicking, and punching the chest. Traumatic ventriculo-septal defects have also been reported following child abuse (Rees et al. 1975; Karpas et al. 2002). Three cases of atrial intimal tears were reported by

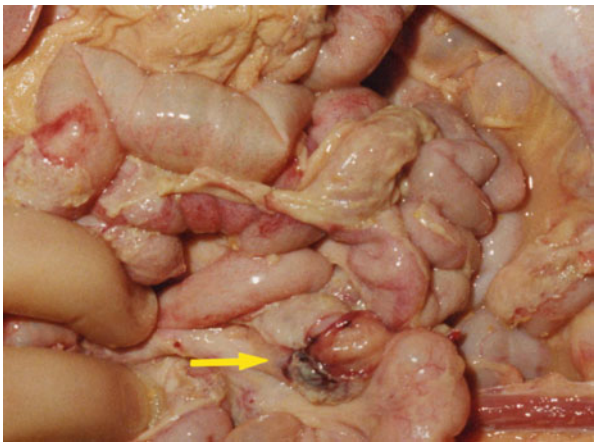

Fig. 13.26 Peritonitis from ruptured duodenum

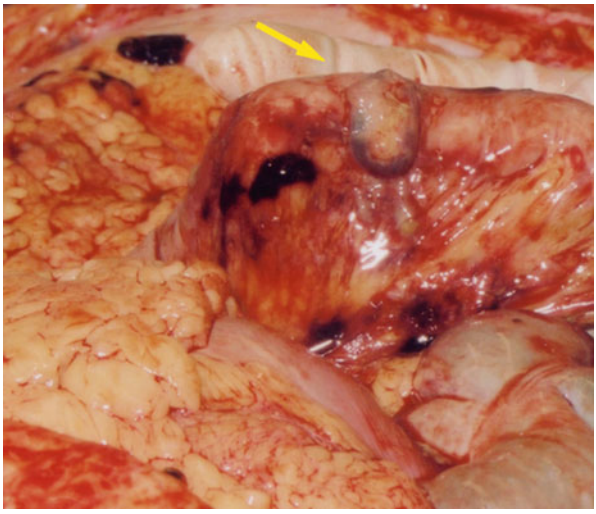

Fig. 13.27 Ruptured jejunum following blunt force trauma to the abdomen

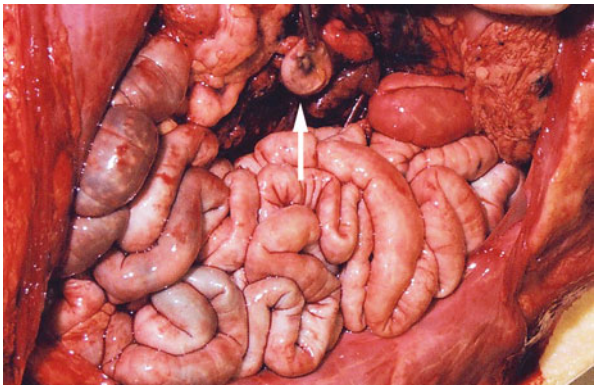

Fig. 13.28 Hemoperitoneum associated with lacerated pancreatico-duodenal rupture in a 2-year-old homicide victim of blunt force trauma

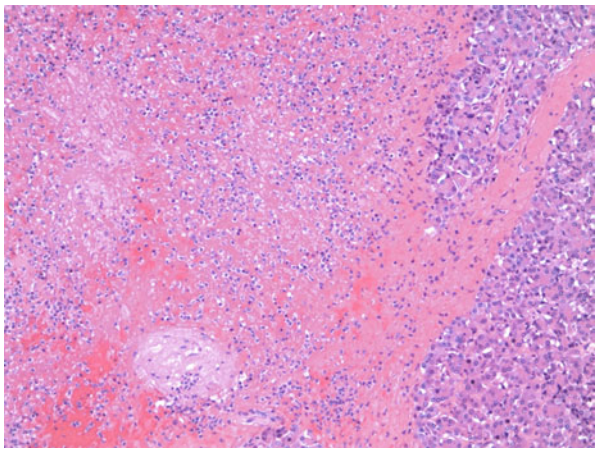

Fig. 13.29 Lacerated pancreas with acute hemorrhage (Hematoxylin and Eosin, H&E × 50)

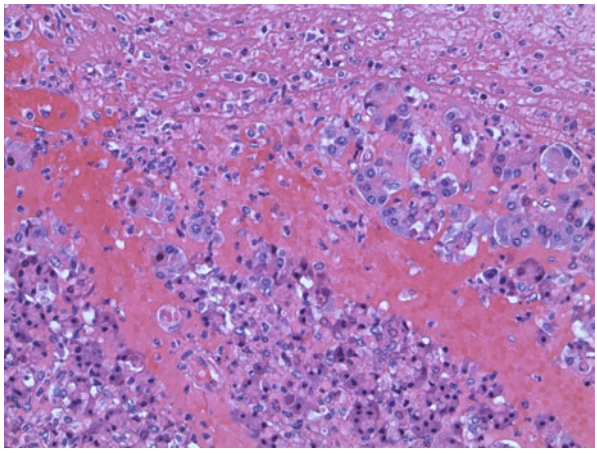

Fig. 13.30 Lacerated pancreas with hemorrhage but no significant inflammatory response (Hematoxylin and Eosin, H&E × 200)

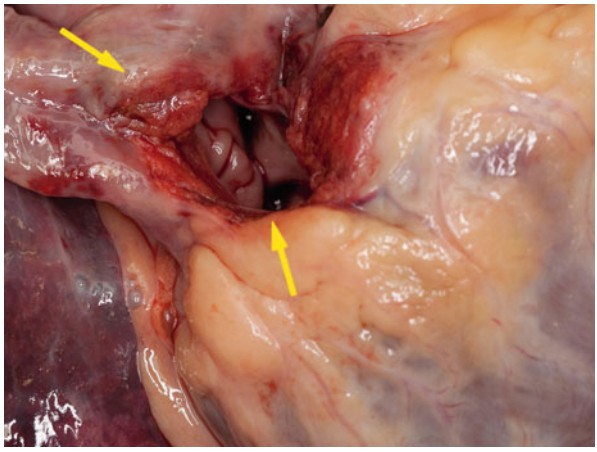

Fig. 13.31 Lacerated cardiac atrium following crushing of the chest by an adult

Cumberland et al. in child abuse cases, with the postulated mechanism being a rapid rise in pressure in the venous system following a blow to the abdomen (Cumberland et al. 1991).

Pulmonary contusions with rib fractures may occur from deliberately inflicted injury (McEniery et al. 1991). Chylothorax has been reported in children with multiple rib fractures (Green 1980; Guleserian et al. 1996; Geismar et al. 1997).

Rib fractures are a common finding in intentionally inflicted injury and are discussed above. Flail chest has been reported as a consequence of child abuse (Gipson and Tobias 2006). Ng and Hall have drawn attention to the presence of fractures of the costo-chondral junction in association with inflicted injury to intra-abdominal organs (Ng and Hall 1998). They presented three cases in children aged 7–36 months. The fractures were described as being analogous to metaphyseal fractures of long bones. Intra-abdominal pathology was present that included pancreatico-duodenal injury.

Injuries in Resuscitation

The principal interest to the pathologist with injuries caused by resuscitation is whether they can mimic or overlap with injuries inflicted in life. A number of studies have looked at whether resuscitation may cause intrathoracic and abdominal injuries, as well as injuries to other areas of the body (Feldman and Brewer 1984; Waldman et al. 1984; Spevak et al. 1994; Bush et al. 1996; Price et al. 2000; Gunther et al. 2000; Maguire et al. 2006; Ryan et al. 2003). It is important to distinguish between theses injuries, as inflicted injury may be claimed to be the result of efforts at resuscitation.

A variety of thoracic and abdominal injuries have been recorded in the pediatric age group. In the chest, these have included chest wall bruising and abrasion, myocardial contusion, atrial rupture, rib fractures, pulmonary contusion, pneumothorax and hemothorax, aspiration, and diaphragmatic laceration (Fig. 13.32). In the abdomen, gastric perforation, laceration of the liver and spleen, hemoperitoneum, pneumoperitoneum, and retroperitoneal hematoma have all been reported. Two hundred and eleven children under 12 years of age who had undergone resuscitation and in whom there was no historical physical evidence of trauma were examined for the effects of resuscitation (Bush et al. 1996). The mean age of the children was 19 months, and they had undergone resuscitation for a mean time of 45 min. The most common injury pattern was chest wall bruising and abrasions present in eight cases. Two had retroperitoneal hematomas and there were single cases of epicardial hematoma, small pneumothorax, pulmonary interstitial hemorrhage, rib fractures, splenic contusion, stomach perforation (2 mm), and trace hemoperitoneum. The authors concluded that life-threatening or consequential resuscitation injuries occurred in only 3 % of cases.

A study from Victoria, Australia, examining 204 children aged up to 14 years who had undergone cardiopulmonary resuscitation found seven cases of pulmonary contusion and one hematoma of the spleen, as well as minor skin bruises and

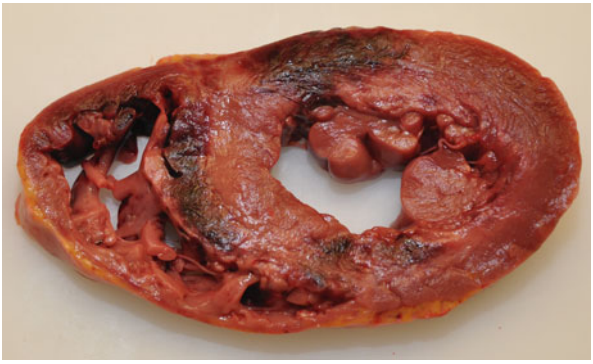

Fig. 13.32 Cardiac contusions from cardiopulmonary resuscitation in a teenager vigorously resuscitated by medical staff for over an hour

abrasions and airway injury (Ryan et al. 2003). No rib fractures of major visceral injuries were detected in this study.

In a study of 33 child homicides with fatal abdominal injuries, 24 (73 %) had undergone resuscitation and 9 had not (Price et al. 2000). There was no difference in the nature and severity of injuries between the two groups. In addition, 324 cases of natural deaths in children who had undergone resuscitation were reviewed. No traumatic abdominal injuries were found in any of these children. Four children did have evidence of extra-abdominal trauma related to resuscitation. The authors concluded that the likelihood of resuscitation-related primary abdominal trauma was very low.

Blast Injuries

Blast injury represents a distinct form of trauma that nevertheless has features that overlap with blunt trauma (DePalma et al. 2005). Children are occasionally victims of blast injury (Quintana et al. 1997). Blast injuries can be classified into four groups called primary, secondary, tertiary, and quaternary. Primary blast injuries are caused by barotrauma and most commonly involve organs at the air-fluid interface and air-filled organs. Lung damage and rupture of hollow viscera are important primary blast injuries that affect the thoracic and abdominal organs. Thoracic injury includes pulmonary contusion, pulmonary hemorrhage, pneumothorax and hemothorax, pneumomediastinum, and subcutaneous emphysema.

In the abdomen, the most common injury is rupture of the colon and less commonly the small bowel. Damage and disruption of the solid organs may occur but is usually associated with proximity to the center of the blast.

Secondary blast injuries involve damage from fragmentation of devices secondary to the explosion and penetration of the body by these fragments. Tertiary blast injuries are caused by structural damage to buildings and vehicles. These may be associated with blunt trauma to the chest and abdomen as well as to other organ systems. Quaternary blast injuries include burns, inhalation of toxic substances and dust, and radiation damage.

Data on injury to children from explosions is less detailed than in adults, though a number of studies have looked at blast injuries in childhood (Quintana et al. 1997; Aharonson-Daniel et al. 2003; Amir et al. 2005; Kim et al. 2010; Edwards et al. 2012; Arul et al. 2012). Following the Oklahoma City, USA, truck bomb in 1995, there were 66 pediatric victims, 19 of whom died and another 7 required hospitalization (Quintana et al. 1997). Crushing injury was seen and one treated child had a splenic hematoma. Thoracic and abdominal injury was more common in fatalities than in survivors. In an analysis of terrorism-related injuries to hospitalized children in Israel, 67 % were due to explosions (Aharonson-Daniel et al. 2003). Overall there was thoracic trauma present in 18 % of cases and abdominal injuries in 17 %, with most cases being penetrating injuries. Further analysis of the Israeli dated showed 16.7 % of cases of explosion had thoracic trauma and 14.9 % abdominal trauma (Amir et al. 2005).

In an analysis of children injured in explosions in Iraq and Afghanistan and seen in US military hospitals, the most common areas severely injured in blast injury were the head and neck with burns to the skin, but with the thorax involved in approximately 20 % of cases and the abdomen in approximately 10 % of cases.

Conclusions

Blunt thoracic and abdominal injuries remain important causes of morbidity and mortality in childhood. While motor vehicle collisions and falls remain leading causes of these injuries, inflicted injuries are an important cause of death in childhood. The circumstances will usually allow clear determination of the cause of these injuries, though accurate documentation remains important. In inflicted injury, the differential diagnosis is typically a fall or some other accident. External injury may be absent, and detailed histology in these cases is required to confirm injury and assist in the dating of any damage. Where there is obvious inflicted injury, timing of the injury is often the main point of contention. Resuscitation artifacts may complicate autopsy findings and must be considered in any analysis of the case, though resuscitation damage is unlikely to account for serious injuries present.

Blast injuries represent a separate category of trauma that has features that overlap with blunt trauma. Where blast injuries have occurred, there may also be blunt trauma from the victim being thrown against a solid object or collapse of the surrounding superstructure. Blast injury remains an important cause of injury in children in war zones and in acts of urban terrorism.

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Cardiopulmonary Resuscitation Injuries in Children

14

Kim A. Collins, Christina J. Tatum, and Patrick E. Lantz

Contents

Abstract

Cardiopulmonary resuscitation (CPR) is an emergency intervention to maintain circulation and breathing in an unresponsive individual suffering from cardiopulmonary arrest. However, CPR is not without its own risks. Injuries secondary to compression and ventilation are well documented in the medical and scientific literature. Most of these injuries are minor, but some can result in significant morbidity and even death. It is important to identify those injuries that could be secondary to CPR versus inflicted traumatic injuries of child maltreatment.

Introduction

Besides medical personnel, members of the general public have been trained to perform CPR. Manual external CPR involves chest compressions at a rate of

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at least 100 per minute for all age groups, at a depth of at least 5 cm in adults, and at least 1/3 of the depth of the anteroposterior chest diameter in infants and children below the age of puberty. Often a child is brought to the attention of a health-care professional or death investigator, and the etiology of injuries, in particular CPR versus inflicted blunt force trauma, becomes a crucial issue. Perpetrators may claim that injuries were caused by CPR, either by themselves or by emergency personnel. It is important to understand those injuries known to be secondary to CPR in order to better identify and classify inflicted injuries of child maltreatment.

Resuscitation Injuries

Injuries secondary to CPR are usually pathophysiologically insignificant (Bush et al. 1996; Plunkett 2006; Matshes and Lew 2010a; Ryan et al. 2006; Matshes and Lew 2010b; Reyes et al. 2011). Such injuries may be external and/or internal. It is best to divide the injuries into categories: head and neck, thorax and abdomen, barotrauma, and iatrogenic artifacts. Most CPR injuries involve the head/neck and rarely the thorax and abdomen. These injuries are due to the compressions and to ventilation/intubation. One should be aware of the resuscitative technique used on children and note if the resuscitator is experienced in this technique (Reyes et al. 2011). The techniques include one-handed compressions ("two finger"), two-handed compressions ("two-thumb-encircling hands"), and abdominal compressions. The emergency medical services (EMS) personnel or physician can easily demonstrate how he/she performed CPR. The investigator can correlate injuries with points of contact during compressions and ventilation. A doll can be used as well as the same type and size of mask. If available, the exact mask used during the resuscitation should be retained. It must be noted that some studies of many resuscitated children report no injuries. In other studies, injuries were noted, but none were significant or abdominal (Matshes and Lew 2010a, b; Price et al. 2000; Feldman and Brewer 1984).

1. *Head and Neck*: Most CPR-related injuries in children are soft tissue injuries of the head and neck from ventilatory efforts (Kaplan and Fossum 1994). These include facial abrasions (nasal bridge, undersurface of the nose, anterior chin) from the air-bag-valve mask, which are usually symmetrical. As the resuscitator positions his/her hand on the child, fingertip contusions beneath the chin and on the side of the head may be produced. If a mask is not used but instead mouth-to-mouth, one may see scrapes/fingernail scratches over the perinasal area.

   Intubation can result in abrasions and/or contusions of the oropharynx, gingiva, buccal mucosa, frenulum, epiglottis, base of the tongue, larynx, and trachea. The lips may be contused or lacerated from the victim's own teeth or by the endotracheal tube (Fig. 14.1). Teeth can also be broken during intubation. The child's oropharynx is more susceptible to damage by forceful digital

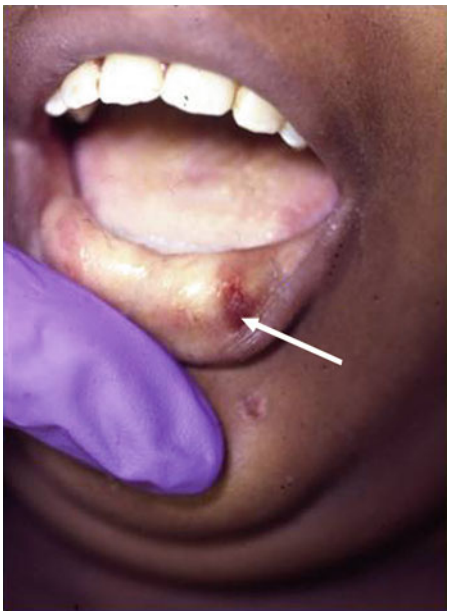

Fig. 14.1 Lip abrasion and contusion from endotracheal tube

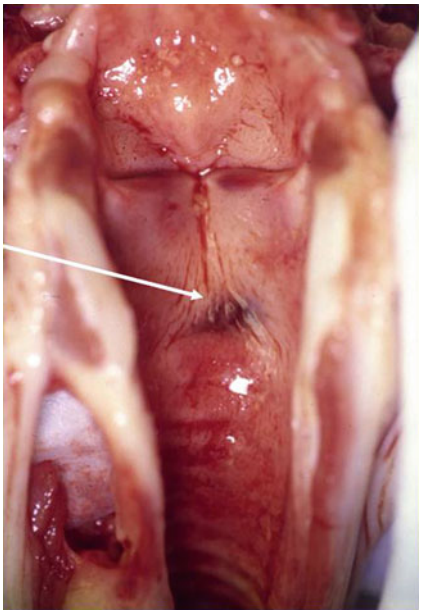

Fig. 14.2 Anterior laryngeal submucosal hemorrhage secondary to intubation

clearing and suction as well as by endoscopic instruments (Figs. 14.2, 14.3). Traumatic mucosal tears and hypopharyngeal perforation have occurred and are not uncommon (Galvis and Kelley 1979).

2. *Thorax and Abdomen*: Chest compressions can result in midsternal abrasions and/or slight contusions. Epicardial hematoma, pleural petechiae or ecchymosis,

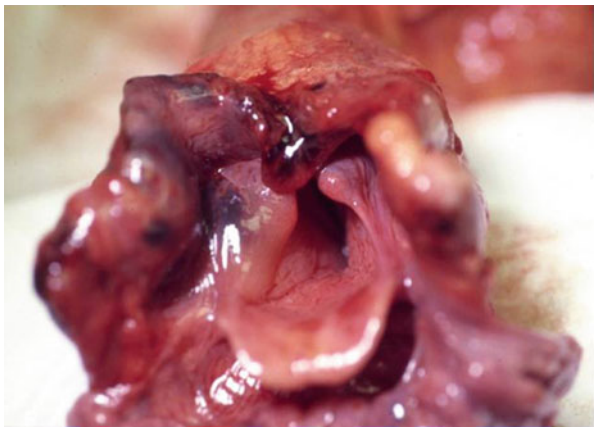

Fig. 14.3 Pharyngeal edema and soft tissue hemorrhage secondary to finger sweep examination, intubation, and ventilation

and pulmonary interstitial hemorrhage can also occur (Bush et al. 1996; Matshes and Lew 2010b; Price et al. 2000) (Fig. 14.4a–c). Rib fractures secondary to CPR are rarely reported and are more often the result of inflicted trauma (Bush et al. 1996; Gunther et al. 2000; Spevak et al. 1994; Maguire et al. 2006; Dolinak 2007). Rib fractures are discussed further in the latter portion of this chapter.

Although extremely rare, compressions in children may result in pancreatic hemorrhage, hepatic/splenic contusion or laceration, retroperitoneal hemorrhage, and gastric perforation (Bush et al. 1996; Ryan et al. 2006; Waldman et al. 1984; Custer et al. 1987; Krischer et al. 1987). Note if abdominal compressions were performed (Waldman et al. 1984).

3. *Barotrauma*: Various forms of CPR-related barotrauma have been described in children (Cullen 2001). These include tympanic membrane injury, pneumothorax, pneumoperitoneum, pneumoscrotum, and air embolism (especially in the premature newborn) (Bush et al. 1996). Less commonly, gastric rupture (usually lesser curvature) due to overdistension during ventilation may result.
4. *Artifacts/Iatrogenic Marks Other than from Compression/Ventilation*: Artifacts include defibrillator marks over the thorax, venipuncture and intraosseous line access marks, bruising about the neck from attempted vascular access, and adhesive marks from taping the endotracheal tube. Defibrillation can produce subepicardial myofibril disintegration. One can also see cardiac contraction band necrosis and focal hemorrhage with the administration of catecholamines during prolonged resuscitation.

Issues Often Raised Concerning CPR

- *Retinal Hemorrhages* (RHs): Previous studies and collaborative research have concluded that CPR alone does not cause retinal hemorrhages in children with normal coagulation and platelet count (Odom et al. 1997). In patients with nontraumatic illnesses and coagulopathies, small, punctate retinal hemorrhages

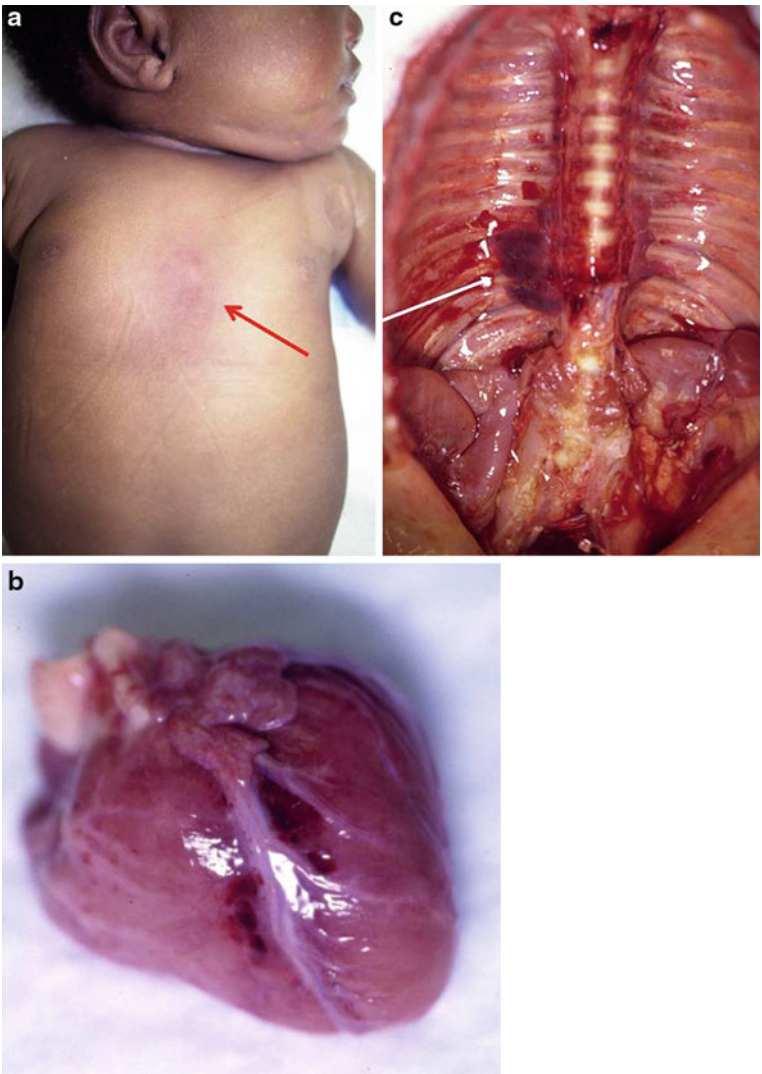

Fig. 14.4 (**a**) Infant after 45 min of CPR. Note the anterior chest erythema. (**b**) Anterior epicardial hemorrhage secondary to chest compressions. (**c**) After 45 min of chest compressions, no rib fractures were identified. Only slight posterior intercostal hemorrhage

may be present (Odom et al. 1997). Infants found unresponsive invariably undergo resuscitative efforts, often for prolonged periods of time. Forensic pathologists must be aware that retinal hemorrhages can be seen in infants who die suddenly and unexpectedly, following cardiopulmonary resuscitation, and are not specific for abusive head trauma. Infants found unresponsive without evidence of head trauma or natural disease processes that have had CPR,

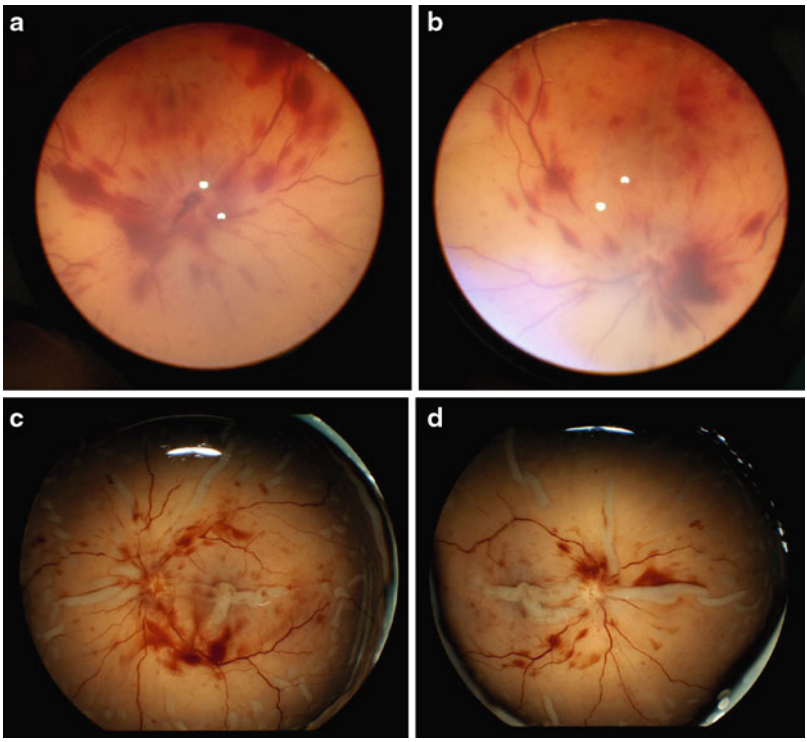

Fig. 14.5 Resuscitation-associated multiple, multi-layered retinal hemorrhages extending past equator and focally abutting ora serrata are likely secondary to hypoxia and reperfusion. (**a**) Postmortem Indirect Ophthalmoscopy of the left eye. (**b**) Postmortem Indirect Ophthalmoscopy of the right eye. Fundal images of the left eye (**c**) and the right eye (**d**) after enucleation, formalin fixation, and removal of the anterior structures (cornea, iris, ciliary body, and lens). It replicates the clinical view with a direct ophthalmoscope

especially those with restoration of circulation, can have RHs that may be few in number or numerous with extension to the ora serrata (Fig. 14.5a–d) (Tatum et al. 2012).

- *Visceral Injuries*: Several studies report no visceral injuries to children secondary to CPR (Matshes and Lew 2010a, b; Price et al. 2000; Feldman and Brewer 1984; Cohle et al. 1995). Others report that, if present, these CPR-related injuries are not significant or life-threatening (Matshes and Lew 2010b). Abdominal visceral injury is uncommon (Price et al. 2000); however, if present, note if abdominal compressions were performed (Waldman et al. 1984).
- *Rib Fractures*: Unlike adults, ribs in children are flexible and more resilient to fracture. In the absence of radiographic evidence of underlying bone disorder, unexplained rib fractures are indicative of abuse. Often rib fractures are associated with other signs of abuse and/or different stages of healing. However, recent studies using axial radiography have shown rib head fractures related to CPR, especially using the two-handed "two thumbs encircling hands" technique

(Matshes and Lew 2010a; Reyes et al. 2011). Length of compression time does not appear to correlate with an increased chance of rib fractures. Below is a more in-depth discussion of this challenging area in differentiating rib fracture from resuscitation versus inflicted trauma.

Rib Fractures

Current recommendations by the American Heart Association place emphasis on high-quality chest compressions (Field et al. 2010). The two acceptable techniques for chest compressions in infants are the use of either the first and second fingers on one hand or the two-handed technique. Since 2006, the preferred technique for chest compressions is two-handed, with the thumbs generating pressure on the sternum and the second through fifth fingers offering light support on the back (Kattwinkel 2006) (Fig. 14.6).

Reports of CPR in adults suggest fractures of the ribs occur at an incidence of 20–65 %, but such injuries are reportedly rarely seen in children (Ryan et al. 2006; Feldman and Brewer 1984; Krischer et al. 1987; Powner et al. 1984). Prior to the introduction of the preferred two-handed compression technique in 2006, there were only three reported cases of resuscitation-related injuries in children (Maguire et al. 2006). Compared to an adult, the rib cage of a child has greater elasticity and plasticity due to incomplete bone development and therefore may be able to tolerate larger degrees of pressure before a fracture occurs.

Rib fractures found in children with no clinical history of trauma or underlying bone disorders are most often associated with child abuse, accounting for 5–27 % of all skeletal injuries in abused children (Barsness et al. 2003; Platt et al. 2006). Most abusive rib fractures are believed to occur from anteroposterior compression, with the hands wrapped around the infant's chest, produced by excessive squeezing or indirectly generated by shaking. Although abusive compression can cause anterolateral rib fractures, it has been attributed to injuries of the posterior ribs near the costovertebral junction and may involve the rib head, rib neck, and posterior rib arc. The compressive force levers the posterior ribs over the transverse processes of the spine (Kleinman and Schlesinger 1997; Bulloch et al. 2000). Since one-handed CPR is typically performed with the child on a firm surface, this posterior levering should not occur.

When rib fractures are present in an infant who has received CPR, the forensic pathologist must take care to distinguish abusive fractures from those that are related to resuscitative efforts. This is especially true with the two-handed technique, given that significant anterior compression may be produced (Matshes and Lew 2010a; Reyes et al. 2011). Resuscitation-related rib fractures are usually located either anteriorly or anterolaterally and are often multiple, linear, bilateral, or symmetrical (Fig. 14.7). These fractures usually occur near ribs 4 and 5 but have also been reported in ribs 2 through 9, the clavicle, and the sternochondral junction (Bush et al. 1996; Betz and Liebhardt 1994). If resuscitative efforts are unsuccessful, CPR-induced posterior rib fractures often have minimal associated hemorrhage and may be difficult to identify unless the parietal pleura has been reflected (Fig. 14.8).

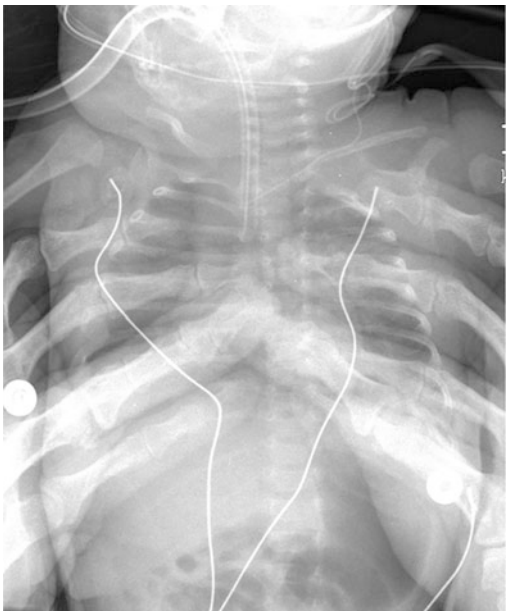

Fig. 14.6 Anterior-posterior radiograph taken while two-handed compression technique was performed in the neonatal intensive care unit (NICU) on a 10-week-old infant. A 2-year-old with a history of upper respiratory infection positive for coronavirus was found unresponsive. He was resuscitated for 40 min and survived 24 h. No injuries were identified

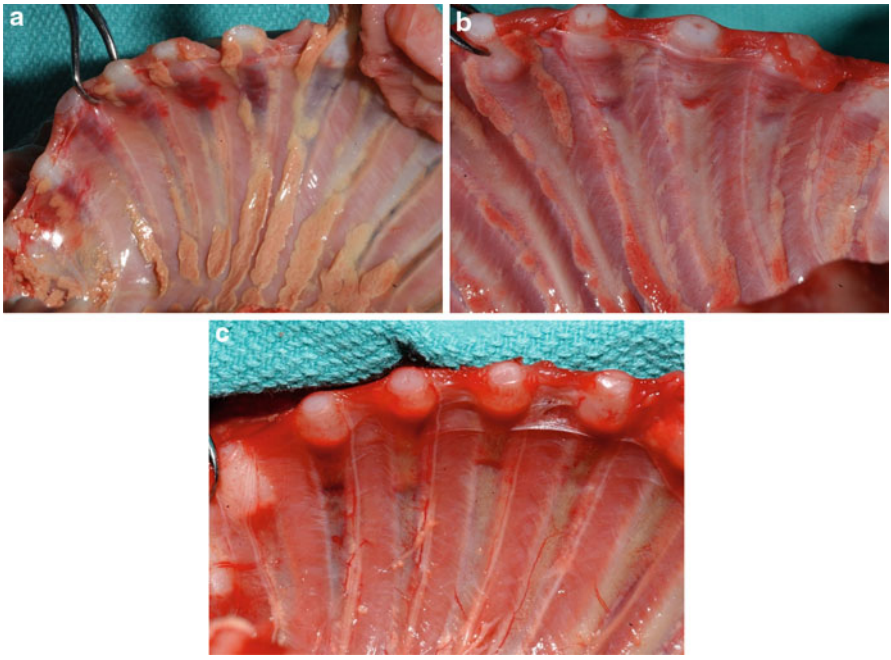

Fig. 14.7 (**a**) Fractures of left anterior ribs 2–6 with intact pleura in a 10-week-old infant following CPR. (**b**) Fractures of right anterior ribs 3–5 in a 5-week-old who died suddenly and unexpectedly. (**c**) Left anterior rib fracture shown with pleura stripped in a 3-month-old after 20 min of CPR

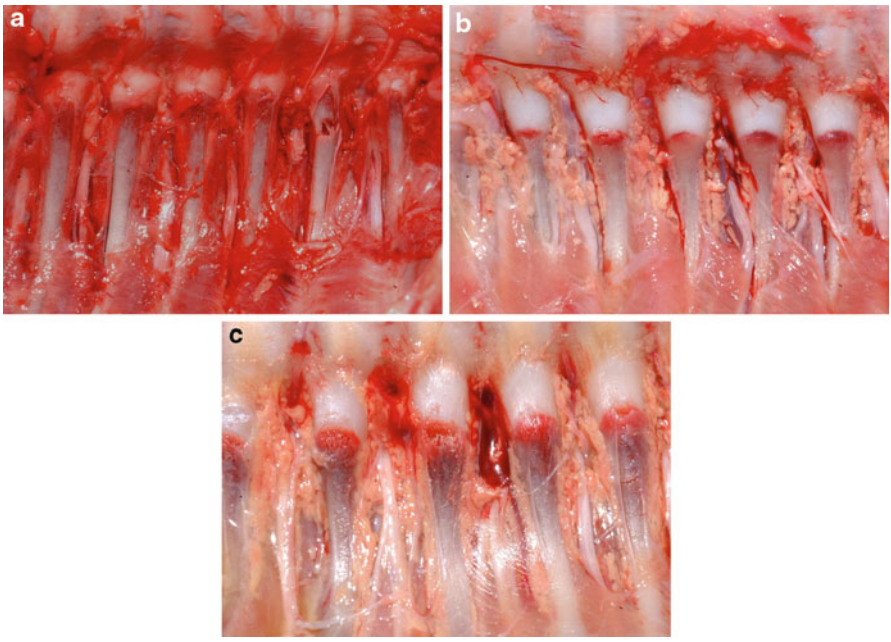

Fig. 14.8 (**a**) Fracture of the left fourth posterior rib in a 4-month-old who underwent two-handed compression technique. (**b**) Acute posterior rib head fractures in a 2-day-old who was delivered via emergency C-section following a motor vehicle accident and underwent CPR. (**c**) Three-month-old infant with fracture of posterior rib/neck after receiving CPR in the NICU

Autopsy

To detect and confirm the presence of rib fractures at autopsy, a radiologic skeletal survey consisting of full-body, anteroposterior radiographs should always be performed prior to beginning the autopsy. Fresh rib fractures may be missed by radiography, but can be detected at autopsy by stripping the parietal pleura from the thorax and carefully examining each rib by visual inspection and manual palpation. Often the rib fractures will be subtle, bending or buckle fractures, with little or no associated hemorrhage. Microscopic examination of resuscitation-related fractures should show no surrounding tissue reaction with minimal associated extravasated blood histologically (Dolinak 2007; Weber et al. 2009).

Conclusion

Although usually pathologically insignificant, injuries secondary to CPR do occur and must be distinguished from inflicted injuries of child maltreatment. The investigator must be aware of common injuries of CPR and how these may differ from abusive trauma. Knowledge of the type of resuscitation, mask, and intubation

instruments used is needed to assess any injuries that may be identified. Doll reenactment may be useful during the investigation. Special attention should be paid to bony fractures and visceral injury as these are not commonly identified as secondary to CPR. Also, any remote injuries should raise suspicion. A complete autopsy preceded by radiologic skeletal survey should be performed.

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Evaluation of Pediatric Fractures at Autopsy

15

Andrew M. Baker

Contents

Abstract

Examination of the skeletal system of the deceased child, particularly in cases where physical abuse may have occurred, is a critical part of the postmortem examination. Since some injuries, particularly metaphyseal injuries, would not be discernible with a traditional autopsy approach, radiographic imaging of the deceased child is critical. The presence of healing fractures in the setting of fatal visceral trauma may distinguish a single acute event from a pattern of inflicted injury ("battered child syndrome"). Though many pathologists may have little experience handling or interpreting bony injuries, most bony findings are readily

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removed at autopsy and can be decalcified and subjected to histological evaluation with very little investment in special techniques or tools. Correlation of the radiographic, gross, and microscopic findings is invaluable to the radiologist, pediatrician, and pathologist alike.

Introduction

The importance of confirming or refuting the presence of fractures in the deceased infant or young child cannot be overemphasized. Because fractures are often present in the extremities and/or lack corresponding external evidence of injury, radiography in the deceased child is critically important if such fractures are to be found.

When radiographs are negative for bony injury, they:
- Provide assurance to family, friends, and caretakers.
- Provide an extra measure of comfort to the pathologist.

When radiographs are positive for bony injury, they:
- Guide the pathologist to areas not normally examined.
- Effectively rule out the diagnosis of sudden infant death syndrome (SIDS).
- Provide graphic demonstration of injury.

Why bother finding fractures?
- In most cases, fractures are evidence of trauma.
- Quality evaluation of fractures by the pathologist facilitates radiological–pathological correlation; in some cases, it may confirm or refute inconclusive radiographic findings.
- Fracture evaluation can confirm the multiplicity and/or chronicity of injuries.
- Histological evaluation can assist with the assessment of the stage of healing.
- Histological evaluation may assist in confirming or refuting underlying diseases or conditions.
- Some fractures have a very high specificity for inflicted injury.

The traditional autopsy is an excellent tool for finding external, visceral, cerebral, and ocular injuries. While some bones (e.g., the skull, ribs, parts of the spine, parts of the pelvis) can be examined grossly, the autopsy is limited in its ability to detect injuries of the extremities in the infant and small child (Figs. 15.1–15.3).

Basic Bone and Fracture Histology

Bone Structure

Compact bone makes up the cortex, where there is little soft tissue. *Cancellous bone* makes up the central region (medulla), where spicules of bone are admixed

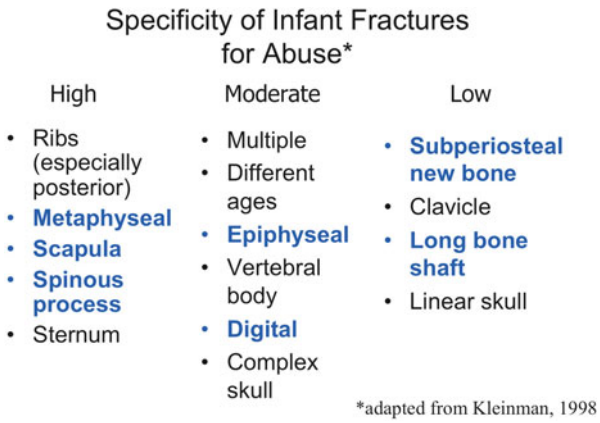

Fig. 15.1 Fractures in infants can be categorized by their specificity for abuse. Fractures highlighted in *blue*, without the use of radiographs, would be very difficult to find in a standard autopsy

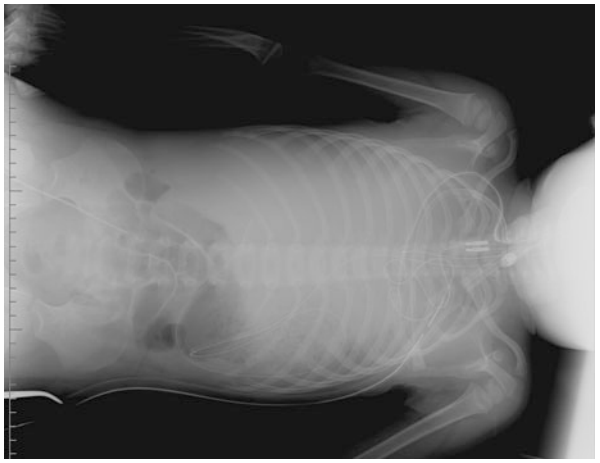

Fig. 15.2 A "babygram" is inadequate for finding subtle skeletal injuries, particularly of the extremities. In this "babygram," for example, no comment can be made about the metaphyses of the right elbow

with soft tissue. At the microscopic level, one can distinguish lamellar bone (regularly arranged sheets) and woven bone (an irregular feltwork). *Lamellar bone* predominates in areas of slow growth and remodeling, and deposition of lamellar bone requires a preexisting lattice of woven bone or lamellar bone. *Woven bone* predominates in areas of rapid bone growth, including embryonic bone, Codman's triangle, tumor bone, and fracture callus. While woven bone is flexible and allows rapid mineralization, bone formation, and bone resorption, it is also less rigid and has less strength than lamellar bone.

Periosteum surrounds the bony cortex except in articular cartilage. Periosteum has two layers: the outer fibrous layer and the inner cellular (cambium) layer. Sharpey's fibers anchor periosteum and tendons to bone. These fibers are less developed in children, and fractures of children's bone often result in fraying or displacement,

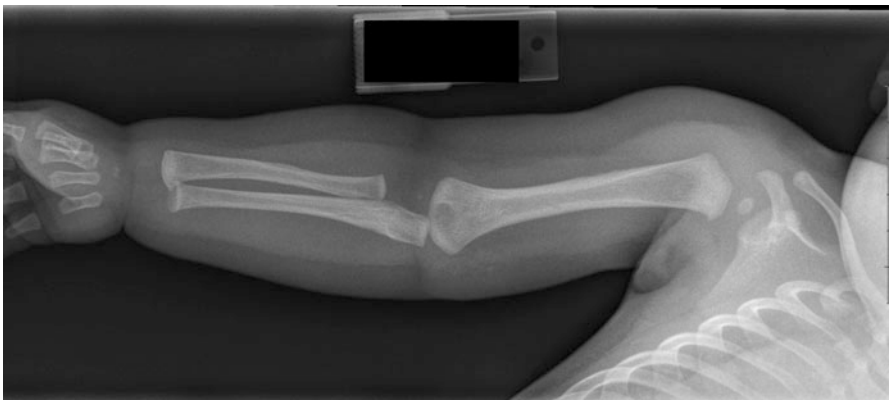

Fig. 15.3 A complete pediatric skeletal survey with collimated views of the long bones, akin to that which is performed on living children suspected of having been abused, is strongly recommended in deceased infants and small children. In this radiograph, for example, the metaphyses and diaphyses of the long bones of the right arm are clearly visualized

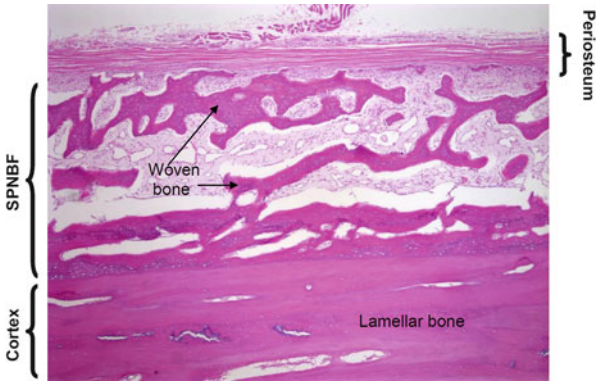

Fig. 15.4 Bony cortex of the ulna of a fatally battered 8-week-old. The normal cortex and periosteum are separated by subperiosteal new bone formation (*SPNBF*), and the appearances of woven bone and lamellar bone are readily distinguished (Hematoxylin and Eosin, H&E ×20)

rather than actual breaking of the periosteum. Subperiosteal new bone formation (SNBF) in children is a sequel of periosteal–cortical separation, occurring in response to hemorrhage beneath the periosteum and is often readily visible on radiographs. In adults, the periosteum is firmly adherent due to Sharpey's fibers, with the periosteum tending to break at the bony fracture site (Fig. 15.4).

Bone Formation

Enchondral and intramembranous formation are the two mechanisms of bone embryogenesis in humans. In *enchondral bone formation*, bone replaces

a preexisting cartilaginous model. This occurs in the long bones: ribs, vertebrae, and extremities. Eventually, the only continuous enchondral growth occurs at the physis. In *intramembranous bone formation*, progenitor cells organize into trabeculae, differentiate into osteoblasts, and form trabeculae of woven bone. It is upon these trabeculae of woven bone that lamellar bone is then placed. Bone growth occurs via inner resorption and outer apposition of new bone. Intramembranous growth occurs in the flat bones of the skull and face. Fracture healing is essentially the process of bone regeneration, recapitulating embryonic intramembranous bone formation.

Fracture Healing

The stages of fracture healing may be divided into four broad ranges: inflammation and induction, soft callus, hard callus, and remodeling.

Inflammation and induction spans the time from injury to the appearance of new bone. This stage consists of two competing processes: osteolytic activity along with removal of hemorrhage and dead tissue and deposition of granulation tissue, fibrous tissue, and osteoid. The lysis taking place within the fracture site explains the radiolucency often appreciated on radiographs. When examining fractures under the microscope, the pathologist must take care not to interpret the resorption of normal bone adjacent to a fracture as evidence of bony dysplasia.

Soft callus is thought to begin at about 10–14 days post-injury in older children and probably earlier in infants. New woven bone and cartilage are laid down, with the woven bone gradually maturing into trabeculae. The progenitor cells entering the fracture site are actually pluripotent and can differentiate into osteoblasts (producing osteoid), chondroblasts (producing cartilage), or fibroblasts (producing fibrous tissue). The predominant pathway taken depends on how well immobilized and oxygenated the fracture site is. Unlike many animal models, a callus composed largely of cartilage is not the preferred route in humans. The soft callus stage usually lasts about 3–4 weeks. At the end of the stage the ends of bony fragments are no longer easily moved, and there is obliteration of the radiographic fracture line.

In the *hard callus* stage, both periosteal callus (outside the bone cortex) and endosteal callus (inside the bone cortex) are converted to lamellar bone. Nearly all of the hematoma, inflammation, and necrotic tissue have been removed from the fracture site, although it should be noted that histologically, the healing of the endosteal portion of a fracture may lag far behind the periosteal portion. At the end of the hard callus stage, the fracture is now radiographically solidly united.

The goal of *remodeling* is complete restoration of the medullary cavity and the cortex. While this might never occur completely in some adult fractures, in children it may occur despite wide displacement or angulation of the fracture (Figs. 15.5–15.15).

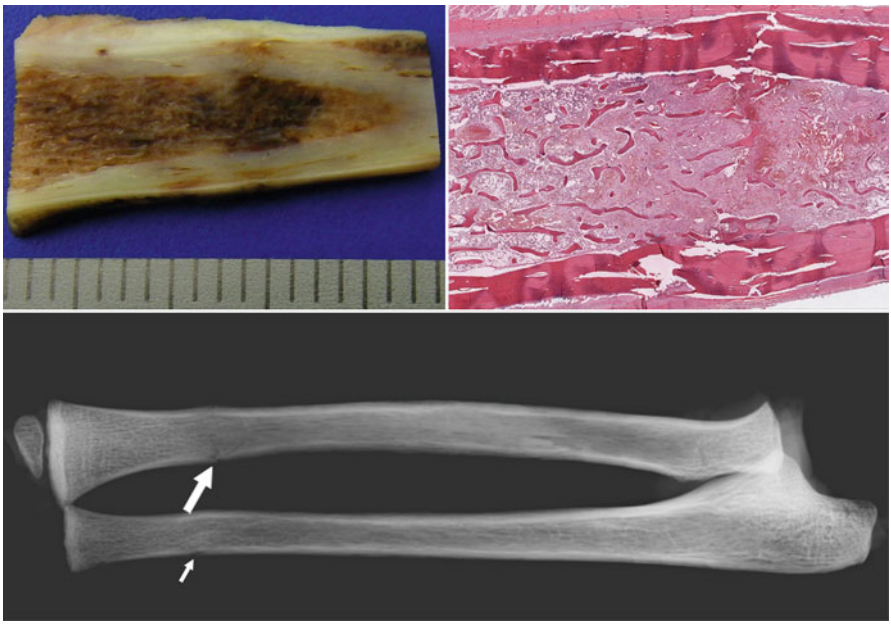

Fig. 15.5 Distal radius (*large arrow*) and ulna (*small arrow*) fractures in a battered 3-year-old. These would have been completely undetected clinically and at autopsy without a skeletal survey. The gross (*upper left*) and microscopic (*upper right*) images are the radial fracture (Hematoxylin and Eosin, H&E ×10)

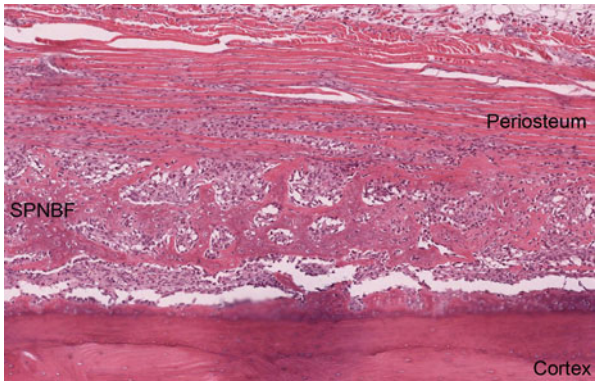

Fig. 15.6 SPNBF associated with the radial fracture shown in Fig. 15.5 (Hematoxylin and Eosin, H&E ×20)

Handling Bones

When bony injuries (or apparent bony abnormalities) are detected radiographically, it is usually best to resect the bone in question as well as the

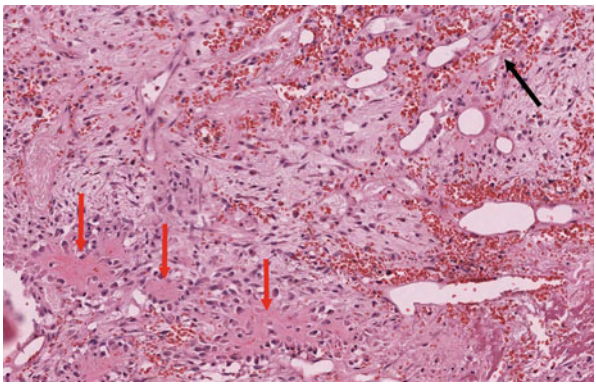

Fig. 15.7 The endosteal (medullary) part of the callus from the radius in Fig. 15.5 consists largely of granulation tissue and loose mesenchyme (*black arrow*); however, islands of very early osteoid (*red arrows*) are ringed by osteoblasts (Hematoxylin and Eosin, H&E ×200)

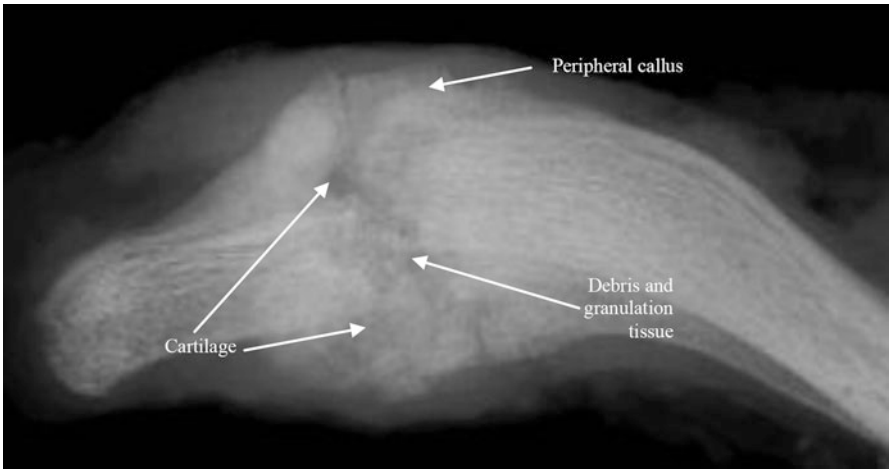

Fig. 15.8 Radiograph of a healing clavicle fracture found in a deceased infant. Features that correspond to the histology (Fig. 15.9) are highlighted

contralateral normal bone if possible for a control. Resected specimens should then be reradiographed, before or after fixation, but before decalcification. Larger specimens often produce very nice post-resection radiographs if they are bivalved. A small wet tile saw (if available) or a hand held coping saw works well for this. In the event that multiple contiguous posterior rib fractures are present, these are best resected en bloc with the corresponding vertebral bodies and contralateral posterior ribs. After fixation, the rib–vertebra–rib complexes can be separated one by one and reradiographed in the axial plane (Figs. 15.16–15.19).

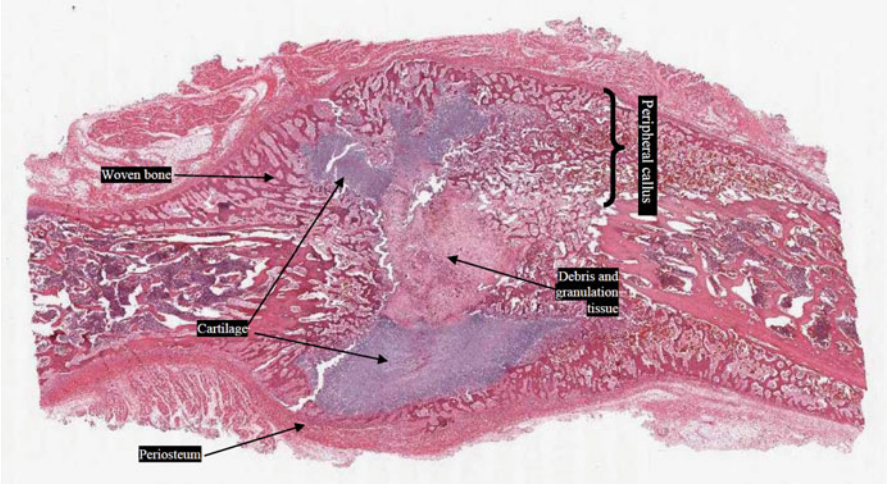

Fig. 15.9 Whole-mount histology of the healing clavicle fracture radiographed in Fig. 15.8 (Hematoxylin and Eosin, H&E ×1)

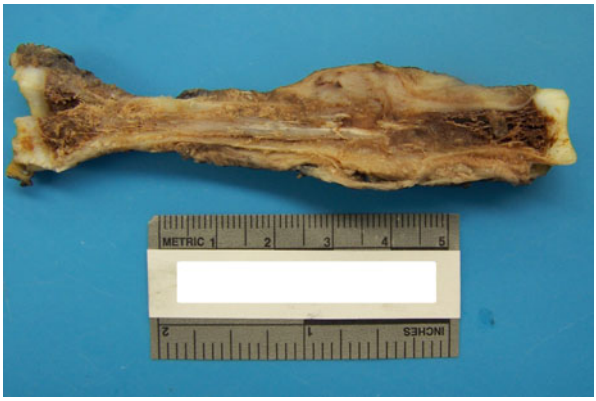

Fig. 15.10 Gross appearance of a radial fracture in a fatally abused 13-month-old

The Classic Metaphyseal Lesion (CML)

Of all the fractures described in child abuse, none appears more specific than the metaphyseal fracture, first described by the pediatric radiologist John Caffey. Injuries corresponding to CMLs were not reported in Caffey's landmark paper (1946) that described subdural hematomas and long bone fractures in infants. It was not until 1957 that Caffey introduced the terms "bucket handle" and "corner fracture" to describe the radiographic appearance of CMLs (Caffey 1957). Caffey believed that these lesions were the result of avulsion of peripheral metaphyseal

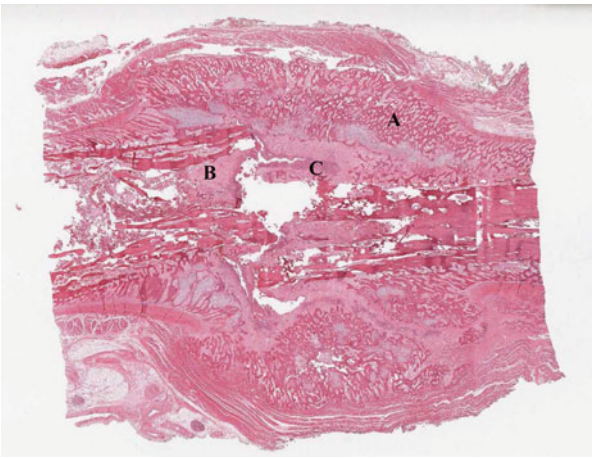

Fig. 15.11 Low power microscopy of the fracture in Fig. 15.10. Areas *A*, *B*, and *C* are discussed in Fig. 15.12 (Hematoxylin and Eosin, H&E ×1)

fragments at the point of periosteal insertion. However, subsequent postmortem studies of these lesions have shown them to be more extensive than is generally appreciated radiographically (Kleinman 2008).

Kleinman et al. introduced the term *classic metaphyseal lesion* (CML) to describe the injury. CMLs are the most frequently encountered long bone injuries in infants dying with evidence of abuse. CMLs are highly specific for abuse, although they are observed in half or fewer of cases. CMLs most often occur in the distal femur, proximal tibia, distal tibia, and proximal humerus and are seen almost exclusively in children less than 2 years old. The lesion is a series of microfractures across the metaphysis, roughly parallel to the physis, although it may not travel the entire width of the bone. The long-term sequelae of CMLs appear to be minimal. Rarely, CMLs have been described in settings other than abuse, such as in accidents, cesarean sections, small premature infants, infants with rickets who undergo a vigorous passive range of motion exercises, and during physical therapy or orthopedic manipulation for club foot. Metaphyseal irregularity and fragmentation have been described in a variety of skeletal dysplasias, although the diagnosis generally becomes clearer when viewed in the context of clinical and additional radiological findings. Follow-up skeletal imaging will generally show no change in such metaphyseal fragments, in contrast to the healing of the CML (described below) (Kleinman 2008, 2009).

The work of Kleinman et al. documented the histological appearance of the CML as a series of microfractures in the subepiphyseal region of bone. This region is the primary spongiosa, and it is the most immature area of the mineralized matrix in the growing metaphysis. When complete, the fracture fragment may be conceptualized as a wafer or disk of bone separated from the shaft by the series of metaphyseal microfractures. The CML, when complete, is a disk with a broad, thin center and a thick circumferential rim. Centrally, the fracture abuts the chondro-osseous junction and peripherally tends to turn away from the physis to undercut the subperiosteal bone collar (Kleinman et al. 1986; Lonergan et al. 2003).

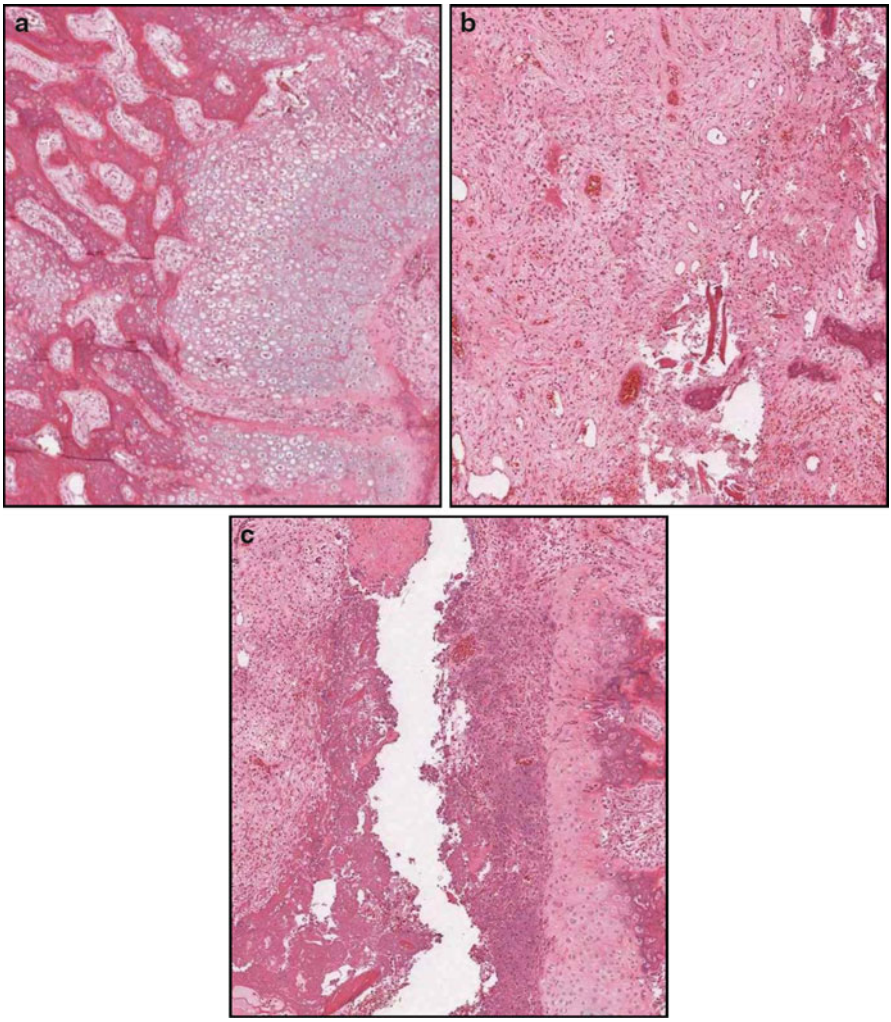

Fig. 15.12 Higher power microscopy of the areas labeled in Fig. 15.11. The periphery of the fracture callus (**a**) is composed of cartilage and woven bone (with very early lamellar bone), while the central part of the callus consists of granulation tissue (**b**) and persistent necrotic debris (**c**). When assessing "age" of the fracture, one must look at the whole fracture and not just selected areas. In most instances, the healing of the central part of the callus will lag far behind the periphery (Hematoxylin and Eosin, H&E a, b ×40; c ×20)

There is typically minimal or no periosteal disruption and little or no callus formation. However, changes at the physis subjacent to a CML may indicate a subacute CML. The normal physis is a disk of chondrocytes that extends in columns toward the metaphysis. Uninjured regions of the metaphysis–physis

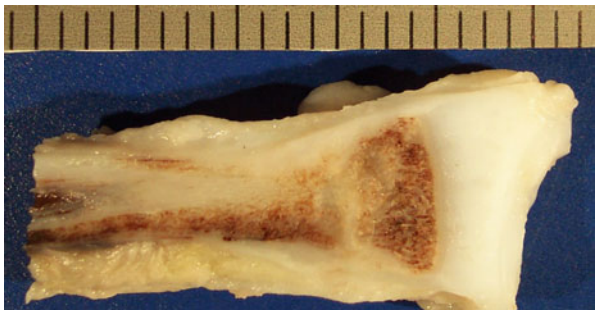

Fig. 15.13 Gross photograph of a distal radius fracture in a fatally abused 15-month-old

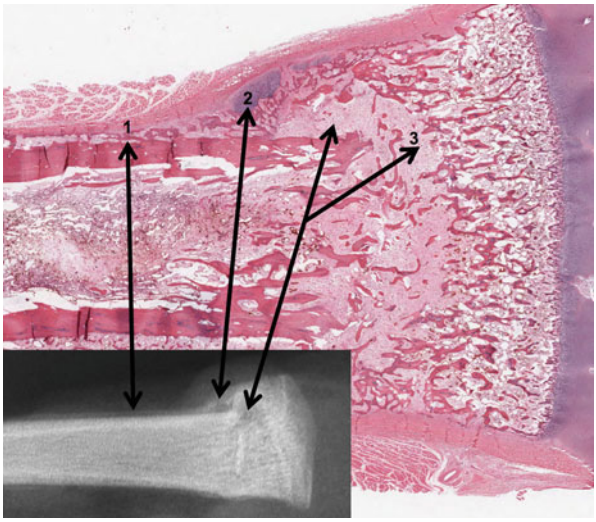

Fig. 15.14 The radiographic features of the fracture (*lower left inset*) from Fig. 15.13, such as SPNBF (*1*), cartilage in the fracture periphery (*2*), and granulation tissue in the central callus (*3*), are clearly demonstrated histologically (Hematoxylin and Eosin, H&E ×20)

complex will grow and mineralize normally around the fractured area; however, the area distal to the CML does not mineralize normally, resulting in the chondrocytes of the physis persisting abnormally. Histologically, this pattern appears as an area of hypertrophic chondrocytes (Kleinman et al. 1991).

When an x-ray beam is perpendicular to the long axis of the metaphysis, the comparatively thicker ends of the metaphyseal lesion appear as relatively discrete, triangular bony fragments, hence the term "corner fracture." When the x-ray beam is angled relative to the long axis of the metaphysis, the appearance resembles a "bucket handle." The two terms refer to the same injury, with the appearance of the injury depending on the radiographic projection. Contusions overlying CMLs are often absent. Precise dating criteria are not published, though Kleinman (1998, 2008) suggests that most healing CMLs become radiographically inconspicuous at 4 weeks and completely healed at 6 weeks (Figs. 15.20–15.29).

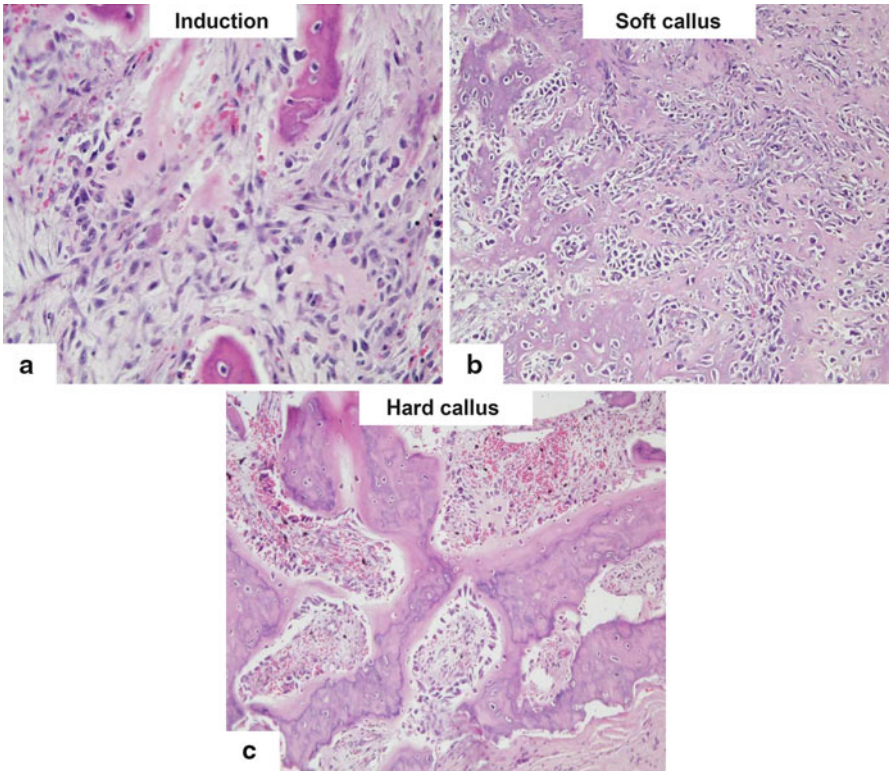

Fig. 15.15 (**a**–**c**) Three (of 52) rib fractures in a fatally battered 7-week-old. The fractures are in various stages of healing, as illustrated by the early organization of osteoblasts into trabeculae, with osteoid production (**a**); formation of mineralizing trabeculae of woven bone (**b**); and mineralized trabeculae of woven bone upon which lamellar bone is being deposited (**c**). **a**, **b**, and **c** represent the "oldest" areas in three different fractures (Hematoxylin and Eosin, H&E a ×200; b, c ×100)

Rib Fractures

In older children and adults, rib fractures occur as a result of recognizable trauma such as motor vehicle accidents and falls. Outside the setting of abuse, rib fractures are distinctly unusual injuries in infants. Rib fractures are the most common fractures found in infants dying from inflicted injury. A very tight hold around the infant chest by adult hands generates a squeezing force on the immature skeleton and may result in fractures of the anterior, lateral, and posterior aspects of the rib. In rare cases, rib fractures (including posterior rib fracture) have been reported as a result of birth trauma. In a large series of children admitted to a major medical center for trauma, the positive predictive value of a rib fracture as an

Fig. 15.16 Numerous bones can be placed on a single x-ray film. Radiography of resected bones often provides more detail than the original skeletal survey

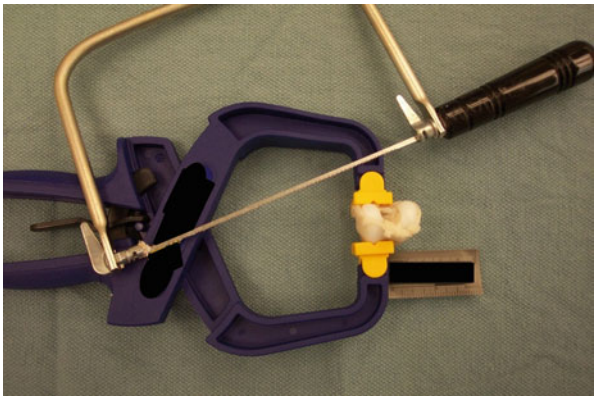

Fig. 15.17 Bisecting larger specimens will improve fixation and can be accomplished with fairly inexpensive tools

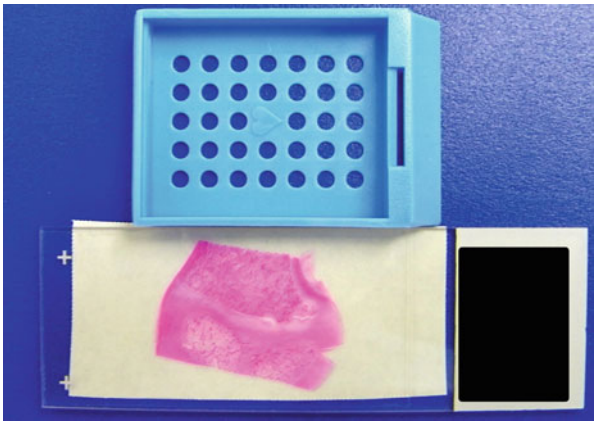

Fig. 15.18 Most infant and small child bony abnormalities (such as the metaphyseal lesion in this proximal humerus) can readily fit into standard histology cassettes when appropriately decalcified and trimmed

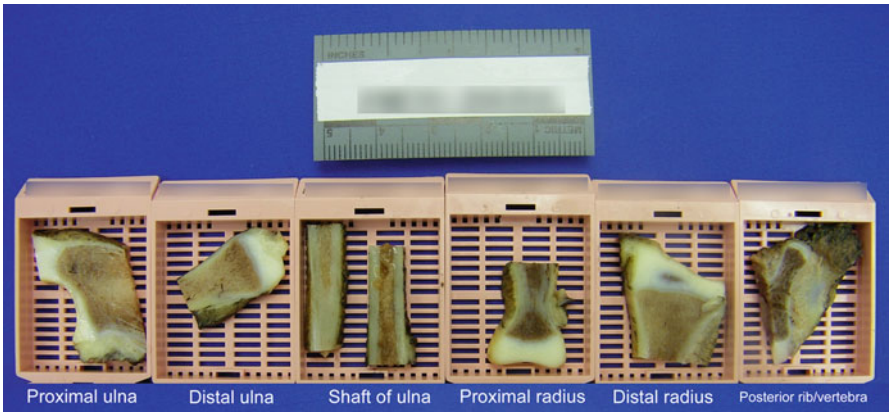

Fig. 15.19 Multiple bones (some injured, some normal controls in this case from a fatally abused 3-year-old) can be readily processed for routine histology in standard cassettes after decalcification

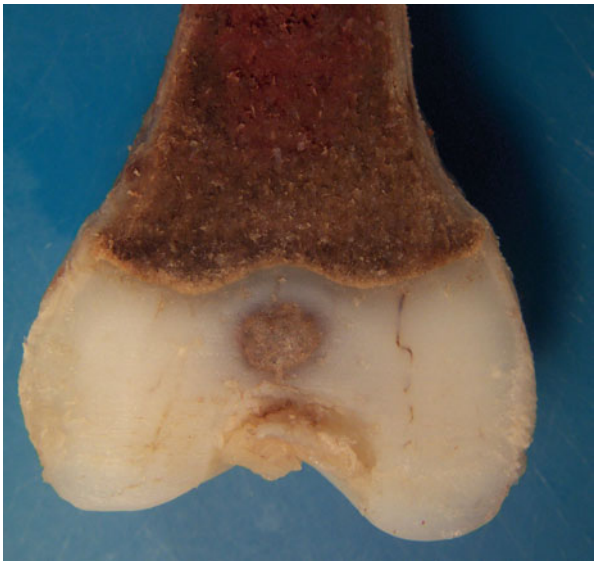

Fig. 15.20 Gross appearance of the normal distal femur from a 16-week-old

indicator of nonaccidental injury in children younger than 3 years of age was 95 %; this increased to 100 % when other causes were excluded by historical and clinical circumstances (Barsness et al. 2003).

Maguire et al. (2006) published a review on cardiopulmonary resuscitation (CPR) and rib fractures spanning the medical literature from 1950 to 2005. They concluded that rib fractures related to CPR (three of 923 children) were most likely to be anterior and could be multiple. They did not find posterior rib fractures related to CPR, noting

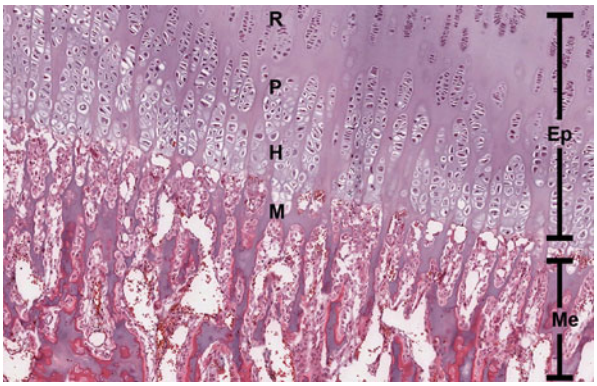

Fig. 15.21 Histology of the normal distal femoral physis photographed in Fig. 15.20. The chondrocytes mature from resting (*R*) to proliferating (*P*) to hypertrophying (*H*) in the epiphysis (*Ep*) and then mineralize (*M*) in the metaphysis (*Me*) (Hematoxylin and Eosin, H&E ×40)

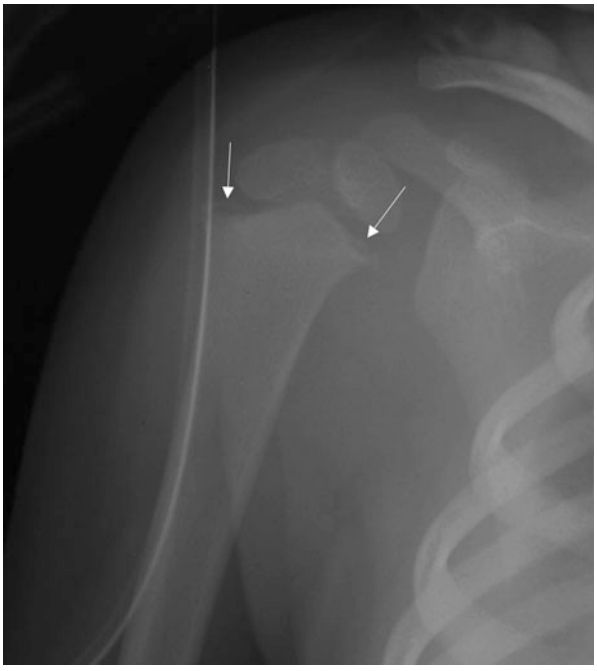

Fig. 15.22 The radiograph depicts a proximal humeral metaphyseal fracture (*arrows*) in a fatally battered 15-month-old. Note the "bucket handle" appearance

"sound biomechanical reasons for this." They did note that weaknesses in the literature were likely related to the degree to which rib fractures were actually being sought, radiographically and/or at autopsy.

A recent study by Dolinak (2007) suggests that anterolateral fractures from CPR may be more common in infants than previously appreciated; such fractures would not be expected to be visible on radiographs. In this study, 8 of 70 deceased infants with no autopsy or historical evidence of injury were found to have anterolateral rib

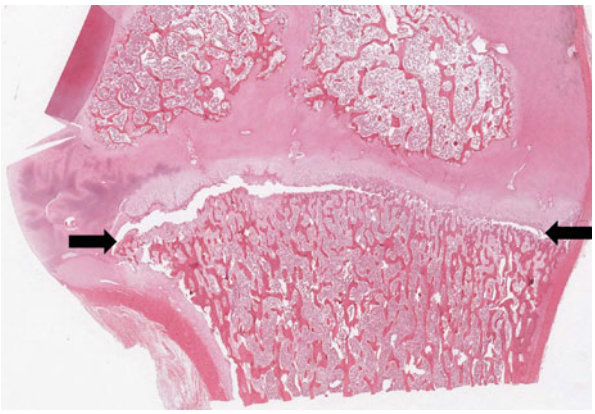

Fig. 15.23 The low power microscopy of the humerus in Fig. 15.22 shows the metaphyseal fracture (*arrows*) spanning the width of the physis (Hematoxylin and Eosin, H&E ×1)

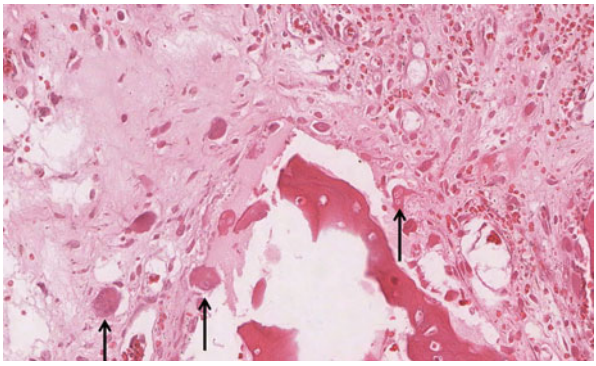

Fig. 15.24 Granulation tissue with osteoclastic activity (*arrows*) in the fracture site from Fig. 15.22 (Hematoxylin and Eosin, H&E ×200)

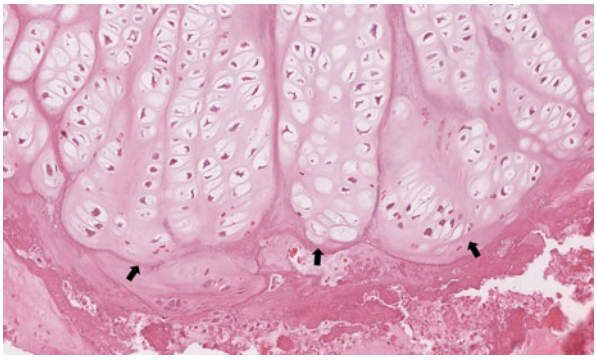

Fig. 15.25 Abnormal persistence of hypertrophied chondrocytes, forming billowing islands of cartilage that protrude into the fracture site from Fig. 15.22 (Hematoxylin and Eosin, H&E ×200)

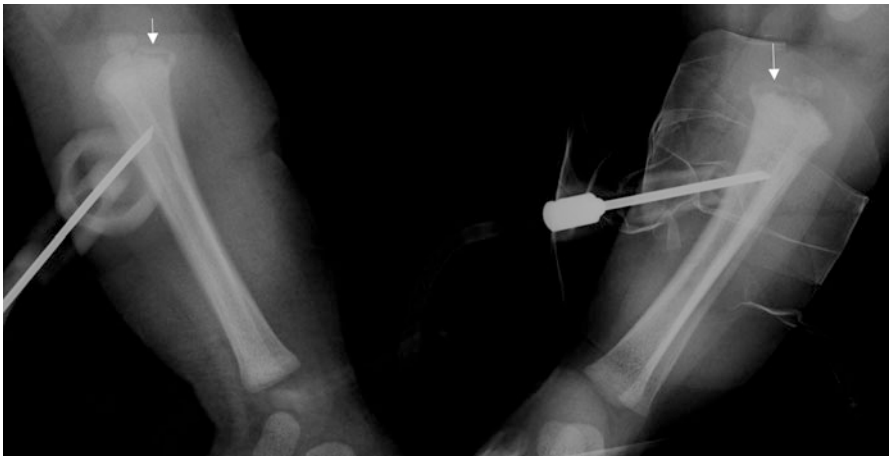

Fig. 15.26 Bilateral proximal tibia CMLs in a fatally abused 4-month-old. Note the "bucket handle" appearance (*arrows*)

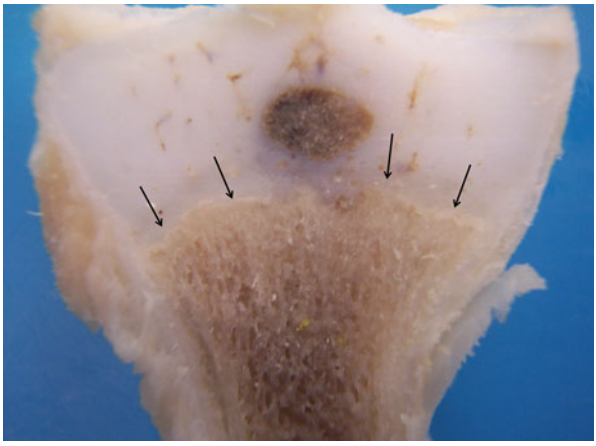

Fig. 15.27 Gross appearance of a proximal tibia CML from the radiograph in Fig. 15.26. Note the ragged, moth-eaten appearance of the metaphysis (*arrows*) compared to the normal metaphysis in Fig. 15.20

fractures. Most of these involved multiple ribs, in many instances bilateral. In all cases, the fractures were noted to be "subtle," with "little if any associated blood extravasation," and "would have been easily missed had the parietal pleura not been stripped."

Clouse and Lantz, in work presented in 2008, described four cases of hospitalized neonates and infants who were found to have posterior rib fractures apparently related to CPR performed in accordance with current American Heart Association recommendations for infants (thumbs on the sternum with the fingers encircling the chest and back). Three of their cases were classified as

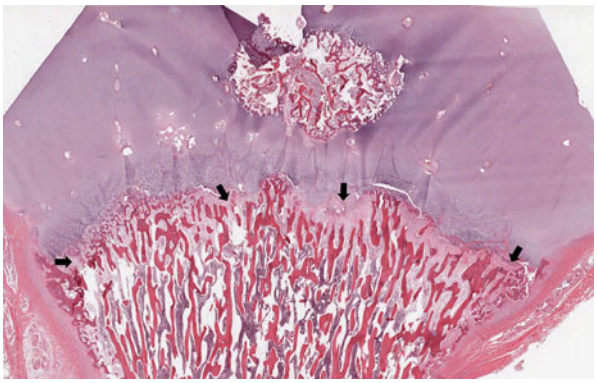

Fig. 15.28 Whole-mount appearance of the CML depicted in Fig. 15.27. The fracture spans the width of the metaphysis (*arrows*) (Hematoxylin and Eosin, H&E ×1)

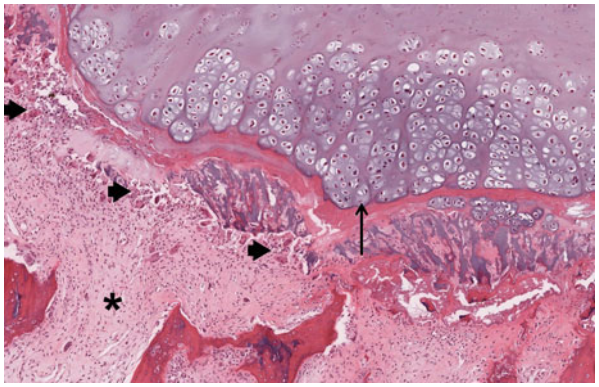

Fig. 15.29 Microscopy of the CML in Fig. 15.27. Reactive tissue changes (*), abundant osteoclasts (*arrowheads*), and billowing islands of persistently hypertrophied chondrocytes (*arrow*) are seen (Hematoxylin and Eosin, H&E ×100)

acute fractures; one case had evidence of healing ascribed to prior episodes of CPR. Though noting that rib fractures in small children are most commonly the result of nonaccidental injury, the authors wisely point out that such injuries must be interpreted in the context of "a complete autopsy and a thorough investigation of the circumstances of death." Duval and Andrew reported a case in 2007 in which posterior rib fractures, presumably related to this method of CPR, were found in a previously healthy 47-day-old.

Weber et al. (2009), in a series of 546 postmortem examinations for sudden unexplained infant deaths, found rib fractures in 24 cases. In 15 cases the fractures were healing, and 10 of the 15 cases had other physical findings considered due to nonaccidental injury. Of the nine cases in which the fractures appeared fresh, all of the fractures were anterolateral, and in seven of the nine cases, there were no other physical findings to suggest trauma. Though all seven of the cases remained "undetermined" in manner, this latter group of rib fractures was regarded as

resuscitation-related. The authors also point out that while 93 % of the healing rib fractures were demonstrable on routine radiographic skeletal surveys, only 22 % of the fresh fractures were identified this way.

More recently, Matshes and Lew (2010) described rib fractures in five deceased infants who had received two-handed CPR as described above. All of the fractures, which ranged from as few as two and unilateral to nine and bilateral, were noted to be on the anterolateral arc and minimally displaced, with only subtle associated gross hemorrhage. No posterior rib fractures were found. Interestingly, none of the fractures was identified on primary radiographic screening, and in only one case were fractures even suggested on rescreening.

Different mechanical forces are exerted on different parts of the rib cage when an infant is squeezed around the chest. Posteriorly, the ribs are attached to the vertebral bodies and transverse processes. As the ribs are squeezed, the posterior rib arc is levered over the transverse process, resulting in ventral (and sometimes complete) cortical disruption. Squeezing creates both anterior and posterior compressive forces laterally, resulting in buckling of the inner cortex and distraction of the outer cortical fracture margins. Sternal compression produces inward bending of the anterior costochondral junction, leading to fracture (Kleinman et al. 1992, 1996; Kleinman and Schlesinger 1997).

Acute fractures of the rib are characterized by disruption of the cortex and subjacent bony trabeculae. Hemorrhage is often observed at the fracture site. Radiographically, acute rib fractures may be quite difficult to discern, especially if the fracture is incomplete, nondisplaced, and viewed in an area with many superimposed structures or if the fracture line is oblique to the x-ray beam. Fractures of the costovertebral articulation are particularly difficult to appreciate radiologically for all of these reasons (Kleinman et al. 1988). Such acute fractures are optimally visualized with computed tomography (CT) scanning, although this may be unavailable to most pathologists autopsying infants pronounced dead before such radiographic evaluation could occur. With healing, most fractures become more visible on radiographs, as subperiosteal new bone and callus become evident (Figs. 15.30–15.49).

Skull Fractures

Skull fractures in infants and small children can be the result of abuse, accidental falls, and other forms of trauma. Although some types of skull fractures (complex, multiple, diastatic) may be more common in inflicted injury than in accidental injury, no skull injury pattern is diagnostic of abuse. The radiographic and histological appearance of healing skull fractures differs from most other fractures in that there is very little subperiosteal reaction and little (if any) formation of endosteal or periosteal callus (Rao and Carty 1999). Skull fractures may remain radiologically detectable for several months after the injury.

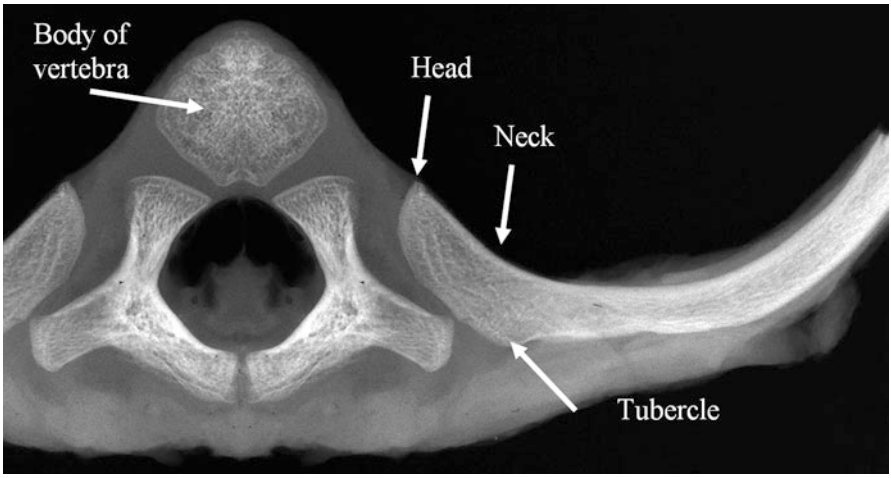

Fig. 15.30 Radiograph of a resected vertebral body with the posterior arcs of the ribs (normal infant)

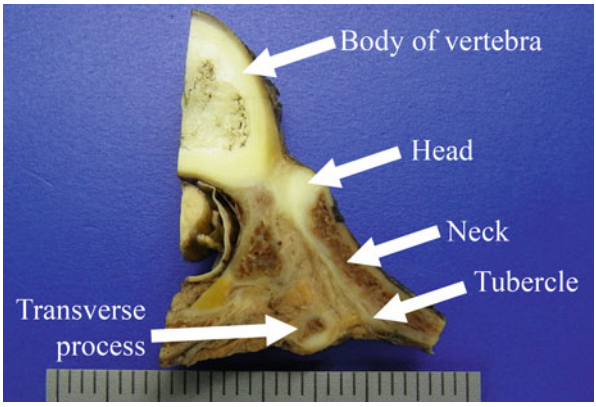

Fig. 15.31 Gross appearance of the normal posterior rib-vertebral articulation from a 3-year-old

Microscopically, the healing skull fracture may consist largely of fibrous tissue, without the production of osteoid or cartilage. For all of these reasons, very little can be said about the age of a skull fracture other than that it is healing (Fig. 15.50).

Mimics of Abuse

A variety of disease processes may account for unexplained fractures in infancy (Bishop et al. 2007). Although an exhaustive discussion of entities that can

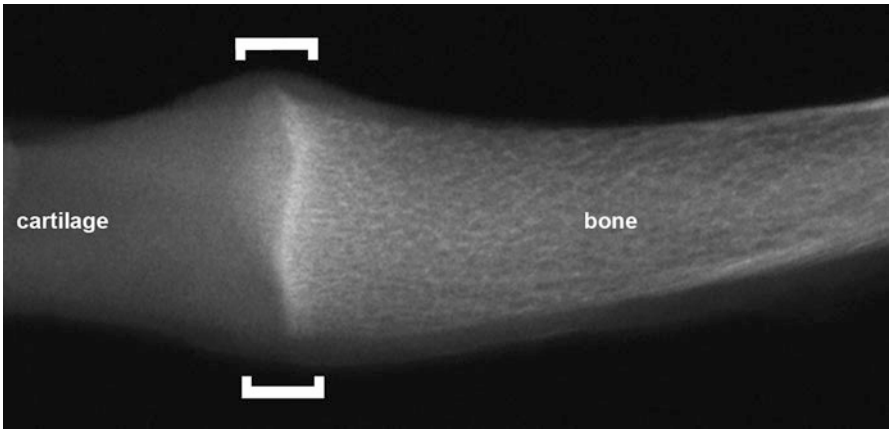

Fig. 15.32 Radiograph of a normal infant costochondral junction illustrating bone, cartilage, and the chondro-osseous junction (*brackets*)

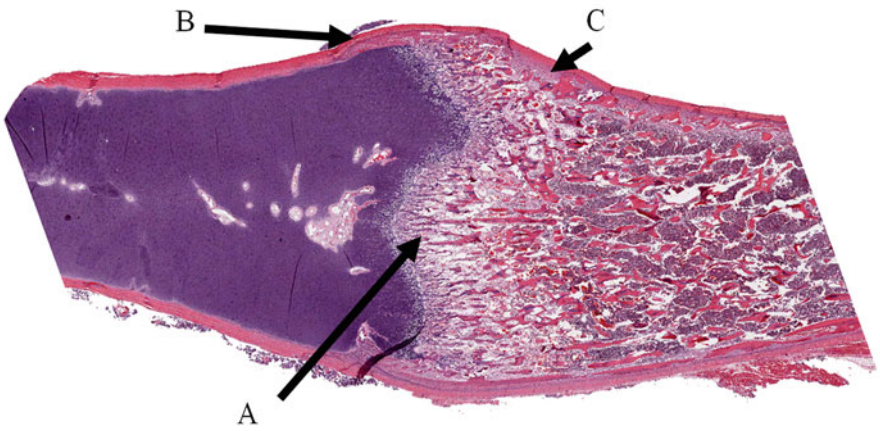

Fig. 15.33 Whole-mount microscopy of a normal infant chondro-osseous (costochondral) junction. Specific features (*A*, *B*, *C*) are described in Fig. 15.34a–c (Hematoxylin and Eosin, H&E ×1)

predispose to or mimic fractures is beyond the scope of this text, three commonly posited entities warrant further discussion here: "temporary brittle bone disease" (TBBD), subclinical vitamin D deficiency, and osteogenesis imperfecta.

First proposed by Paterson in 1993 and further described by Miller (Miller 1999, 2003; Miller and Hangartner 1999), TBBD is purportedly a self-limited condition that mimics abusive skeletal injury because there are multiple fractures with denial of harm to the child, there are no reported episodes of trauma, no other internal or external injuries are found, and there is no radiographic or laboratory evidence of metabolic or genetic bone disease. While the *concept* that there

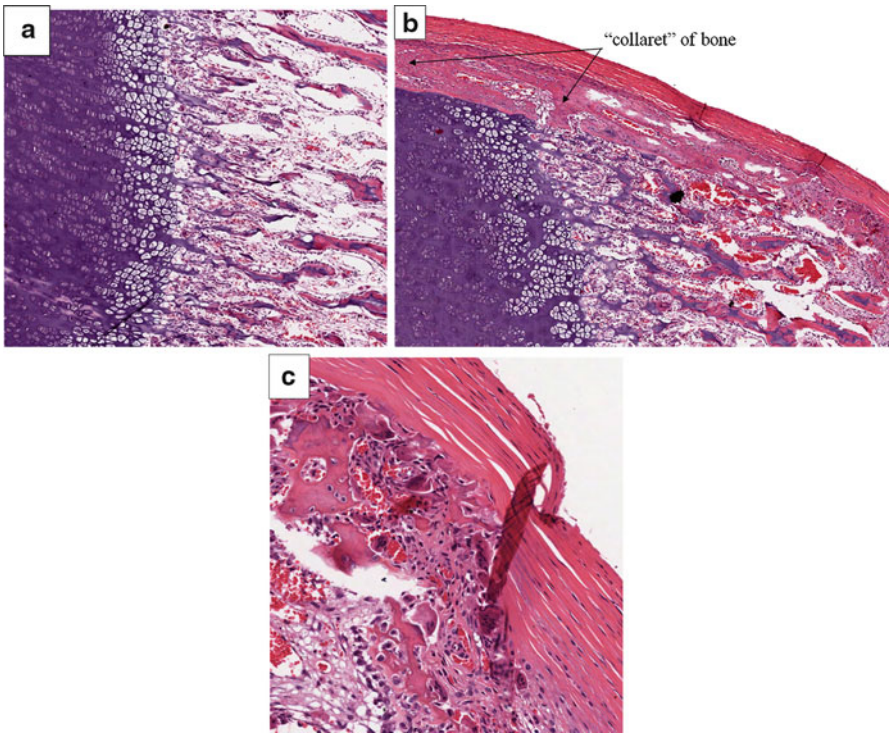

Fig. 15.34 (**a**–**c**) The metaphysis of the normal infant costochondral junction looks like the metaphysis of any growing long bone (**a**). A "collaret" of bone typically surrounds the chondro-osseous junction (**b**). The cortex near the chondro-osseous junction often appears osteopenic due to the remodeling and "cutback" that takes place during longitudinal growth (note the numerous osteoclasts). This is true of all growing long bones (**c**) (Hematoxylin and Eosin, H&E a, b ×20; c ×40)

are disease entities that can predispose to fractures is useful to remember, TBBD as a specific condition has not been accepted as a disease entity in the wider medical community and has been criticized in the literature (Mendelson 2007; Sprigg 2011).

Subclinical vitamin D deficiency has been offered as an explanation for fractures otherwise regarded as inflicted in young children. To date, however, studies have not found a link between vitamin D deficiency alone (in the absence of rickets) and increased fracture risk.

Chapman et al. (2010) described 40 children, age 2–24 months, with rickets. Thirty-eight of the 40 had osteopenia evident radiographically. Seven (17.5 %) of these children had fractures, and their radiographic studies demonstrated obvious rachitic changes and widespread metaphyseal fraying/cupping. None of the fractures occurred in radiographically normal bone or bone with only subtle rachitic

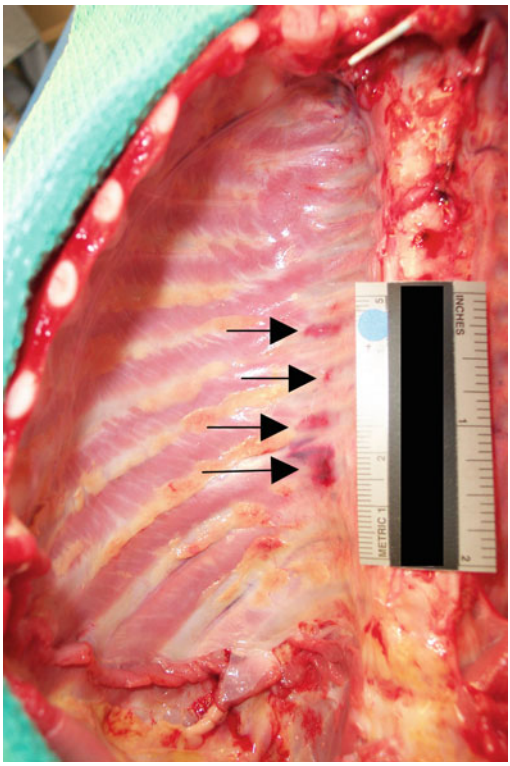

Fig. 15.35 Acute posterior rib fractures in a fatally abused toddler. When the thoracic cavity is initially inspected, the only clue to injury is the blush of hemorrhage (*arrows*) beneath the parietal pleura

changes, and all of the fractures occurred in mobile infants and toddlers. No CMLs or posterior–medial rib fractures occurred. The authors concluded that their study could not support the claim that multiple fractures occur in infants with radiographically subclinical vitamin D deficiency.

Schilling et al. (2011) described 118 children younger than 2 years of age admitted to the hospital with fractures, the majority of which were accidental. Thirty-nine percent of the children had deficient or insufficient vitamin D levels. When compared to the group of children with fractures who had normal vitamin D levels, there was no association between vitamin D levels and a child abuse diagnosis, multiple fractures, rib fractures, or metaphyseal fractures.

Untreated rickets can result in dwarfism, genu valgum, bowed legs, frontal bossing, scoliosis, and fractures in severe cases. Plain radiographs show widening of the growth plate and bowing of long bones. Histologically, in addition to the globally decreased mineralization, rickets also demonstrates disordered enchondral ossification with persistence of the cartilage growth plate penetrating into the medullary cavity (Horvai and Boyce 2011) (Figs. 15.51, 15.52).

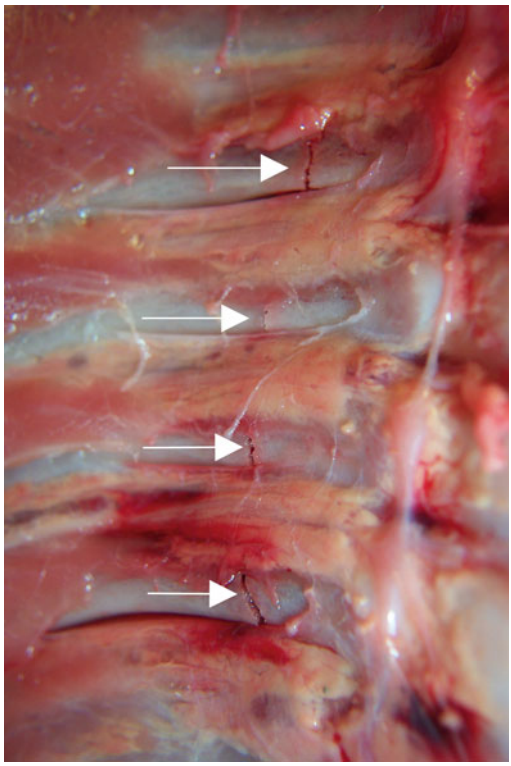

Fig. 15.36 Stripping the pleura from the ribs in Fig. 15.35 reveals the rib fractures (*arrows*). It is incumbent upon the pathologist to actively seek such fractures since, because of their acute nature and the presence of the vertebral transverse process behind them, these fractures would likely be missed on plain film radiography (Reproduced, with permission, from Lonergan et al. (2003). From the archives of the AFIP. Child abuse: radiologic-pathologic correlation. *RadioGraphics*, 23:818)

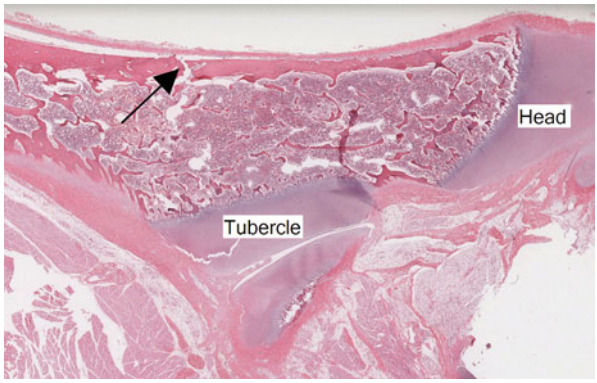

Fig. 15.37 Histological evaluation of a fracture from Fig. 15.35 shows that only the ventral cortex (*arrow*) is fractured in this instance. As would be expected based on the mechanics of how such fractures occur, the fracture is in the head-neck-tubercle complex of the posterior rib, where the rib is levered over the transverse process of the vertebra (Hematoxylin and Eosin, H&E ×1)

Osteogenesis imperfecta (OI) is a genetic disease caused, in most cases, by a mutation in one of the genes that encodes the α chain of type 1 collagen. A number of different genetic mutations have been identified, and the disease has a wide span of clinical severity that ranges from neonatal deaths with

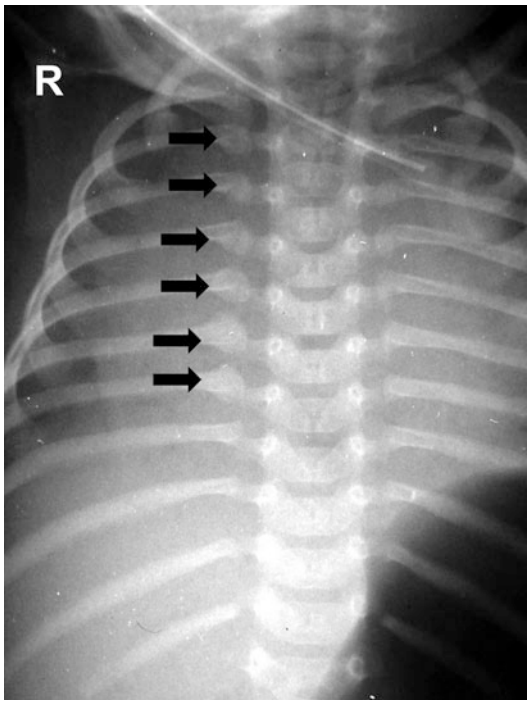

Fig. 15.38 These healing posterior rib fractures (*arrows*) in a fatally abused infant, though plainly visible on the pre-autopsy radiograph, were missed at the time of original autopsy. Only after a subsequent infant died, also a victim of homicide, was the first child exhumed and the rib fractures photographed and evaluated (Fig. 15.39). Reproduced, with permission, from Lonergan et al. (2003)

numerous fractures to mild osteopenia with few fractures throughout life. Most patients fall into one of the four (I–IV) phenotypes of the Sillence classification, though other phenotypes are recognized (Rauch and Glorieux 2004). In type I, the most common and mildest form of the disease, fractures are less common than in other types and osteopenia is less severe. All patients with type I have blue sclerae. Type II is lethal and may present as stillbirth with numerous intrauterine fractures. Liveborn infants generally survive only a few weeks. Type III patients, who may have blue, gray, or white sclerae, have severe progressive disease that may result in scores of fractures before adulthood. Infants have bowed limbs. Typical radiographic features include thin cortices, widening of the metaphysis and epiphysis, and intramedullary islands of calcified cartilage. Type IV patients have disease that is intermediate in severity between types I and III. Type II and type III cases should be readily diagnosable on clinical and radiological criteria (Bishop et al. 2007). However, a small percentage of children with unexplained fractures initially thought to be inflicted may be found to have OI when tested (Marlow et al. 2002).

The histological features of bone in type I OI are osteopenia with decreased cortical thickness and trabecular volume. The architecture is normal, the bone is lamellar, and Haversian systems are present. The more severe forms of OI (II, III, IV) have an increased number of osteocytes in both cortical and trabecular bone. Another feature is

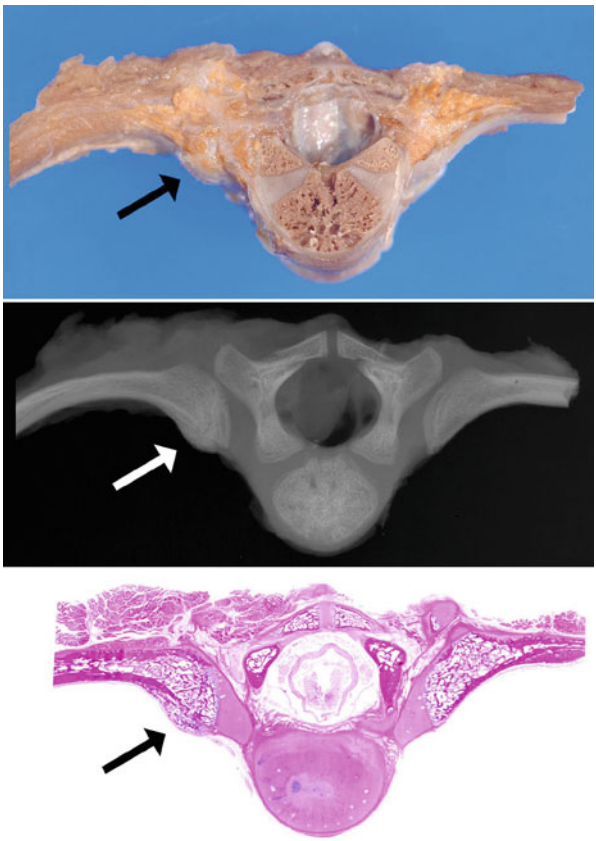

Fig. 15.39 From Fig. 15.38, a healing posterior rib fracture (*arrows*) is documented grossly (*top frame*), radiographically (*middle frame*), and microscopically (*bottom frame*). As would be expected based on the mechanics of how such fractures occur, the fracture is in the head-neck-tubercle complex of the posterior rib where the rib is levered over the transverse process of the vertebra (Hematoxylin and Eosin, H&E ×1)

the persistence of woven bone. Woven bone is most abundant in type II OI, with almost no lamellar bone. In types III and IV OI, most bone is lamellar, although some woven bone persists (McCarthy 2011). By histomorphometry, cortical bone width and cancellous bone volume are decreased in types I, III, and IV, compared to normal controls (Rauch et al. 2000) (Figs. 15.53–15.55).

Recommendations

1. Obtain a complete skeletal survey on all deceased infants and young children that present to the medical examiner as sudden, unexpected, or unnatural deaths The Society for Pediatric Radiology and the National Association of Medical Examiners write (Mendelson et al. 2004):

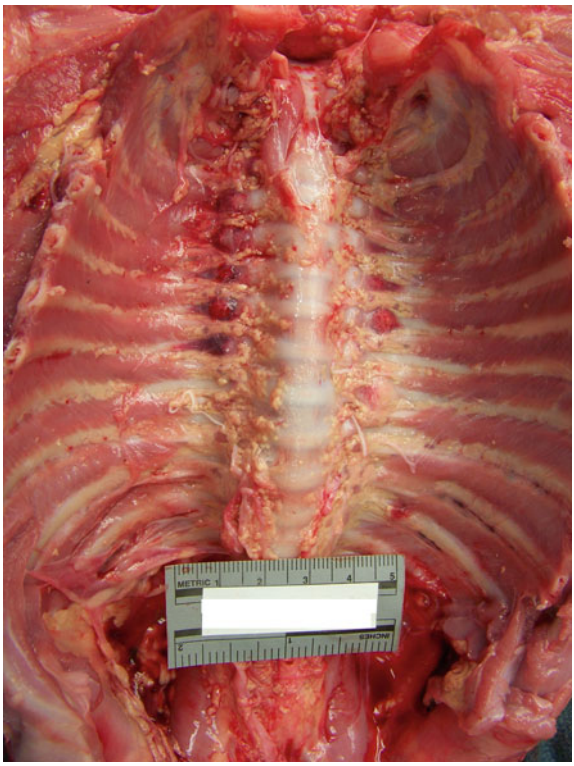

Fig. 15.40 In situ view of healing posterior rib fractures in a fatally abused infant. Fracture calluses appear as rounded enlargements of the bone and would be expected to be visible with plain film radiography of the chest

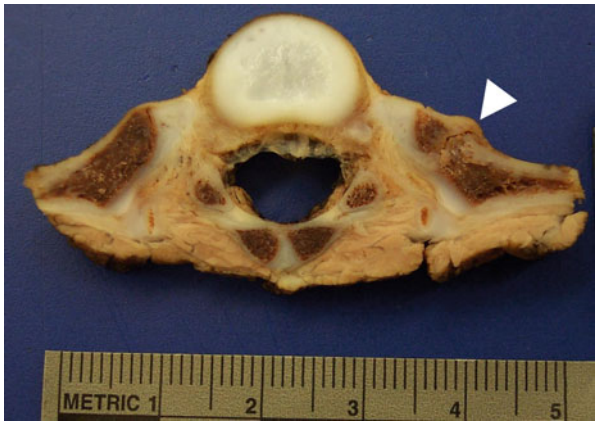

Fig. 15. 41 Gross appearance of one of the resected posterior rib fractures (*arrow*) depicted in Fig. 15.40. The fracture line is through the ventral cortex and deep into the marrow, but does not quite breach the posterior cortex

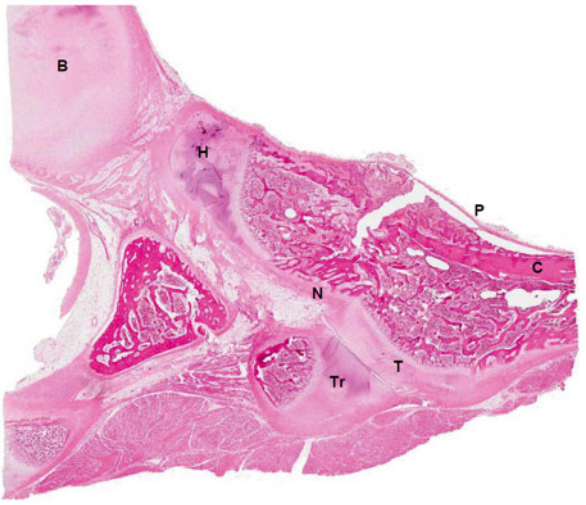

Fig. 15.42 Whole-mount microscopy of the healing fracture in Fig. 15.41. Landmarks for orientation include the body (*B*) and transverse process (*Tr*) of the vertebra and the head (*H*)-neck (*N*)-tubercle (*T*) complex of the posterior rib. The rib periosteum (*P*) remains intact but is lifted of the ventral cortex (*C*) of the rib by fracture callus (Hematoxylin and Eosin, H&E ×1)

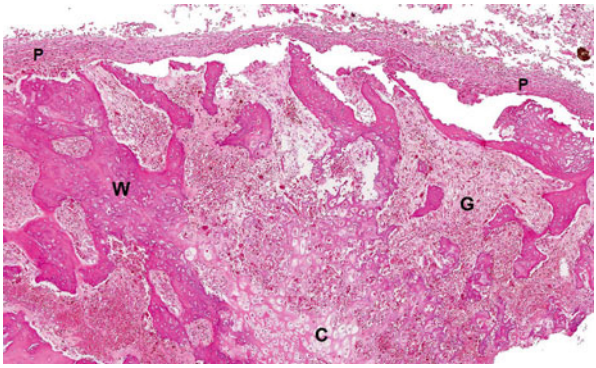

Fig. 15.43 Higher power magnification of the fracture in Fig. 15.42 shows fracture callus composed of cartilage (*C*), woven bone (*W*), and granulation tissue (*G*). The periosteum (*P*), as is often the case with infant fractures, is lifted off the fracture by fracture callus (Hematoxylin and Eosin, H&E ×40)

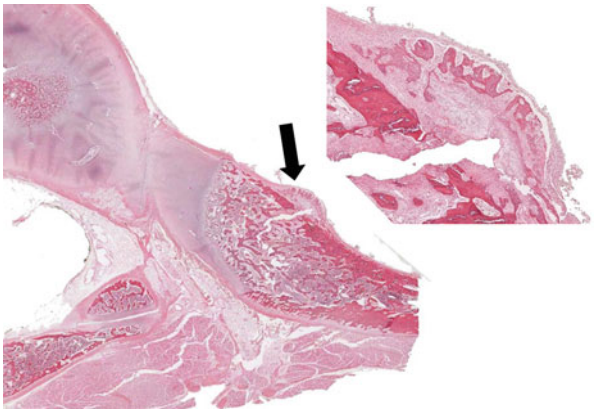

Fig. 15.44 A posterior rib fracture viewed at low magnification (*arrow*) and higher magnification (*inset*, Hematoxylin and Eosin, H&E ×20). Note the mixture of tissues in the callus as well as the intact periosteum surrounding the callus (Hematoxylin and Eosin, H&E ×1)

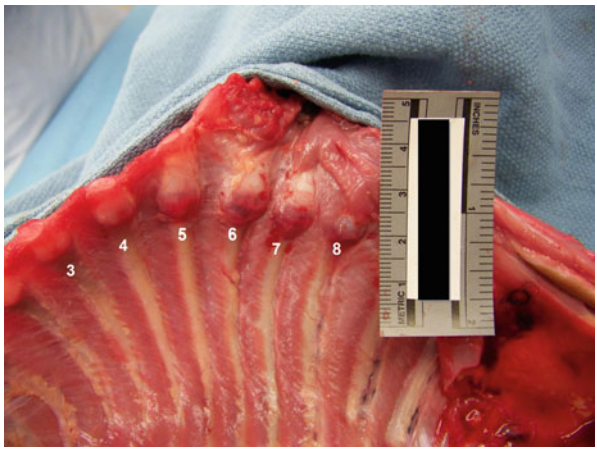

Fig. 15.45 Healing anterior rib fractures (5–8) in a fatally battered infant. The costochondral junction can normally be quite bulbous in infants (note the appearance of ribs 3–4, which are normal). If there is any question of fracture, the concerning bones should be resected and evaluated histologically

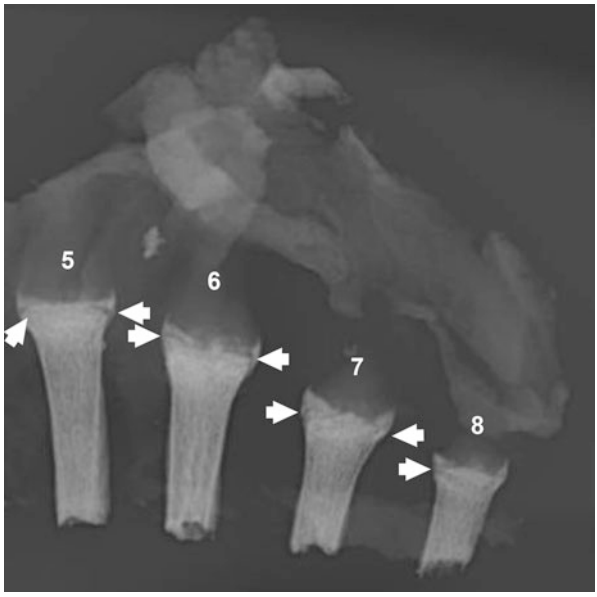

Fig. 15.46 Radiograph of the resected costochondral junctions photographed in Fig. 15.45. The fractures (*arrows*) look strikingly similar to the CMLs seen on long bones of the extremities

The skeletal survey is an important component of the forensic evaluation of unexplained death that is suspicious for abuse in infants younger than 2 years of age. It may detect highly specific inflicted injuries (such as the CML) that may otherwise be missed at autopsy or during a less than complete radiographic assessment. Accurate forensic analysis of all injuries, including those documented

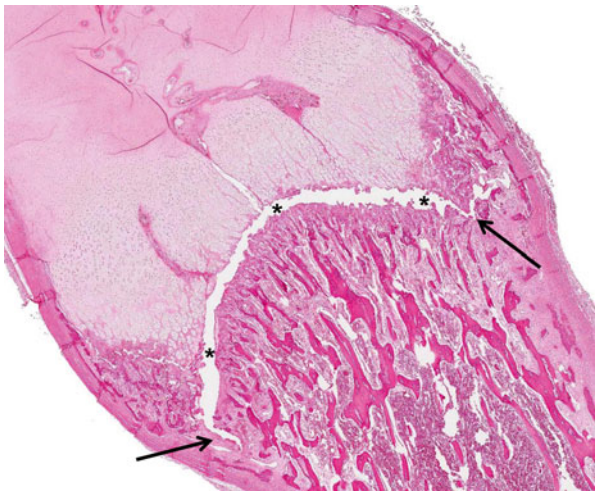

Fig. 15.47 Healing costochondral fracture from Figs. 15.45 and 15.46. The low magnification view corresponds well with the radiographic appearance, demonstrating the fracture line (*) and the undercutting of the peripheral bone collaret as the fracture approaches the outer edges of the bone (*arrows*) (Hematoxylin and Eosin, H&E ×40)

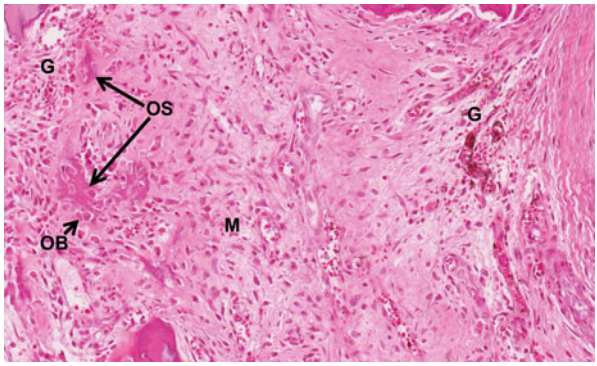

Fig. 15.48 Healing costochondral fracture from Figs. 15.45, 15.46, and 15.47. Higher magnification shows granulation tissue (*G*) and plump mesenchymal cells (*M*) in the callus, some of which have differentiated into osteoblasts (*OB*) and begun osteoid (*OS*) production (Hematoxylin and Eosin, H&E ×200)

radiographically, yields the best and most thorough information about the manner and cause of death.

- *Radiographic studies should be obtained in all unexplained deaths that are suspicious for abuse in children under 2 years of age. These should consist of, at minimum, well-collimated views of the long bones, with additional views obtained as necessary.*
- *When possible, studies should be performed by certified radiographic technicians. If this is not possible, jurisdictions need to ensure that the employees performing the studies receive adequate training. Certified radiographic facilities within the jurisdiction should make technologists available to conduct occasional training sessions where the postmortem radiographs will be obtained.*

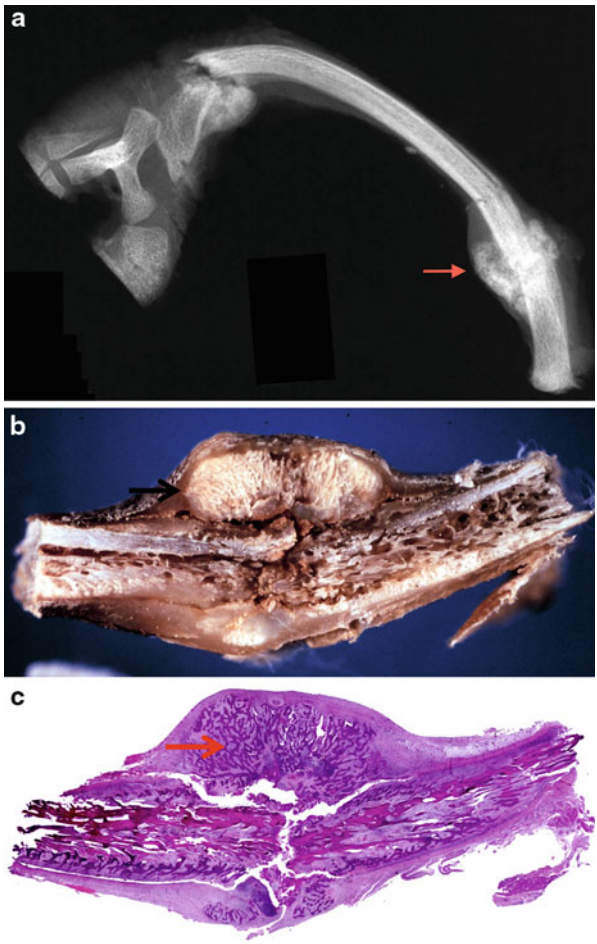

Fig. 15.49 (**a**–**c**) Axial radiograph (**a**), gross photograph (**b**), and whole-mount histologic section (**c**) of a healing rib fracture in a battered 7-week-old. Hard callus is visible radiographically, grossly, and histologically (*arrows*) (Hematoxylin and Eosin, H&E ×1)

- *It is the civic responsibility of pediatric radiologists to work with the Medical Examiner/Coroner's Office in their jurisdiction to make sure that postmortem radiological examinations are optimally performed and interpreted. Professional fees, when charged, should be at a rate that would not preclude the jurisdiction from availing itself of radiological services.*

2. Always strip the pleura from the ribs to ensure that acute fractures are not missed.
3. Resect any bones that are radiographically or grossly suspicious for acute or healing injury. It is very helpful to resect the contralateral normal bone for comparison.
4. Resected bones should be completely fixed before they are decalcified.

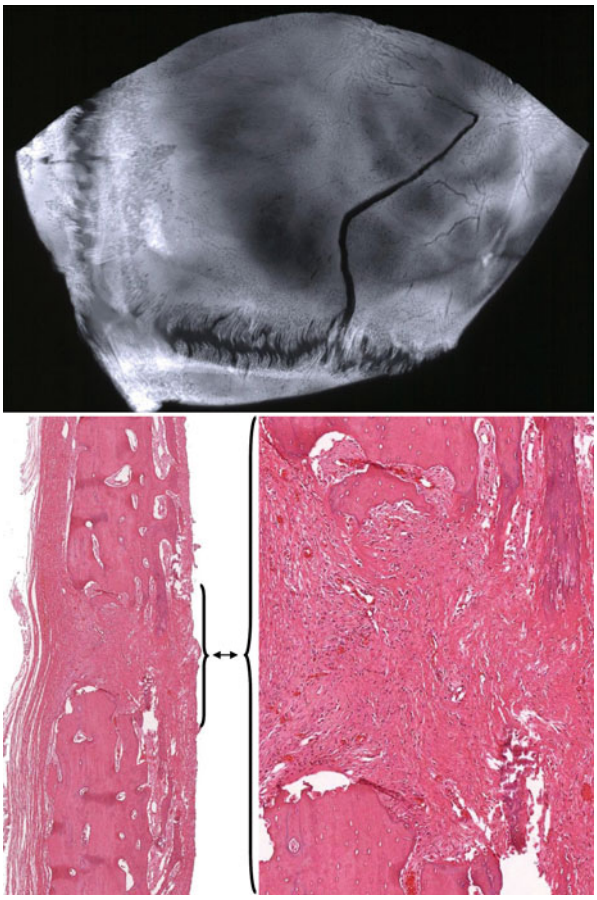

Fig. 15.50 A 5-month-old infant died of positional asphyxia in an unsafe sleeping environment. Approximately 1 month before death, he had a witnessed fall (sitting in a car seat on top of a running clothes dryer) that did not result in a discernible injury other than a right-sided scalp contusion. A linear parietal skull fracture was seen on the pre-autopsy radiographs. The specimen radiograph (*top*) shows no radiological signs of fracture healing. The largely fibrous nature of the healing process (*bottom*) bears little resemblance to the healing of long bone fractures or metaphyseal lesions. Note the absence of bone or cartilage callus (Hematoxylin and Eosin, H&E ×20, ×40)

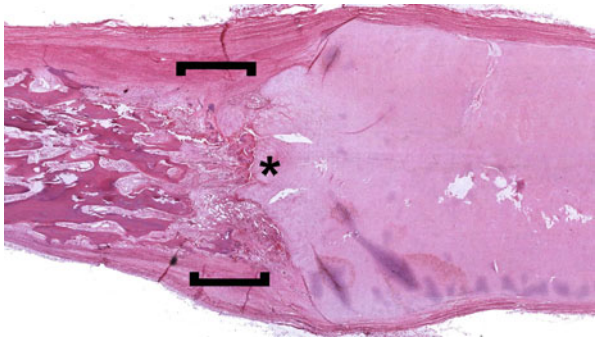

Fig. 15.51 Rachitic costochondral junction from a 7-year-old boy. An enlarged mass of unmineralized cartilage persists in the central part of the physis (*), with a large area of absent mineralization in the metaphysis (*brackets*) (Hematoxylin and Eosin, H&E ×40)

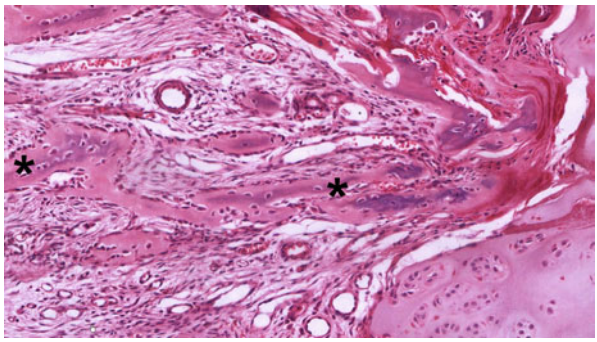

Fig. 15.52 Higher magnification of the metaphysis of the rib in Fig. 15.51. There is no normal progression of chondrocytes into the primary spongiosa, and the production of bone (*) in the metaphysis bears little resemblance to normal bone growth (Hematoxylin and Eosin, H&E ×100)

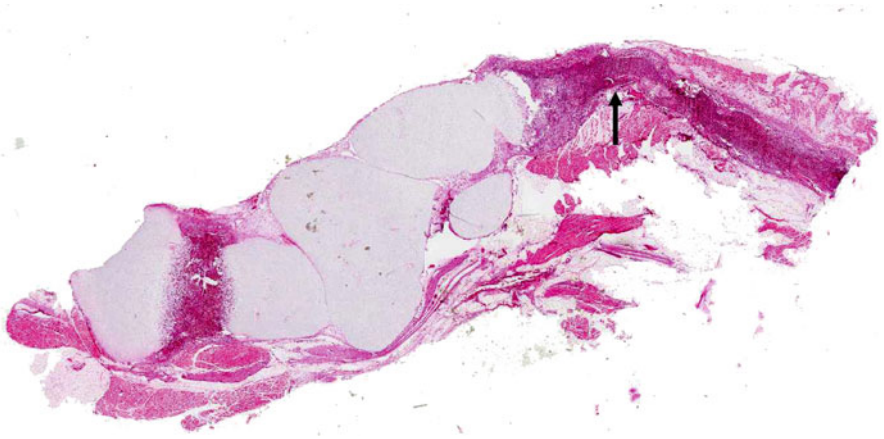

Fig. 15.53 Distal tibia (*arrow*) in a severe case of osteogenesis imperfecta. This child died within minutes of birth. Note the extreme bowing of the bone (Hematoxylin and Eosin, H&E ×1)

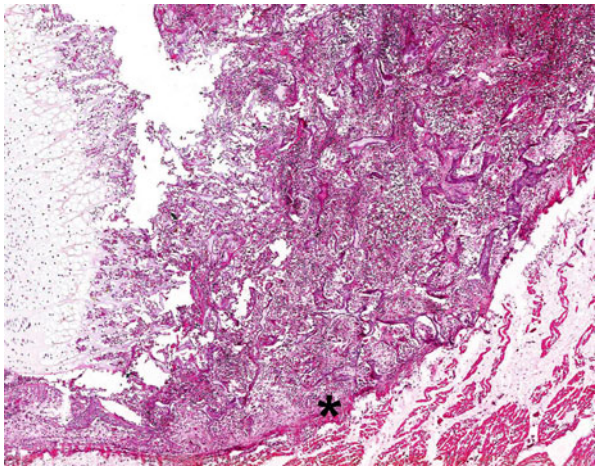

Fig. 15.54 At higher power, the bone in Fig. 15.53 has ossification at the metaphysis that is nearly absent, while woven bone in the medulla is bizarrely organized, and the cortex (*) is largely nonexistent (Hematoxylin and Eosin, H&E ×40)

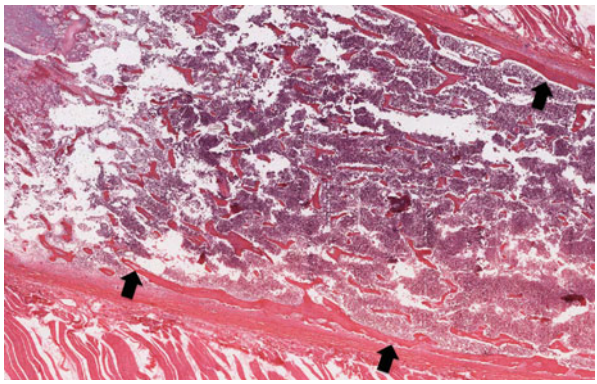

Fig. 15.55 Longitudinal rib section from a 27-day-old with short extremities and bowed femurs who died of respiratory failure, diagnosed with osteogenesis imperfecta. The cortices (*arrows*) appear thinned and discontinuous (Hematoxylin and Eosin, H&E ×100)

5. Decalcified bones should be carefully sectioned, ideally in the same plane as any radiographs, to allow radiological–histological correlation.
6. The features of healing of injuries should be described in the autopsy report, but be very cautious in any attempt to "date" injuries. Very little, if any, actual data exist that allow dating of bony injuries. Radiographic ability to "date" long bone injuries is also extremely limited (Halliday et al. 2011).

Conclusions

- Some fractures in infants and very young children, especially posterior rib fractures and CMLs, have a very high specificity for inflicted injury.
- It is incumbent upon the pathologist to actively seek out, via radiography, gross inspection, and microscopy, fractures in the deceased child who may have been abused.
- Little data exist to meaningfully "date" fractures, though different stages of healing are readily recognized microscopically.
- Skull fracture healing bears little resemblance to the healing of diaphyseal fractures in long bones.

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Dating of Other Injuries in Children

16

Neil E. I. Langlois

Contents

Abstract

This chapter will review the features of wound healing that may be used to routinely assist with determining the age of an injury. Incised wounds, bruises, burns, and fractures are covered. It is acknowledged that wounds may not exhibit expected temporal changes, and reasons for this are given. Finally, a practical approach is suggested.

Introduction

This chapter will focus on practicalities of estimating the age of wounds (cuts, burns, bruises, and fractures) from published data on the healing of injuries in

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humans, using the process of healing of incised wounds as a model. The chapter will be restricted to histological changes that are accessible to the routine practice of pathology.

Incised Wound Healing

Following injury, neutrophils are described as the first inflammatory cells to arrive. In the human brain following injury, the earliest they have been reported is at 5 and 10 minutes; whereas, in injuries of human skin the earliest emigration into the wound has been identified within 10 minutes (Oehmichen 2004), 15 minutes, and 20–30 minutes (Betz 1994), with numbers of neutrophils being numerous by 2 hours. Other authors have reported times of 2–8 h for neutrophils to be recognized in the wounded area, and they were present in wound samples taken at 3 h in a further study. In a study of healing abrasions from autopsy cases, neutrophils were first observed in a perivascular location in injuries 2 h old and below the raw skin surface after 8 h. It was noted that the perivascular response was more marked when there was also injury to the subcutaneous fat and it has also been noted that neutrophil infiltration occurs earlier in the subcutaneous fat than in the upper layers of the skin (Nádvorník 1985).

In the skin and subcutis, the numbers of neutrophils peak around 1–2 days post-injury, then they are overtaken by macrophages, which become the predominant inflammatory cell. In studies of human skin wounds, macrophages have been recorded to first appear at 3 h. Peak numbers of macrophages may be seen at 1–2 days, but can outnumber neutrophils from 20 h (Betz 1994). However, others have described monocytes (macrophages) in a perivascular location adjacent to the wound at 1 day, with increasing numbers over 2–3 days to become the predominant cell by 5 days with clear phagocytosis of wound debris seen in 3-day and 5-day samples. Unambiguous macrophages containing ingested red blood cells are present by 3 days post-injury. However, the earliest erythophages may be seen at 12 h (Oehmichen 2004), while others have reported their presence ranging from 15–17 h (Laiho 1995) to 1–2 days (Püschel et al. 1995), with numbers peaking at 2–4 days (Oehmichen 2004). The macrophage response tends to decline by a week into the wound healing process.

An epithelial response can commence by 24 h. Initially there is migration of epithelial cells into the area of injury: Cells become flattened and develop pseudopod-like projections. The migrating cells do not proliferate. Behind the migrating zone is a proliferating zone commencing 1–2 days after injury with the epithelium becoming hyperplastic by 2 days (Kirsner and Eaglstein 1993; Clark 1995). In a study of abrasions sustained from accidental injury, the regenerating epithelium with "clear cells" was seen as early as 24 h post-injury with a tongue of cells 1–2 layers thick having developed between the eschar and non-necrotic collagen by 30 h. If the wound edges have been opposed or if wounds are small (up to 5 mm), they can be bridged by 2–5 days (Püschel et al. 1995). Superficial fine linear incised wounds can be covered by 2–3 days with the epithelial thickness returning to

near normal by 5–7 days (Odland and Ross 1968). Keratinization may be seen at 4 days post-injury.

Granulation tissue "invades" the wound with the purpose of cleaning the area and providing blood supply in order to support production of new matrix. The earliest fibroblasts have been observed to migrate into a wound study device in children 2 days post-injury, but were more evident by 3 days. However, they were recorded at 20 h in an ultrastructural study. Fibroblast proliferation was seen at the edges of wounds at 2 days, although even at 4 days, they were rare except in the subcutaneous fat. Granulation tissue was not seen prior to 5 days in one study and was recorded as absent on day 3, but present at day 6 in another. Regression of granulation tissue started by 12 days in healing abrasions. In a series of small wounds, vessel density almost doubled by day 4 and remained constant in the 7-day and 10-day samples.

The temporal response of lymphocytes in wounds is not clear. Some report a variable response (Betz 1994) while others record lymphocyte numbers to be relatively constant with the cells distributed around vessels. However, the temporal pattern of lymphocyte accumulation in wounds may depend upon whether all lymphocytes are included or if T-lymphocytes alone are studied as T-, but not B-lymphocytes, appear to play a role in wound healing (Schäffer and Barbul 1998). It has been noted that T-lymphocytes may be seen in the wound by 3 days with a progressive increase to day 8 and decreasing by day 14. Lymphocyte predominance after day 14 has also been recorded, and lymphocyte cuffing of vessels may persist for weeks.

Collagen III networks may be detected by immunohistochemistry 2–3 days post-injury with collagen I appearing later, around 4–5 days. A morphological study reported little or no fibrosis at day 4 (although fibrinoid degeneration could be seen). Collagen formation was seen in muscle at 6–7 days, but the most marked reaction was in the subcutaneous fat at that time as collagen fiber formation increased rapidly for days 8–10. Reticulin fibers have been recorded at day 8 and day 10 (Robertson and Hodge 1972). Elastic fibers were not seen for months in a study of surgical wounds and were noted to be fewer in number than in adjacent uninjured tissue for weeks after healing (Kirsner and Eaglstein 1993).

A study of 3.5-mm punch biopsy sample sites in women revealed a reduction in wound size at 9 days and the time for healing ranged from 4 to 8 weeks. Wound healing of a 3.5-mm punch biopsy site was studied in 2 groups that were randomized to exercise or not exercise; healing took 3–7 weeks in the group of exercising subjects aged 61 $\pm$ 5.5 years, and 5–7 weeks in the non-exercising subjects (Emery et al. 2005). A median healing time of 28 days was recorded for a 2.0-mm skin punch biopsy wound.

Bruises

Blunt force trauma sufficient to break the vessels within the skin and deeper levels without causing the skin to break will result in a bruise (Vanezis 2001).

A distinction should be made between a bruise, caused by local blunt trauma, and an ecchymosis which represents an extravasation of blood not due to blunt trauma (Nash et al. 2009). For example, an ecchymosis will result when blood tracks in the tissue following a fracture. As light will only penetrate a short distance into the skin, a bruise may not be externally visible. If the bruise is visible, its initial color depends on (1) hemoglobin contained in erythrocytes released from blood vessels into the tissue and (2) the depth of the blood within the skin. Blood near the surface of the skin will appear red, but blood deeper in the tissue can appear blue, an effect that is attributed to Rayleigh scattering, absorption coefficients of skin, and interpretation by the visual system. With time, the color changes due to diffusion and removal of hemoglobin by the inflammatory response, which is triggered by the release of blood into the tissue and accentuated by tissue damage caused by blunt trauma. Macrophages ingest erythrocytes and break down hemoglobin into biliverdin using the inducible enzyme, heme oxygenase. Biliverdin is a green pigment that is rapidly changed to bilirubin, a yellow pigment, by the enzyme biliverdin reductase. The iron that is released from the hemoglobin is locally bound to ferritin, which polymerizes to form hemosiderin that has a rusty brown color.

The inaccuracy of the visual aging of bruises has been highlighted by research conducted by three observers describing the colors of 58 bruises on 44 children (Munang et al. 2002). Bruises were directly assessed, photographed, and later shown to the same observers who described the bruise. There was agreement between two observers in only 27 % of direct observations and in 24 % of the photographs. A later study of bruises in 50 children confirmed that clinicians' ability to age bruises from direct examination has poor interobserver correlation as well as large individual variability, with low accuracy. Thus, the ability to clinically assess local features, such as pain and induration that are associated with a recent bruise (Nash and Sheridan 2009), was not of much use in reliably estimating the age of a bruise. Another study using forensic experts showed that age estimates of a bruise from photographs are unreliable (Pilling et al. 2010; Grossman et al. 2011). Variability in color perception between observers may be one reason for the poor correlation.

Colors reported as red, blue, purple, black, or green do not provide valuable clues regarding the age of a bruise. The development of a yellow color in bruises has been attributed to the local production of bilirubin. The production of bilirubin and hemosiderin at the site of a bruise requires time for macrophage recruitment, inducement of heme oxygenase, and catabolism of hemoglobin. This would provide an explanation for the observation that a bruise that is yellow is not recent (Langlois 2007). Studies of bruises in children have recorded that yellow was not observed in bruises less than 24–48 h of age, suggesting that the appearance of yellow color is a significant discriminator of bruise age. An important criterion of this statement is that it is observation of yellow, not orange or brown, that defines a bruise as over 24–48 h (Fig. 16.1). Estimation of the age of bruises by histology is based on general principles of wound healing and the search for hemosiderin. Hemosiderin in

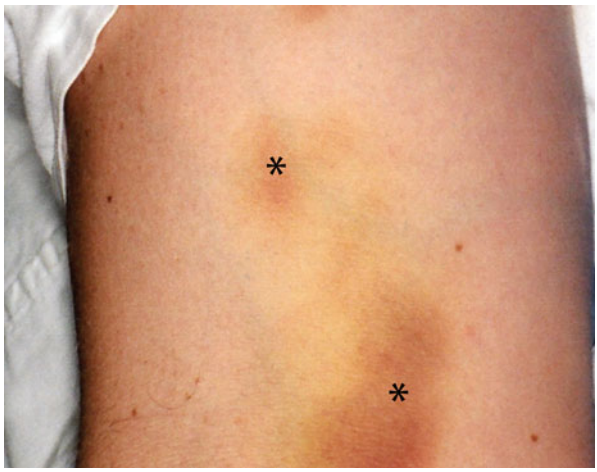

Fig. 16.1 Areas of bruising (*) showing *orange*/*brown* color with *yellow* between. The presence of true *yellow* color, not *orange* or *brown*, is significant to the age of the bruise

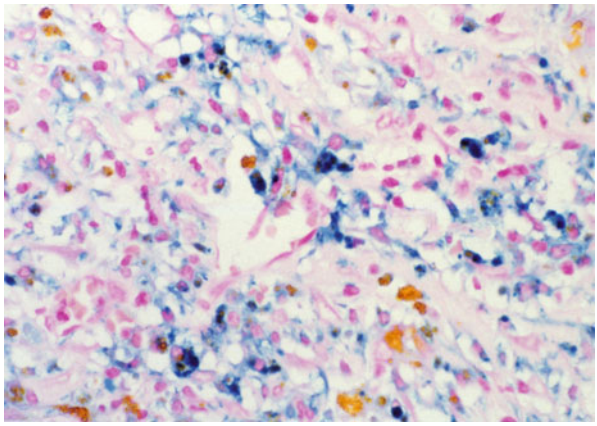

Fig. 16.2 Histological section stained using Perls Prussian Blue method. Abundant stainable iron (hemosiderin) is present with deposits of hematoidin (*yellow*), which represents accumulation of bilirubin. This is not often seen as it is water soluble and frequently removed by tissue processing (× 40)

the tissue can be stained bright blue using Perls Prussian Blue stain (Fig. 16.2). The literature indicates that hemosiderin is not seen in wounds of the skin until 3 days post-injury (Püschel et al. 1995).

Burns

The effects or severity of a burn are dependent on the temperature and exposure time; the most severe damage occurs at the point of heat application with surrounding zones of decreasing cellular damage and change. The changes may develop rapidly with coagulative necrosis developing in the epidermis within 24 h of burning. Mild thermal injury induces a transient immediate response of postcapillary venular dilation and increased permeability, which may be manifest

as erythema of the skin, but this will not be manifest histologically. First-degree burns damage only the epidermis and generally heal within a few days without a scar. These may display a biphasic vascular response that results in dermal edema and blisters, the presence of which has been interpreted as at least 36 h of age; however, blisters can occur earlier (Converse and Wood-Smith 1977). The influx of neutrophils may be delayed due to local effects, such as stasis and impaired chemotaxis, but in burns patients, there may also be a systemic impairment of neutrophil response, further delaying and minimizing infiltration (Tarran et al. 2006). A study of biopsies from human survivors of burn injuries revealed that neutrophil counts were generally high in the 6–48 h samples, but were not elevated in all samples. The neutrophil response was seen best in samples from within the burnt area. In biopsy specimens from fatal burn victims, neutrophil counts were not elevated from a sample at 6 h, but the macrophage response was best seen in samples from the edge of the burn, with a rise in numbers seen from 2 days. Again, there were a number of samples with minimal response (Tarran et al. 2006). A granulation tissue response in burn wounds may be delayed until 10 days post-injury. Hemosiderin has been detected from 5 days at the burn wound edge and 10 days in the wound center using Perls stain (author's unpublished observation from a series of burn injuries.

Fractures

Bone is mineralized tissue that provides structural support and protection to areas of the body. It is composed of subtypes, which include lamellar (also called compact) bone that is composed of concentric parallel layers, and woven bone (also called cancellous bone) that is a spongy network of less organized tissue. Initially, there is a fracture hematoma, which becomes a blood clot and acute inflammation follows. This acute phase is identical to other wound healings, culminating in the formation of granulation tissue. Next is the repair phase. Osteogenic cells are recruited, the origin of which is uncertain, but may include cells from the inner layer of the periosteum and from within the bone. Cartilage is formed in the granulation tissue that has invaded the clot, resulting in a soft callus (Frost 1989). Woven bone is formed by mineralization of the cartilaginous granulation tissue matrix (endochondral ossification), forming hard callus. Intramembranous ossification also occurs under the periosteum. With time, the woven bone is remodeled to lamellar bone. Direct fracture healing requires anatomical alignment without a gap and lack of movement. If the gap is less than 0.01 mm with minimal strain contact, healing can occur. In this process, osteoclasts create cutting cones at a rate of 50–100 μm per day across the fracture line; these are filled with new bone by osteoblasts, resulting in restoration of the continuity of the bone. Direct gap healing occurs when the gap is less than 1 mm by the action of osteoblasts that deposit new bone perpendicular to the long axis in the fracture line, which is subsequently remodeled (Marsell and Einhorn 2011). Direct healing may occur in fractures of the skull, and it may be that this could lead to difficulties in estimating the age of fractures.

A study of healing fractures in human adults divided the histological appearances into seven grades. Cartilage formation was seen in a sample 11 days old (from the radius) and cartilage with woven bone was recorded in samples from 12 to 15 days. Lamellar bone formation was found in samples after 17, 21, and 28 days. It was noted that inflammatory cells were spatially and temporally distributed, with macrophages being present early in granulation tissue. In another study of human fracture callus, new cartilage and bone was present in the samples that ranged from 2 to 9.5 weeks post-fracture (Kloen et al. 2003). A review of a skeletal collection from the American Civil War revealed the earliest response comprised evidence of an osteoclastic response at 5 days; none had an osseous response in the first week, but this was present in some samples from 2 weeks and in all by the sixth week post injury (Barbian and Sledzik 2008).

Rib fractures may be found in cases of child abuse, and the age of the injuries may be important to the case. There is little literature addressing this issue, but the available material (mostly based on animal studies) has been reviewed. Extrapolation from this suggests cellular granulation tissue with cartilage (callus) can develop by 4–5 days, but is more common 7–14 days post-injury. New bone can be found between 4 and 5 days, but is more common at 7–14 days (Zumwalt and Fanizza-Orphanos 1990).

It has been suggested to this author that radiological assessment would be better than histology for determining the age of fractures. However, a systematic review has shown dating of fractures by radiology is an inexact science (Prosser et al. 2005) and fracture age determination by histology has been reported to be superior to radiology. Notwithstanding this, much of the knowledge of fracture healing has been gained from animal experiments and may be difficult to apply, particularly to healing fractures in children. Other features, such as evidence of soft tissue swelling over a recent skull fracture, may be useful in assisting with fracture age estimation.

Muscle

Observations of muscle samples following trauma resulting in long bone fracture, revealed a mixture of normal, intact, but swollen and fragmented muscle fibers at 6 h, with an infiltration of erythrocytes and neutrophils; eosinophilic change of the cytoplasm affected some fibers. By 3 days, there were fibers with vacuoles that had lost their striations, degenerate hyaline fibers, granular fibers, and discoid degeneration (disk-like separation of sarcoplasm); neutrophils were present in some fibers. At 4 days, phagocytosis of disintegrated fibers was seen. By 10 days, phagocytosis of fibers that disintegrated within their sarcolemmal sheaths was advanced; myoblasts with basophilic cytoplasm could be seen in groups (attempting to repair the muscle.) Small basophilic staining fibers with central chains of nuclei were present at 13 days. At 18 days, the regenerating muscle fibers were thicker with less basophilic staining; some peripheral nuclei were present and cross-striations

could be seen. Samples at 1, 3, and 6 months revealed increased collagen at the injury site, but the muscle fiber regeneration was complete (Allbrook et al. 1966). An animal model–based study indicated that the rate of the healing process is affected by treatment with more rapid resolution of hematoma and inflammation with mobilization.

Intra-abdominal Injuries

Studies of peritoneal fluid following blunt abdominal trauma, although largely based on an animal (dog) model, suggests that increased neutrophils can be found around 2 h after injury in humans. The observation of neutrophils in biopsy samples taken from the liver following operative procedures indicates that an acute inflammatory reaction can develop rapidly, within a few hours, although whether it is related to trauma or other effects has to be proved (Fenster 1987). The rapid development of inflammation following blunt force trauma and laceration of the liver is supported by the finding of a neutrophilic reaction in a study of trauma victims who survived 15 min to just over 7 h (Kohlmeier et al. 2008).

With regard to findings in the mesentery in children, the observation of fibrosis and hemosiderin implies that the injury is not acute (Byard and Heath 2010).

Intra-cranial Injuries

The earliest feature of intra-cranial injury is brain swelling, which can occur rapidly (Byard et al. 2012). Neutrophils were first observed in samples from cerebral contusions as early as 5 min after injury and macrophages at 11.5 h. Macrophages containing erythrocytes were observed at 12 h, containing lipid at 17 h, and hemosiderin at just over 4 days (Oehmichen et al. 2003). A vascular proliferative reaction can be seen around 5–7 days post-injury and an astrocytic reaction occurs by 7–10 days. It is possible that indicators of axonal injury may provide additional information with regard to the age of a head injury as β-amyloid precursor protein staining occurs early (within 30 min), microglial clusters can be found by 15 h, and myelin degeneration can be demonstrated after a month.

Histological aging of subdural hematomas is largely based on assessment of the fibroblastic reaction and it is generally agreed that histological appearances provide only limited information. A study that collated the findings from 222 cases noted that neutrophils could be seen as early as 2.5 h, but were only present in a small number of cases. Macrophages were more commonly present and could be seen as early as 12 h with erythrophagocytosis occurring at 20 h and hemosiderin at just over 3 days. Fibroblasts, collagen, and membrane formation were all first observed at 5 days; erythrocytes persisted up to 4 months (Walter et al. 2009).

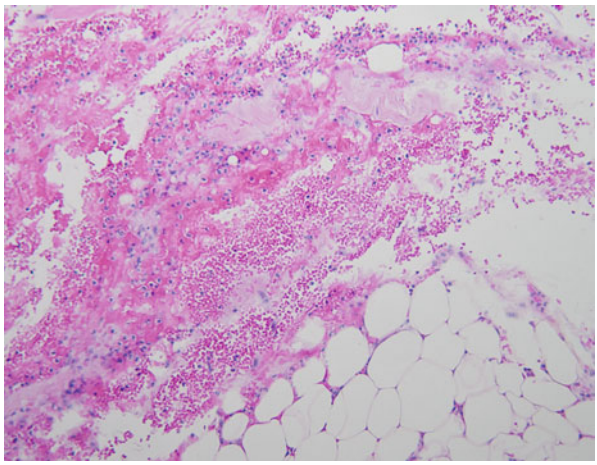

Fig. 16.3 Bruise 35 h old showing predominantly neutrophilic infiltrate. Although much of the extravasated blood has lyzed into homogeneous masses, intact erythrocytes survive. Macrophages, which would be expected at this time, are not a feature (Hematoxylin and Eosin, H&E × 10)

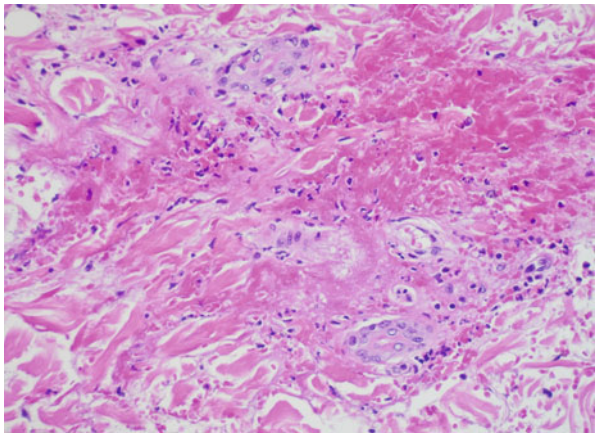

Fig. 16.4 Bruise 7 days old. Not too dissimilar to Fig. 16.3, despite being 4 days older (Hematoxylin and Eosin, H&E × 20)

General Considerations

Except where specified, the information above on the temporal changes in healing wounds has been gleaned from studies involving humans. Although animal-based research undoubtedly has a role in investigating the wound healing process (Zumwalt and Fanizza-Orphanos 1990), animal data may not be directly applicable to determining the age of wounds in humans. There are also temporal differences in the inflammatory and healing response between animal species, which may limit their use for acquiring data to use in estimating the age of wounds in humans. Of particular relevance to determining the age of bruises is the observation that hemosiderin may be identified at 24 h in the mouse.

Wound healing may not proceed over the expected time course and an inflammatory reaction may not occur even following a period of some hours between injury and death (Figs. 16.3–16.6). This is most clearly evident in

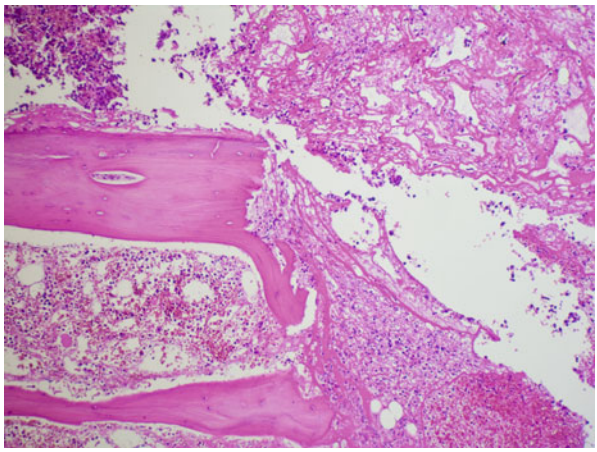

Fig. 16.5 Rib fracture 2 days old. Note the absence of a cellular reaction (Hematoxylin and Eosin, H&E × 10)

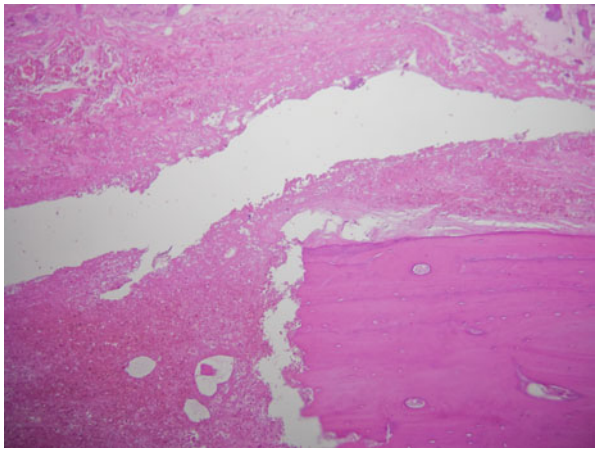

Fig. 16.6 Rib fracture 4 days old (Hematoxylin and Eosin, H&E × 10)

burns where the inflammatory response may be apparently absent at a given time point or the neutrophil response may be sustained for several days (Tarran et al. 2006). An absence of inflammatory response has been observed in postmortem samples derived from bruises of the scalp of children who were in a moribund state for a period prior to their death (Byard et al. 2008). In bruises, it may be that the inflammatory reaction is more likely to develop at the site of trauma than in areas into which blood has tracked – thus which areas were sampled may account for the observation that some of the bruises in the reported children did have the expected inflammatory reaction. Trauma and the development of a moribund state or severe illness may have an adverse effect

on the wound healing reaction (Clark et al. 2000), with a decrease in collagen deposition (measured by assay of hydroxyproline) in sponge implants in victims of trauma compared to controls. Patients undergoing major surgery showed lower collagen deposition compared to non-traumatized patients or those undergoing minor surgery. Many other factors can influence wound healing, including psychological stress, pain, nutritional status of the victim including vitamin C deficiency, cigarette smoking, diabetes mellitus, obesity, administration of drugs including corticosteroids and, in the case of fractures, administration of anticoagulants. Local factors, such as hypoxia and poor tissue perfusion, can also adversely affect wound healing. Infection can be a major impairment to healing. Locally it can result in a sustained neutrophil response, whereas systemically sepsis can result in impaired neutrophil function with reduced migration. Wound dressings can also influence healing, with wounds healing faster in a moist environment. However, topical antiseptic agents (such as iodine and chlorhexidine) can impair wound healing. The presence of foreign bodies (iatrogenic or otherwise) can modify the healing response. Local pressure can be a significant factor in impairment of healing with sustained local pressure creating ulceration. Necrotic tissue will impair or prevent wound healing, with its debridement acting as a stimulus to the healing process.

Animal experiments have suggested that healing can be faster in the young compared to the old and it is assumed that a similar situation exists in humans, which is supported by some experimental data. The author's study on the development of yellow color in bruises indicated that there was a statistically significant difference between subjects aged under 65 years and those aged 65 years and older, with the older group taking longer to develop a yellow color. However, this was not encountered in a later study of bruises in which age was not a statistically significant factor in bruise age determination. A study of healing of dental extraction sites noted that there was a noticeable difference between the under 20 years old group that healed faster than the over 50 years old group, but in a study of hydroxyproline accumulation there was no difference between subjects aged over 50 years and those younger. Overall, the effect of age on wound healing is unclear (Ashcroft et al. 1995).

It is also unclear if the site on the external surface of the body influences wound healing, with differences being reported in a rat model and a human study (Raekallio and Vijlanto 1975), but not by others in wound studies (Pajulo et al. 2000) or bruises in humans. There are definitely differences in wound healing rates between the skin and the mucosa. A range of healing times has been recorded in studies using standardized punch biopsy wounds, indicating that when wounds are standardized, biological variation between subjects exists. The sex of the subject appears to influence wound healing. Bruises were observed to resolve faster in female subjects and collagen accumulation was also greater in females. Experiments have shown that estrogen has an effect on wound healing, resulting in acceleration of the healing process; however, this may not be relevant to the prepubertal child.

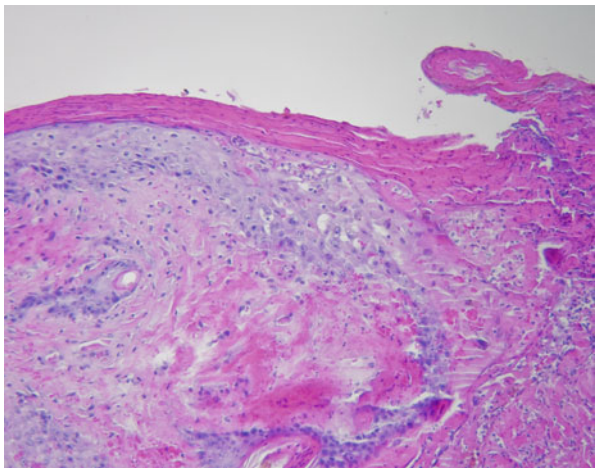

Fig. 16.7 Epithelial healing response, which can be a useful guide to indicate a wound that is at least some days old (Hematoxylin and Eosin, H&E × 20)

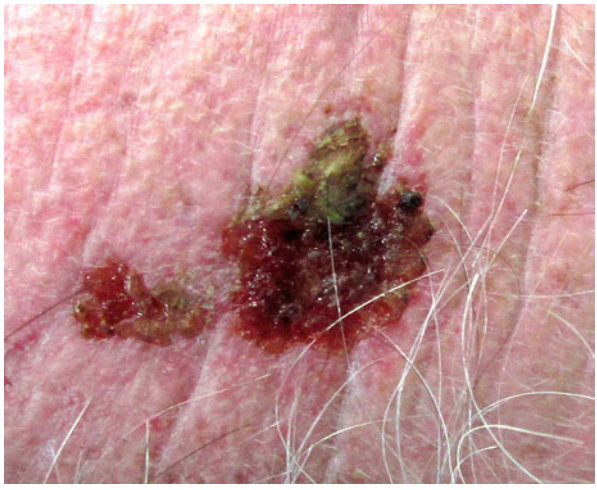

Fig. 16.8 Abrasion. This injury is 2 days old, but the macroscopic appearance would fit with an injury that is more recent

Conclusion

From the above observations of healing of human wounds, the following can be surmised. Neutrophils may be numerous from a few hours and can persist for several days. The relevance of macrophages to estimating the age of the wound is not when they are first detected, but when they outnumber neutrophils; when they are the dominant cells; a minimum wound age of 1–2 days can be suggested. Fibroblast (and epithelial cells – Fig. 16.7) proliferation would be expected at 2–3 days, with granulation tissue at 4–5 days. Stainable iron (hemosiderin) is not

found until 3 days and is probably the best indicator of an "old" wound. However, the persistence of hemosiderin is not known and its observation in apparently uninjured areas suggests that some caution should be applied in interpreting its significance. Histologically, stainable new collagen fibers may be seen by 6–7 days, but are more likely by 8–10 days. Reticulin probably appears around 10 days. However, from the discussion above, it will be apparent that there are numerous factors that can result in variation from this suggested temporal scheme. Burn wounds especially may not adhere to this plan, but in any wound, the absence of a cellular reaction can occur and the absence of a response does not imply that a wound has not yet reached the time when it would be expected. The estimation of the age of a wound by visual appearance would appear to be even more difficult (Fig. 16.8). The only suggestion that can be reliably made is that the appearance of yellow color indicates a wound (usually a bruise) is not recent.

It is the opinion of this author that wounds should be documented by photography and then sampled at postmortem examination (which is easily achieved using a punch biopsy device). On a routine basis, documentation of the histological findings is sufficient without a comment on estimated wound age, unless specifically required for the case. If asked to proffer an opinion, then the reason for the request should be ascertained. It may be simply the curiosity of the investigative agent and of no direct value to the case; such requests to estimate the age of a wound should be refused. The approach should be to ascertain the issue that would be answered by providing an estimate of the age of the wound and to inquire what time windows are in question. Thus, the age of a wound can be given as in keeping with a suggested age, not compatible with a suggested age, or of indeterminate age (Nash and Sheridan 2009). It should be apparent from the discussion and the illustrations above that injuries may not display the expected inflammatory response for a given point in time; the absence of a response should not be regarded as evidence an injury has not reached a certain age. Thus, extreme caution should be used when estimating the age of a wound.

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Fatal Pediatric Craniocerebral and Spinal Trauma

17

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Contents

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Abstract

This chapter will discuss the topic of lethal head and spinal injuries in infants and young children. Discussion will include injuries sustained through both accidental and inflicted means. Of the accidental injuries, the first category is crushing injuries of the head sustained when a heavy weight falls onto or rolls over the head. The second major category of accidental head injuries occur when children fall from short distances and on rare occasions sustain lethal epidural or subdural hemorrhages associated with increased intracranial pressure. The more common cause of death from head injury in infants and young children is inflicted neurotrauma. This category of head injury is primarily the result of inertial head injury from either impact or shaking or a combination of these mechanisms. Lastly, there will be discussion of second-impact syndrome and spinal injuries.

Introduction

Head injury is the leading cause of death and disability in children (Langlois et al. 2004). Of childhood deaths resulting from head injury, inflicted neurotrauma accounts for the greatest number. Sixty-four percent of head injuries serious enough to warrant admission to the hospital (excluding uncomplicated skull fractures) and 95 % of serious intracranial injuries are the result of inflicted trauma (Bilmire and Myers 1985). It is estimated that 2,000 children die in the United States (USA) each year from abuse and neglect (McClain et al. 1995). Head injury is the leading cause of death from inflicted trauma (Overpeck et al. 1998). Young children fall frequently, and most head injuries in young children are caused by falls, but the great majority of these fall-related head injuries are trivial, and only a few are lethal. Making the distinction between inflicted and accidental head injury is a common problem in the pediatric population and concerns pediatricians, forensic pathologists, neurosurgeons, and other medical specialties. This chapter will closely consider the features and issues necessary in distinguishing abusive head injury from accidental injury or nontraumatic conditions. Several areas in abusive head injury have caused intense discussion among the various physicians and engineers looking at cases. Particular topics of "controversy" include the debate over shaking as a mechanism of head injury in young children, rebleeding of subdural hemorrhages, and the role

that hypoxia might play in the causation of subdural bleeding. These topics will be considered in this chapter. This chapter is intended to provide sufficient detail and depth to be of use to forensic pathologists as well as other physicians, lawyers, and investigators who are concerned with head injuries in the young.

Unique Features of the Head and Neck of Young Children

To fully understand the injuries of the head and neck of young children requires knowledge of the anatomical and developmental differences that exist in the skull, brain, and neck during the early years of human life. These differences are most marked at the earliest ages but exist to some extent up into middle childhood. The infant skull is thin and pliable to enable the passage of the fetal head through the birth canal. The skull at birth is 1 mm thick and unossified. During the first 2 years, the bone increases in thickness, and the double layer of the diploe develops. The thin pliable bone offers little resistance to impact, and force may be readily transmitted through the bone. The fibrous connections between the cranial bones of the infant, the sutures, also permit ready transmission of impact force into the brain. After the sutures are joined through ossification, greater protection is gained. At birth, the brain is large in comparison to other organs of the body and the brain grows rapidly in infancy and early childhood achieving 75 % of its adult weight by age 2 years. Although immature, the young brain is very large and heavy. The cranial cavity grows to accommodate the growing brain, and the head of a young child is a proportionally much greater part of the total body weight (as much as 20 % in infancy and 10 % in early childhood) compared to the adult head which is about 2–3 % of the total body weight (Williams 1995). The brain of an infant and young child is softer in its consistency than it will be later in life due to a very high water content, immaturity of the glial cells which serve as a supporting framework, immaturity of the myelination of the axons, and the small size of the axons. The small size of the axons covered by a thin layer of myelin renders the axons more easily damaged by inertial forces (Gennarelli et al. 1993; Maxwell et al. 1993). The large brain of the young child has a relatively greater surface area which is covered by a large area of subarachnoid space, but the depth of the subarachnoid space is thin, so offering little buttressing protection against impact (Gean 1994). The neck muscles of the infant and young child are very weak and offer little resistance to movement of the head, thus facilitating acceleration of the head on either impact or impulse. Neck strength is a great protector against impulsive movement of the head and thus is helpful in preventing inertial brain injury but is a factor lacking altogether in the very young (Cantu 2000).

Mechanisms of Traumatic Brain Injury

Traumatic brain injury can be classified into static and dynamic injuries depending upon the rate at which force is loaded onto the head. Static injuries occur over

longer periods of time, usually greater than 200 ms, and result in crushing head injuries. Crushing head injury refers to actual crushing of the facial skeleton and skull by a heavy weight, and while relatively rare in the overall number of head injuries, it is an injury seen in accidental childhood head injuries and will be discussed later in this chapter. By far the greater number of head injuries results from dynamic forces which occur when force is rapidly loaded onto the head usually in less than 200 ms and imparts an impulsive motion to the head either as a result of impact to the head which is free to move or as a result of an action to the body which causes the head to move such as the collision of two athletes or violent shaking of an infant. Impulsive loading may create inertial movement of the brain within the cranial cavity which means there is differential movement between the brain (with its attached arachnoid) and the skull (with the attached dura). This inertial movement of the brain within the cranial cavity is the cause of bridging vein failure resulting in subdural and subarachnoid hemorrhage and traumatic diffuse axonal injury. Inertial brain movement is greatest at the periphery of the brain and with greater force extends deeper into the cerebrum and brainstem to damage axons in those regions.

Brain injuries may also be classified as either focal or diffuse injuries. Focal injuries result from direct contact injury to the head and are visible to the naked eye. Focal injuries include scalp contusion and laceration, skull fracture, epidural hemorrhage, focal subdural hemorrhage, and brain contusions. Focal injuries become clinically symptomatic by increasing intracranial pressure which takes place over time and may have a fatal outcome from herniation. These injuries typically have a lucid interval. Diffuse injuries result from inertial forces and include interhemispheric subdural hemorrhage and traumatic diffuse axonal injury. Diffuse injuries may not be visible to the naked eye, and these injuries may become clinically evident by the onset of immediate traumatic unconsciousness and tend not to have a lucid interval (Graham et al. 2000; Margulies and Thibault 1989; Ommaya 1985; Staklhammer 1986).

Accidental Traumatic Head Injury in Children

A study undertaken to demonstrate the differences between accidental and inflicted lethal injuries in young children in a population area of two million from 1975 to 1985 found 160 cases (Case 2008). These cases excluded children who died from gunshot wounds, drowning out of the home, fires, sleeping-related deaths, and vehicular collisions. In this group of 160 deaths, there were 63 (39 %) who died from accidents, 70 (43 %) from homicides, and 27 (16 %) in undetermined manner. Of the 63 accidental deaths, 39 % were under 1 year old, 28 % were 1–2 years old, 8 % were 2–3 years old, and 22 % were 3 years old or older. Of these 63 accidental deaths, 37 (58 %) were asphyxia deaths, 10 (16 %) were head injuries, 7 (11 %) were intoxications, 3 (4 %) were in-home drownings, 2 were burns, 3 were electrocutions, and 1 was from lightning. Of the 10 head injuries, four children were struck by an object (one each by a metal spear, tornado damage, rotary mower,

and heavy pole) and six children fell (3 from the second story, 1 from the ninth story, 1 down 13 basement stairs in a baby walker, and 1 down 10 basement stairs holding onto a toy pushcart). The head injuries sustained by these 10 children included two children with fractures with acute subdural hemorrhages (SDHs), two children with penetrating wounds of the head, and six children (70 %) with massive crushing or penetrating head injuries. This study demonstrated that most accidental deaths in young children in the home (after excluding gunshot wounds, fires, and sleep-related deaths) are asphyxial deaths. The head injuries sustained in the accidental cases were readily recognizable as being due to accidental circumstances. However, injuries which occur in the home may present difficulties in distinguishing between accidental and inflicted mechanisms. Often in these cases, the only witness is the individual caring for the child. Most AHT cases occur in the home rather than in public places which seems in itself a significant feature. So it is helpful to consider the types of accidental head injuries that may occur in the home and to appreciate which of these can be lethal.

Pathology of Accidental Traumatic Head Injury in Children

Crushing Head Injury

Crushing head injuries are static injuries in which a heavy weight crushes the head resulting in fractures of the facial skeleton, skull fractures, and fracture contusions and lacerations of the brain adjacent to the fractures (Russell and Schiller 1949). In the above study, of the 10 accidental head injuries, 70 % were from crushing or penetrating head injury (Case 2008). Crushing and penetrating injuries are similar as both mechanisms occur together when the fractured bones are driven into the brain. The lacerations and contusions should be properly identified as fracture related and not coup or contrecoup contusions. Although these crushing/penetrating injuries appear very severe and obviously many of these injuries are fatal, some are not. These injuries are a collection of multiple focal injuries, and the outcome depends upon how much brain swelling is created or whether the central portion of the brain is totally crushed or penetrated. If the damage crushes into the center of the brain or the brainstem, death is usually immediate. Surprisingly some children with crushing head injuries and even extensive damage have good outcomes (Duhaime et al. 1995; Prasad 1999).

Short Falls

Falls are common experiences for most children, and the great majority of falls result in no significant head injury. A fall, however, is not uncommonly provided as an explanation for a head injury in a child where the head injury was actually an inflicted injury. There is a need to distinguish between these two possible causes of head injuries in young children, and this distinction presents a common problem for

any number of physicians. To assist in understanding what does happen when children fall has led to the accumulation of a literature of cases involving short falls in young children (Chadwick and Salerno 1993; Kravitz et al. 1969; Helfer et al. 1977; Hymel et al. 1998; Lyons and Oates 1993; Nimitiyongskul and Anderson 1987; Williams 1991). In analyzing these papers on short falls, it appears that falls from distances of less than 4–6 ft around the home are associated with primarily contact injuries such as a scalp laceration or contusion, although the great majority of such falls result in no head injury at all. Of those that do have head injury, in 1–3 % of these short falls, there may be a skull fracture, and these fractures tend to be simple linear fractures without any intracranial injury. In a very small proportion of these fractures, less than 1 % of the fractures, an associated epidural hemorrhage will occur and in an even smaller number a focal subdural hemorrhage (Denton and Miluesnic 2003). If the resulting epidural hemorrhage (EDH) enlarges to become a mass lesion or if as in Denton's reported case hemorrhage creates significant associated brain swelling, the resulting increased intracranial pressure may lead to death from such an injury in a short fall. These are very rare occurrences but need to be recognized when they do occur. In a biomechanical study using a test dummy to study bed-related falls in young children, Bertocci et al. found that rolling from a 27 in. high bed onto the floor presented a low risk of contact-type head injury (Bertocci et al. 2003). In a short fall of the type seen in childhood falls, the period over which energy is delivered to the head is so short that there is little deformation of the brain substance distant to the point of impact so that no diffuse brain injury results from these falls (Maxwell et al. 1997; Meythaler et al. 2001). In a short fall, in a small number of cases, there may be a contact injury consisting of a skull fracture or fracture contusion of the brain, but there is no potential for diffuse axonal injury (DAI). A divergent view on this topic is presented by Ommaya et al. who propose that contact injury to the head of a young child may distribute injury widely into the brain (Ommaya et al. 2003). This view is not supported, however, by the literature noted above on the large number of short falls in young children which finds that while contact injury may result, there is no loss of consciousness or neurological deficit which would be indicative of diffuse brain injury in the very great majority of cases.

Falls from Great Heights

Falls from great heights are a major cause of accidental injury and death in children of all ages. Interestingly, many falls from even a considerable height are survived by children. In a study by Musemeche et al. of children from 10 months to 15 years old admitted to the hospital for falls from heights greater than 10 ft and up to 17 stories, all survived their injuries (Musemeche et al. 1991). Of this group of children, 50 % were under 3 years old, and most of their falls were from one to three stories. Fifty-four percent of these children had head injuries which were skull fractures and intracranial hemorrhages. Barlow et al.'s study of 61 children under 16 years of age who fell from heights found that all the children who fell from less

than three stories survived and for those who fell from the fifth to the sixth story, there was a 50 % mortality (Barlow et al. 1983). Of the children who died from these falls, 78 % died from head injury. The head injuries sustained in falling from a great height consist of skull fractures and fractures of the facial skeleton with fracture contusions and lacerations of the brain. These head injuries resemble the types of injuries sustained in crushing head trauma.

Skull Fracture

As noted previously, the skull of a young infant is thin and pliable. At birth, the thickness of the cranial bone is about 1 mm and during early childhood will increase to about 3–4 mm and reach 10 mm when mature. The skull acts to protect the underlying brain from impact force. The sutures, once they are ossified, also protect against impact loading and act as shock absorbers and actually distribute force away from the point of impact (Margulies and Thibault 2000). The cranial bones' strength and properties are not well studied. However, when impact forces exceed the strength of the bone, fracture results.

In Hobb's classic paper on skull fracture and the diagnosis of abuse, of 89 children under age 2 years with skull fractures, 29 were abusive and 60 were accidental injuries (Hobbs 1984). Of the 20 deaths in this study, 19 were in the abusive injury group. The characteristics noted by Hobbs to be more common in the abuse group were multiple or complex fractures, depressed fractures, maximum width of fracture greater than 3 mm, growing fracture, involvement of more than one cranial bone, non parietal fracture, and associated intracranial injury. In the author's collection of abusive head injury cases, 40 % of the cases have skull fractures, and all were associated with intracranial injury (Fig. 17.1a–c). In studies from the literature noted previously in the discussion on short falls, the incidence of skull fractures in such falls is only 1–3 %, these are generally simple linear fractures, and there is very rarely any associated intracranial injury.

The three Weber papers are puzzling in their findings about fractures in infants when compared to information from other studies. Weber's studies were carried out on infant cadavers, and the physical nature of the bone may differ from living bone which may explain these differences (Weber 1984, 1985, 1987). Of the infants studied, 15 were dropped from a horizontal position from a height of 82 cm and all sustained fractures. Weber concluded that low-level falls in infants may result in fractures which are asymptomatic and thus remain unknown to the caretakers.

Epidural Hemorrhage

Epidural hemorrhage (EDH) is hemorrhage that lies on the inner table of the skull between the skull and the dura, is associated with skull fracture in 85 % of cases, and frequently results from tearing of branches of the middle meningeal artery

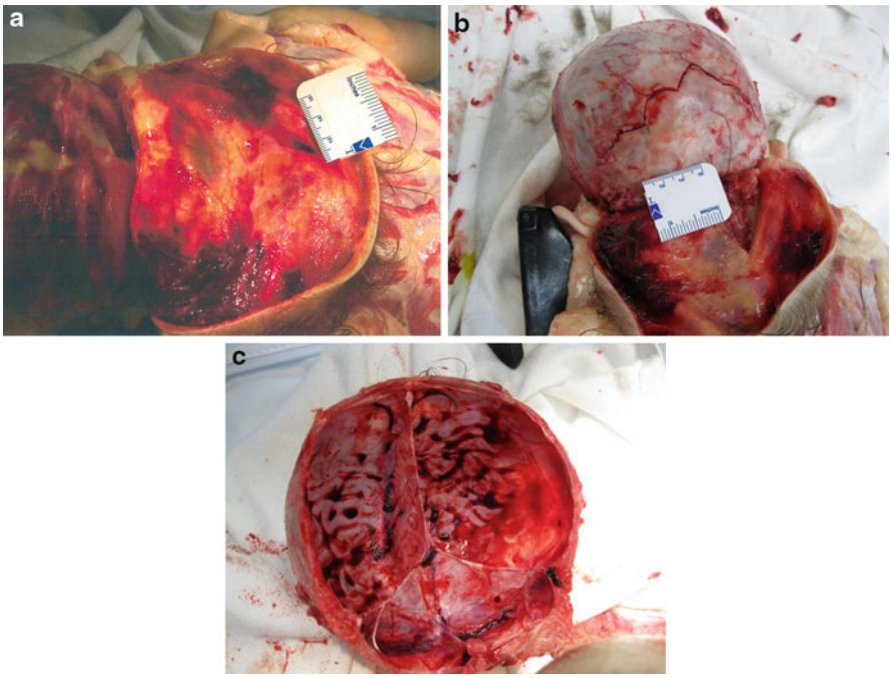

Fig. 17.1 A 10-month-old female infant whose head was slammed against a wooden sofa arm. (**a**) Extensive subgaleal hemorrhages of occipital scalp. (**b**) Fracture across occipital bone. (**c**) Small amounts of SDH over cerebral convexities

which lie in grooves on the inner table of the cranial bones (Rivas et al. 1988). The grooves on the inner table of the cranial bones are not present at birth but develop after the formation of the diploe and are generally present by age 4 years (Freytag 1963). In some cases of EDH, the bleeding results from trauma to a dural sinus or diploic vein rather than the meningeal arteries, and these venous sources may bleed slower than the arterial sources of bleeding.

Traumatic EDH is always associated with impact to the head and can be classified as a focal contact injury. In young children, EDH can occur without skull fracture when the impact force deforms the skull but does not fracture the bone, but the deformation causes the dura to be stripped off the inner table of the bone. EDHs are not common in young children particularly under the age of 2 years because the dura is very firmly adherent to the inner table (Jamieson and Yellan 1968). EDH occurs in 3 % of all head injuries, and the highest incidence occurs between 10 and 30 years old (Baykaner et al. 1988).

EDHs in children are primarily associated with falls, including short falls, but may occur from inflicted trauma if the head is struck by a blow while the head is stationary and not free to move (Fig. 17.2a, b). Epidural hemorrhages occur most commonly over the cerebral convexities, typically in the temporal or parietal

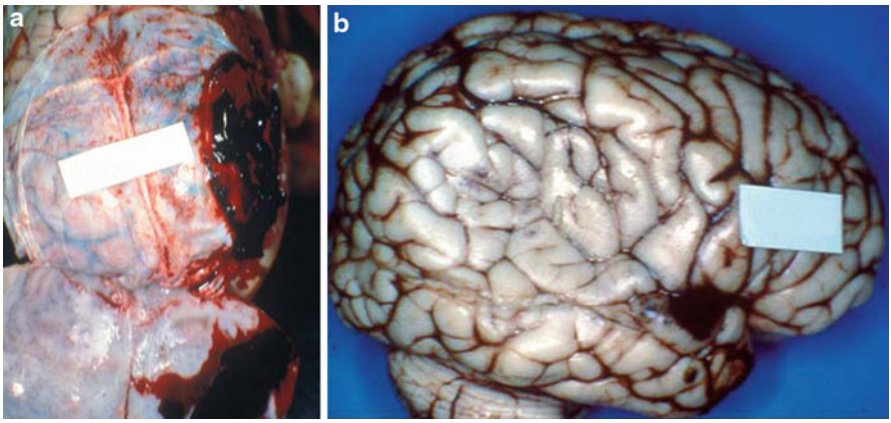

Fig. 17.2 A 4-month-old infant whose head was held on a coffee table while the mother struck the stationary head with a wooden brush. Autopsy demonstrated a fracture of the right temporal bone with a 70 ml EDH over the right temporoparietal convexity as seen in (**a**). The brain demonstrated marked flattening of the of the right temporoparietal region with fracture contusions of the superior and middle temporal gyri as seen in (**b**)

regions, but may occur elsewhere as well as on the basilar surface of the skull. Because the dura is firmly attached at the sagittal suture, EDH usually does not extend across the midline. EDH has a classic appearance of a lens-shaped mass which presses upon the underlying brain and causes a very flattened-out cortical surface. That appearance can be seen on either computed tomography (CT) scan or at autopsy on the gross brain. The gyral surface beneath an EDH will also usually have fracture contusions from the associated skull fracture. The amount of epidural blood necessary to create a mass lesion in an adult is about 100 ml, but less is required in a child (Rivas et al. 1988).

The dura is the periosteum of the skull and in young children is a very reactive structure with a layer of osteoblasts and fibroblasts. Microscopically, the osteoblasts contain brown-yellow pigmented material that may resemble hemosiderin. The epidural layer itself may be misinterpreted as an organizing subdural membrane, even though it is on the epidural side of the dura, by those pathologists unfamiliar with the normal histology. The younger the infant, the more reactive the epidural surface appears. Familiarity gained through studying the microscopic appearance of the normal dura in infants and young children is recommended for all forensic pathologists to avoid mistakenly identifying these normal findings as pathological.

The clinical significance of an EDH depends upon whether it is associated with other head injury and upon the size and rate of development of the hemorrhage. If the EDH is the only head injury, the prognosis is quite good if the hemorrhage is small and not causing increased intracranial pressure. If, however, the EDH is large

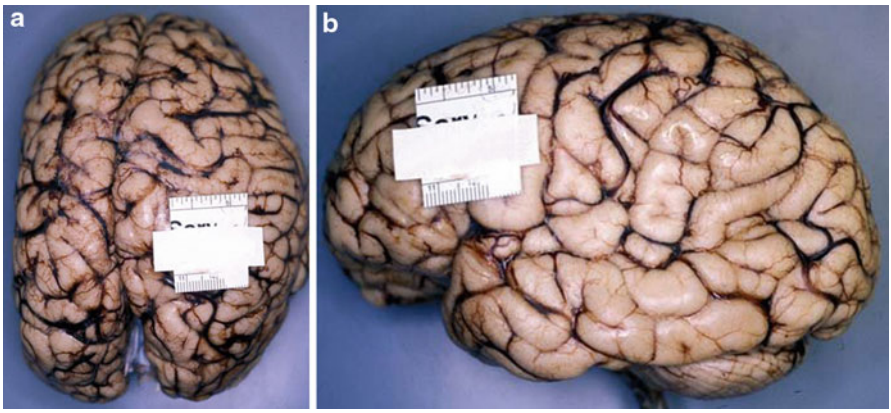

Fig. 17.3 A 2-year-old male who fell out of bed from a height of 21 in., cried, went to sleep, vomited after 1½ h, cleaned up and went back to sleep, and found dead 5 h later. Autopsy demonstrated fracture of the left temporal bone with 100 ml EDH over the left temporoparietal convexity causing marked flattening of left lateral cerebral convexity as shown in (**a**) and (**b**)

enough to create a mass lesion and is not surgically evacuated, then the hemorrhage may be lethal (Fig. 17.3a, b). Not all epidural bleeding progresses, and in many cases it is self-limited and will subsequently resorb.

Subdural Hemorrhage

Subdural hemorrhage (SDH) does not require impact to the head and may result from pure inertial forces which cause diffuse SDH typically arising from the interhemispheric sulcus and spreading out over the cerebral convexities. This type of SDH is more common in inflicted neurotrauma and will be discussed in that section. Rarely, focal SDH may occur, and these are the result of impact and skull fracture (Denton and Miluesnic 2003). Focal SDH appears as a thin accumulation of blood immediately adjacent to a fracture. In older children, the common causes of subdural bleeding are vehicular accidents, falls from heights, and sporting events, but these events are not common activities in infants and young children.

There is a rare situation which the author has seen on two occasions in which diffuse SDH has been found in cases where rocking chairs were alleged to be the source of injury. These cases involved toddler-age children standing on the seat of a rocking chair facing backward and rocking the chair and then losing their grip and catapulting off the chair. In these two cases, there were thin layers of subdural blood over the cerebral convexities, and the eyes had a few retinal hemorrhages (RHs). These cases were considered as an undetermined manner, as the only individual who witnessed the event was the caretaker and the veracity could not be ascertained. The rocking mechanism, however, may well be a legitimate source of inertial brain injury, but because these incidents are rare, little information has

been gathered on them. So it is best to consider that such an incident might well be accidental in manner, but these cases need thorough investigation. Sauvageau et al. reported a similar mechanism involving a playground rocking toy which was described as a motorcycle-shaped structure mounted on a large spring (Sauvageau et al. 2008). A 2-year-old boy was in the care of a 12-year-old who was accompanied by his 3-year-old and 6-year-old brothers. The 2-year-old child was seated on the rocking toy while the 6-year-old was shaking the structure from behind and the 12-year-old was holding onto the handlebars and pushing the toy backward. After 4–5 min of intense violent rocking, the 2-year-old lost his grip and his head hit the handlebar. He cried and a bruise appeared on his forehead, but he returned to play. He went home after a short time and initially appeared fine and about 1 1/2 h later was put to bed. During the night, he appeared to be breathing irregularly and he was taken to the hospital where an SDH was evacuated, but he died during the surgery. At autopsy, he had a 10 × 9 cm bruise to the forehead, evidence of the evacuated SDH on the left and residual right SDH, bilateral subarachnoid hemorrhage (SAH), diffuse cerebral swelling, and multiple bilateral RHs extending out to the ora serrata. Investigation of this death showed that the stories of all three children were consistent and that the details of the incident were truthful.

Brain Contusions

The brain of the young child is softer but stiffer than later in life and tends not to contuse with the same frequency or in the same manner as at later ages. Impact to the young brain is more likely to actually tear the brain. Lesions of the brain called contusion tears will be discussed in the section under "Inflicted Traumatic Head Injury in Children". Contusions do occur in young children adjacent to fractures, and these should be labeled as fracture contusions. Contrecoup contusions do not occur in children under age 4 years. If a coup contusion occurs in a young child, it tends to appear as a blush on the cortical surface. On a cross section through such a contusion, there is a sparse amount of hemorrhage within the cortical lamina with overlying sparse subarachnoid hemorrhage (SAH). Contrecoup contusions result from a moving head accelerated by the body falling from a standing position so that the body torques (Dawson et al. 1980). Young children do not fall in a manner similar to a rigid body which is the type of fall required to sustain contrecoup contusions. Young children are already close to the ground, and in falling from a standing position, the head is not accelerated.

Inflicted Traumatic Head Injury in Children

As noted in the introduction to this chapter, inflicted or abusive head trauma (AHT) is a very common injury and a common cause of death in young children. Of children who sustain abusive injuries, the younger the child, the more likely the injury is to be AHT (Christian et al. 1999). The majority of children who sustain AHT are under the age of 2 years and most are infants, but AHT with identical pathological findings can be seen in children 4 or 5 years of age and even rarely

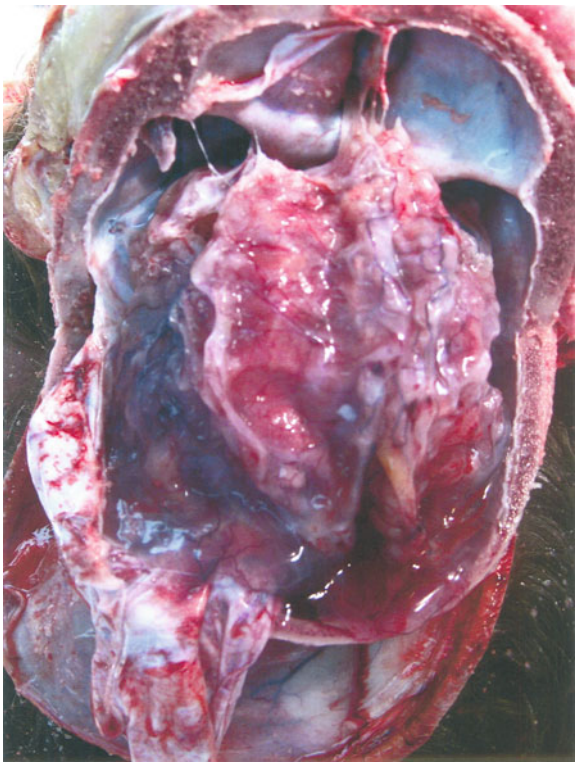

Fig. 17.4 A 13-year-old female who sustained AHT at age 4 months and survived in severely neurologically devastated condition. At autopsy, when the calvarium is removed the 400 g brain is markedly atrophic and appears like a "walnut" with multicystic encephalopathy

older (Duhaime et al. 1998). Of children with AHT, about 30 % die; 30–50 % survive with significant neurological deficits including mental retardation, seizures, blindness, irritability, and learning disorders; and perhaps 30 % recover without deficit (Barlow et al. 2004; Bonnier et al. 1995; Rosenthal et al. 1990) (Fig. 17.4).

Shaking as a Mechanism of Injury in Abusive Head Trauma (AHT)

The mechanisms of traumatic brain injury were discussed earlier in this chapter as were the unique features of the anatomy and development of the young child's head which may modify the thresholds of injury in the very young. Guthkelch, a British neurosurgeon, hypothesized in 1971 that SDH in infants might be created by whiplash forces which tear the bridging veins (Guthkelch 1971). In this paper, Guthkelch suggested that the injuries to infants with SDH might be caused by acceleration–deceleration forces rather than direct impact. Guthkelch made this suggestion based upon his knowledge of research carried out by Ommaya in the 1960s on primates using rotational movement of the head on the neck to produce concussion and SDH (Ommaya et al. 1968). In 1972, Caffey described infants with SDH and/or SAH, RHs, and little or no external marks of trauma to the head as

"whiplash shaken baby syndrome" (Caffey 1972). Since that time, the concept of shaking as a mechanism of injury to young children has been discussed, and the term "shaken baby syndrome" or SBS has been widely used within the medical, legal, and lay populations. In 1987, Duhaime et al. studied a group of 48 children with SDH or SAH, RHs, and a history suggestive of abuse (Duhaime et al. 1987). In this study, all the children who died had evidence of impact, and 63 % of the living children had evidence of impact. A subsequent experimental study used a doll model that could be shaken or impacted. The findings indicated that shaking alone did not reach the thresholds of rotational acceleration to cause significant injury, while impact did generate forces above the thresholds for concussion, SDH, and axonal injury. In the years since the Duhaime study, the question of shaking as a possible mechanism for injury to the heads of young children has been debated and indeed is sometimes noted as a controversial area. The corollary question that arises if shaking is suspected is whether AHT which lacks marks of trauma can be recognized as trauma (Geddes and Plunkett 2004; Donohoe 2003).

In considering the question of shaking as a mechanism of injury in AHT, one must acknowledge that in studying AHT actual experimentation is not possible and that the thresholds established for concussion, SDH, and axonal injury are derived from animal studies, and those thresholds may not be accurate when applied to the human infant. To understand how these thresholds were derived requires knowledge of the original studies on head injury dating back to Holbourn. Holbourn's studies were carried out in the 1940s, and on the basis of his studies, he hypothesized that smaller brains would require greater force than larger brains to produce similar injury and that the critical factor for brain injury is angular acceleration (Holbourn 1943). Holbourn's hypothesis was confirmed by Ommaya's research on nonhuman primates, and he found that the relationship between force and brain mass was the inverse 2/3 power of the brain mass. This principle is the so-called scaling relationship which is used successfully to compare patterns of head injury among animal species (Ommaya and Hirsch 1971). In animals, the scaling relationship works well, and generally it can be stated that the smaller the brain, the greater the angular acceleration it takes to injure the brain. In the animal world, angular acceleration is not a common mechanism of head injury until the primates are reached. In lower animal species, most head injury is crushing or penetrating head injury. Nonetheless, when it comes to humans, the brain of the human infant and young child has a very long developmental and maturational period, much longer by far than any other species. Earlier in this chapter, the unique features of this development and maturation were noted in detail. Using the scaling relationship would imply that the infant brain requires greater angular acceleration forces to injure than what would be required to injure the adult brain, and that seems intuitively unlikely considering those unique features. The Duhaime study of 1987 utilized the scaling relationship to calculate the thresholds for concussion, SDH, and DAI that were used in that study. More recent studies on pediatric brain and skull properties have provided evidence that the traditional scaling approach based simply on brain mass does not explain the vulnerability of the infant brain to inertial

forces and that the scaling relationship is not appropriate to calculate thresholds in infants. Recent studies have found that rotational head injuries in infant and toddler-age piglets, which model well the infant and toddler-age human child, have lower thresholds of injury than adult animals (Ibrahim et al. 2010; Raghupathi et al. 2002). There is also clinical evidence that age significantly affects the response of the brain to trauma. Younger children who sustain brain injury will have more severe cognitive and motor function deficits than will older children (Agran et al. 2003). When young children suffer closed-head trauma, the result is often diffuse brain atrophy, a pattern seldom seen in older children after head injury (Duhaime and Raghupathi 1999).

Forensic pathologists differ somewhat in their approaches to diagnosing the entity of SBS. A recent study from the New York City Medical Examiner's Office took a more direct viewpoint in support of making the diagnosis of SBS than is typical in the field of medical examiners (Gill et al. 2009). In their study of head injury deaths in children under age 2 years over an 8-year period, of 46 homicides, 10 had no marks externally on the scalp or on the undersurface of the scalp. These deaths were certified in their autopsy reports and death certificates as "whiplash shaking." In four of these cases, there was a confession of shaking. The authors noted that they felt no hesitation to diagnose a nonimpact shaking mechanism as the cause of death based on autopsy and circumstances.

An autopsy study was carried out by Gilliland and Folberg on a group of 80 children of whom they defined evidence of shaking as two of the following: (1) fingermarks and/or rib fractures, (2) SDH and/or SAH, and (3) a history of vigorous shaking. From these 80 cases, three groups were distinguished: (1) shaking, (2) combined shaking and impact injuries, and (3) impact injuries. The authors found that 11 % of their cases were shaking injuries, and they concluded that shaking was a valid mechanism of injury (Gilliland and Folberg 1996).

Some forensic pathologists note that they have never had a case of AHT without evidence of impact. In the author's autopsy collection of cases of AHT, about 25 % are probable shaken cases with no evidence of impact. For those forensic pathologists who have never had a case without evidence of impact, the difference may be in the confidence with which these pathologists make the diagnosis of AHT (Molina et al. 2011). The most difficult cases to diagnose as AHT are obviously cases with no marks of impact to the head, a thin layer of subdural blood over the cerebral convexities, and no other injuries (Fig. 17.5a, b). Minns notes that approximately 33 % of cases of AHT in the literature of reported cases are thought to be due to shaking (Minns 2005).

There have been reports of two cases of shaken adult syndrome in the literature. A 30-year-old prisoner was shaken as a form of torture by a much larger prison guard (Pounder 1997). There were multiple episodes of shaking carried out over 3 days. After the final episode, the prisoner became unconscious and died. At autopsy, there was bruising over the chest and shoulders corresponding to the described manner in which he was gripped by the guard and SDH, RHs, and DAI. A similar case in an adult was described by Carrigan in a 34-year-old female

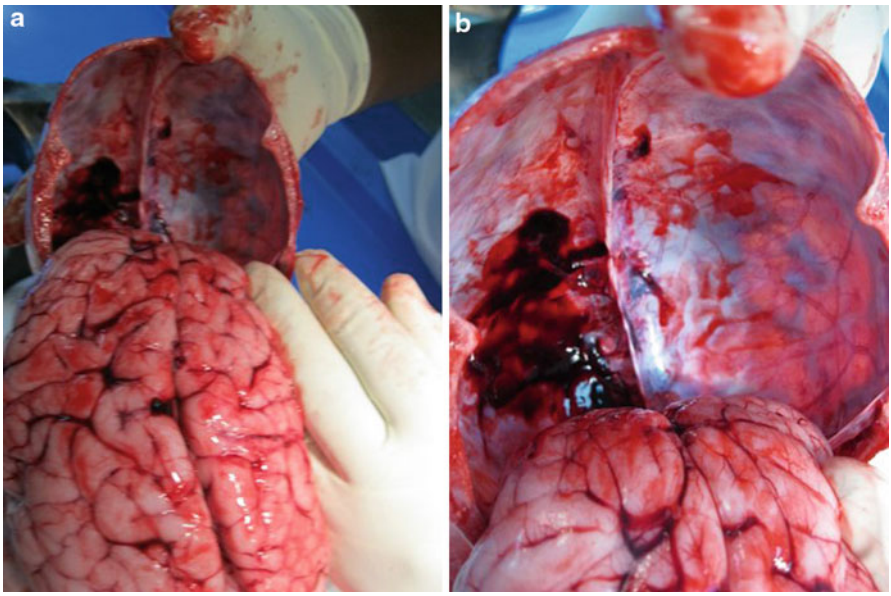

Fig. 17.5 A 4-month-old female infant in the care of mother's cousin who was found dead sitting in a pumpkin seat. Autopsy demonstrated no marks of impacts, thin layer of SDH on right cerebral convexity as seen in (**a**) and (**b**), eyes negative for retinal hemorrhages, and recent 6–10-day-old fractures of left ribs 4, 5, and 6. Confession of shaking was made

who was shaken during an episode of domestic violence (Carrigan et al. 2000). At autopsy, this woman had bruising, SDH, and RHs. In both of the cases of shaken adults, each of the victims was smaller than the assailant but not otherwise unusual. The size difference between the victim and assailant is obviously of some import because the act of shaking requires physical control of the victim by the assailant.

Pathology of Inflicted Traumatic Head Injury in Children

Subdural Hemorrhage

Subdural hemorrhage is the most common pathological finding in AHT and is seen in 90–95 % of fatal cases and in 40–55 % of living patients where it is imaged by either CT or MRI, the latter being the more sensitive (Case et al. 2001; Duhaime et al. 1987; Gilles 1998; Hymel et al. 1997). The SDH in AHT is typical of SDH seen in diffuse brain injuries which results in an interhemispheric SDH that arises posterior in the interhemispheric sulcus and then spreads in a thin film of blood over the cerebral convexities (Gennarelli et al. 1982) (Fig. 17.6). The subdural bleeding may be greater on one side than on the other. While the subdural bleeding are often

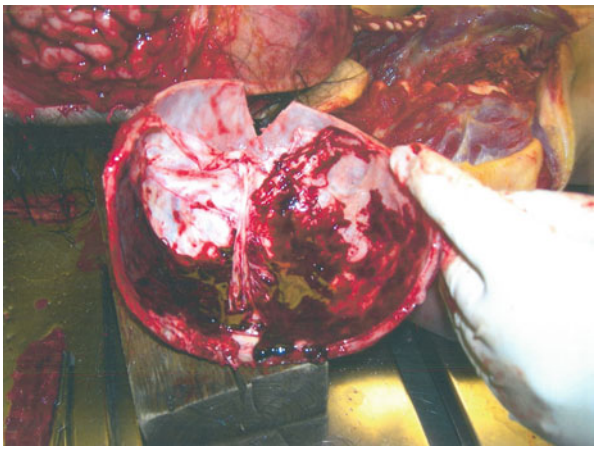

Fig. 17.6 A 5-month-old infant with AHT with SDH over cerebral convexities

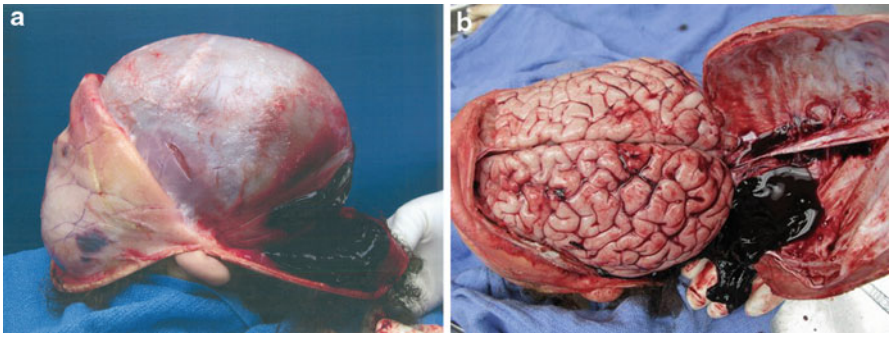

Fig. 17.7 A 12-month-old female infant with massive subgaleal hemorrhage over occipital scalp as shown in (**a**), fracture of occipital bone, SDH greatest over left cerebral convexity as shown in (**b**)

a thin film, sometimes there is a larger collection (Fig. 17.7a, b). The mechanism of SDH related to AHT is the inertial brain motion which creates a differential movement between the brain with the attached arachnoid and the skull with its attached dura. This differential motion between the brain/arachnoid and the skull/dura places tension and stretch on the bridging veins that ascend from the surface of the cerebrum and pass to the dural sinuses. Tearing of the bridging veins causes bleeding into the subdural space and in fact opens this potential space as blood flows into it (Gennarelli 1994; Yamshima and Friede 1984). Wells et al. looked at the types of SDH in 293 children under 3 years old (Wells et al. 2002). The most common distribution of SDH was in the interhemispheric location in 143 children (49 %). Of these interhemispheric SDHs, 73 % were caused by AHT, and of the 15 % caused by accidental head trauma, all were relatively high-force incidents – three falls from heights greater than 2 m, 12 motor vehicle accidents,

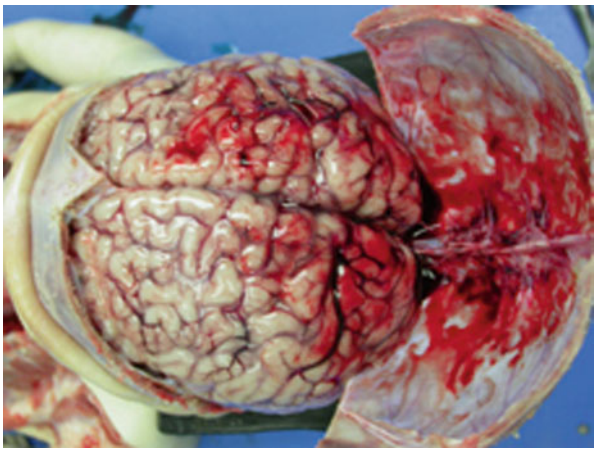

Fig. 17.8 A 3-month-old infant with AHT with small amounts of SDH over cerebral convexities

four falls in infant walkers, and two blows to the head. This study found SDH over the cerebral convexities almost as common as in the interhemispheric region, 47 %, and AHT accounted for 72 % of the convexity SDHs. Of the 10 % convexity SDHs caused by accidental trauma, most were from severe accidental mechanisms – motor vehicle accidents, falls from greater than 2 m, or infant walker falls.

Subdural hemorrhage in AHT in association with skull fracture does not necessarily occur immediately adjacent to the fracture. The amount of the subdural blood in cases of AHT may be very scant and sometimes is less than 5–10 ml of blood (Fig. 17.8). Such a small amount of subdural blood may not be visible on CT scan so that in children with these very small SDHs, the CT may fail to image subdural blood, and it is these latter cases that probably account for the difference in the incidence of SDH between living (40–55 %) and deceased victims (90–95 %) of AHT. Even very small amounts of subdural blood are visible at autopsy. It is imperative that at the time of autopsy, the pathologist and not the assistant be the one to remove the skull cap and make the observation of any blood within the cranial cavity before the calvarium is fully removed and the sinuses breached which may result in artifactual blood within the subdural regions. Subdural blood in the interhemispheric region can be viewed on CT scan but is not readily visible at autopsy (Dias et al. 1998; Kleinman 1990). Magnetic resonance imaging (MRI) is better at demonstrating small amounts of subdural blood than CT (Gean 1994). Subdural blood in AHT is also commonly found within one of more of the cranial fossae which is visible after the brain is removed (Fig. 17.9a, b). Subdural blood is also frequently found within the spinal subdural spaces. This subdural blood descends from the intracranial compartments due to gravity. Rorke-Adams points out that blood in the supratentorial subdural regions does not descend into the spinal subdural space, but subdural blood in the posterior fossa can descend into the spinal zone (Rorke-Adams 2011).

Subdural hemorrhage occurs in association with AHT, accidental head trauma, medical or surgical manipulations, pre- and perinatal conditions, birth trauma,

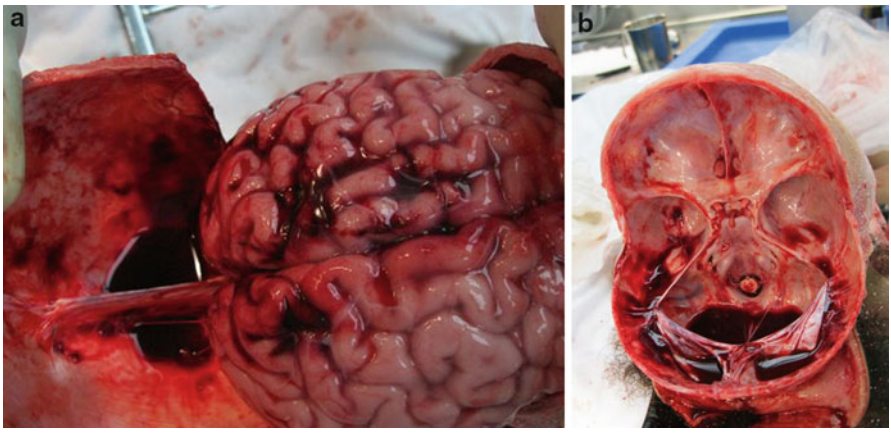

Fig. 17.9 Infant with AHT with SDH and SAH over cerebral convexities as shown in (**a**) and SDH over middle and posterior fossae as shown in (**b**)

metabolic disorders, clotting disorders, tumors, autoimmune disorders, infectious diseases, long-term shunting of hydrocephalus, and miscellaneous other conditions. These conditions and disorders need to be distinguished from AHT. It is imperative to consider other sources of hemorrhage and to examine all aspects of the history, physical examination, radiological imaging, and laboratory studies to exclude other causes. The distribution of subdural blood is a feature that is helpful in the differentiation of AHT from other conditions. Subdural bleeding on the ventral surface of the brain without subdural blood over the cerebral convexities or subdural blood in a very focal area should alert the pathologist that the cause of such blood is not inertial brain injury related to bridging-vein tearing (Prahlow et al. 1998; Weisgold et al. 1995).

Subdural hemorrhage refers to blood in the subdural space and implies that an actual anatomical subdural space is present within the cranial cavity. In the last 30 years, anatomical knowledge about the true "subdural" region has changed this viewpoint. It is currently acknowledged that a true subdural space does not exist (Haines 1991; Haines et al. 1993). The dura is composed of fibroblasts and large amounts of extracellular collagen with an innermost layer, the dural border cell layer, which is continuous with the arachnoid outer barrier cell layer. The dural border cell layer is the weakest portion and with trauma may dissect open to create a "space" between the inner dural border cell layer and the outer arachnoid border cell layer. Blood which enters this opened space is then "subdural" in the older understanding of the term but is actually "intradural" in true anatomical relationships. The trauma that opens this space is inertial motion of the brain/arachnoid component in relationship to the dura/skull component. This chapter continues to refer to "subdural hemorrhage" simply for ease in understanding and relating to the literature that speaks of such a type of bleeding.

Chronic Subdural Hemorrhage and the Question of Rebleeding

Just as the anatomy of the subdural space was an area of misunderstanding in the past, the concept of the chronic SDH is also a concept that has misconception surrounding it. In the older literature, chronic subdural hematoma was thought to be a lesion that evolved from acute subdural blood over time. In fact, most acute subdural blood resolves into a liquefied clot in 4–6 weeks and will be absorbed (Cuatico et al. 1991). Very few cases of acute subdural blood evolve into chronic subdural membranes (Dolinska et al. 1979; Lee et al. 1996; Parent 1992; Duhaime et al. 1996). Chronic subdural hematoma cannot be produced experimentally from acute subdural blood (Goodell and Measley 1963). The lesion of the posttraumatic chronic subdural hematoma is now known to develop from a subdural hygroma (Lee et al. 1998). The subdural hygroma arises from a traumatically caused tear of the arachnoid that allows cerebrospinal fluid (CSF) to enter the subdural space at the same time that acute subdural blood is resolving (Borzone et al. 1983; Murata 1993). Most fresh subdural blood resolves rapidly due to high levels of tissue thromboplastin in the brain and cerebrospinal fluid (Astrup 1965). The neomembrane of the subdural hematoma is produced by proliferation of the dural border cells, and this process is induced by cleavage in the dural border cell zone. Persistence of an intradural space is facilitated by any circumstance that lowers the intracranial pressure such as areas of atrophy (in the alcoholic or the elderly) or encephalomalacia (from brain trauma), prolonged drainage of cerebrospinal fluid, or prolonged use of osmotic agents (Dierckz et al. 1989; Mayfrank et al. 1993). Children with glutaric aciduria type 1 develop frontotemporal cortical atrophy and occasionally develop SDH without trauma in the areas of atrophy on the basis of the lowered intracranial pressure in those areas (Forstner et al. 1999). CSF or remnants of the liquid portion of the acute subdural blood may pass into the cleaved dural border cell layer and create a hygroma which under certain circumstances may develop into a chronic subdural hematoma. The outcome of a subdural hygroma depends upon whether the intracranial pressure remains low, in which case the hygroma may expand, or if the pressure returns to normal, the hygroma will resolve. The process that results in the development of a chronic subdural membrane is the basic process of inflammation and repair, and the subdural membrane consists of fibroblasts and vascular endothelial cells proliferating within the dural border cell layer. The development of the classic multilayered chronic subdural hematoma results from low-pressure venous bleeding in a subdural space that is able to enlarge without significant increase in pressure.

Determining the age of subdural membranes is not very precise because there can be some variation within different areas of the membranes within the same individual. In general, the features used for histological aging of subdural membranes in infants and young children are no different from the histological features used in adults (Munro and Merritt 1936; Blumbergs et al. 2008). The arachnoid side is not as reactive as the dural side but will form a relatively avascular fibroblastic membrane in about 2–3 weeks. Aging is best done by histologic study of the dural

portion of the subdural membrane with attached clot and not simply by examination of the blood clot alone. Within the first 2–3 days, fibroblasts can be seen at the margin between the clot and dura. By 4–5 days, the margin contains 3–5 cell layers of fibroblasts. Macrophages containing hemosiderin can be seen along the margin after 2–3 days. By the end of the first week, the fibroblast layer may be 12–14 cell layers thick. Grossly, a neomembrane will be visible. Red blood cells in the clot remain intact for several days and then lyse. By the end of the first week, endothelial cells can be seen growing from the dural margin into the clot, and by the middle of the next week, fibroblasts migrate to the surface of the clot. During the second week, well-formed capillaries are visible within the clot, and these enlarge over the next 2 months. By the end of the first month, the clot will completely liquefy. Depending upon the thickness of the clot, by 1–3 months, the fibroblastic layer will be equal to the thickness of the dura and filled with hemosiderin-laden macrophages. The capillaries that have penetrated the clot from the dura may tear and cause bleeding which for the most part is microscopic and will be visible in the neomembrane and which will also be organized by the same process as the original clot.

One of the controversial issues in AHT is the question of rebleeding of a chronic subdural hematoma (Chadwick et al. 1998). Such an issue involves the claim that trivial injury-induced rebleeding or spontaneous rebleeding has resulted from a preexisting chronic subdural hematoma despite no evidence of an older membrane or the mere presence of a thin subdural membrane of a few scant layers of cells. About 20–30 % of asymptomatic neonates can be shown to have small amounts of SAH and SDH during the birth process (Looney et al. 2007; Rooks et al. 2008). The subdural blood tends to be in the posterior fossa and its resolution often results in a small area of hemosiderin staining within macrophages and a few layers of granulation tissue on the dura. These small remnants of subdural blood are not at risk of rebleeding. Even in infants and children with thicker chronic subdural membranes, any bleeding resulting from tears of the fragile vessels of the neomembrane is microscopic foci of bleeding; in fact this is the very process by which these membranes form. The subdural bleeding resulting from micro bleeds would not be productive of an abrupt change in the neurological status as is seen in most cases of significant AHT. The evolution of subdural bleeding in an old subdural membrane is slow and in most cases entirely benign (Hymel et al. 2002).

Retinal Hemorrhages

RHs will be covered in greater detail in ▶ Chap. 19, "Ocular Findings in Pediatric Inflicted Injury". Retinal hemorrhages are very common findings in AHT and are found in as many as 85 % of cases (Kivlin 1999; Levin 1990, 1998, 2000). The RHs which are most highly associated with AHT tend to be very numerous hemorrhages in multiple layers of the retina and which extend far laterally to the ora serrata (Fig. 17.10a, b) (Christian et al. 1999; Levin 2002). The RHs are most often bilateral but in some cases appear in only one eye, and often there are more in one eye than

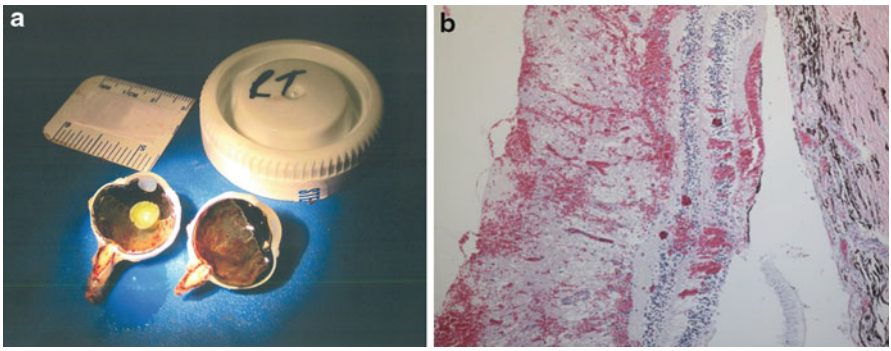

Fig. 17.10 (**a**) An eye from an infant with AHT showing numerous RHs retinal hemorrhages extending far into the periphery and showing optic nerve sheath hemorrhage. (**b**) RHs throughout all the layers of the retina (Hematoxylin and Eosin, H&E ×40)

the other when bilateral. The mechanism for RHs related to AHT is believed to be the same rotational inertial forces that create the brain injuries. Retinal hemorrhages occur in AHT in which there is extensive impact but seem to be most numerous in cases where shaking is more the primary mechanism of injury.

The lesion of retinoschisis is a splitting apart of the layers of the retina with blood filling the cleaved cavity and is thought to be caused by shearing forces as the head is accelerated–decelerated, and the point at which the vitreous is attached to the retina is pulled upon and separates portions of the retina (Levin 2002; Greenwald et al. 1986). At autopsy, retinoschisis may be difficult to recognize due to artifactual wrinkling and disruption of the retina. Retinoschisis can in some cases, however, be identified at autopsy (Salehi-Had et al. 2006). Retinoschisis has been found in two fatal cases of crushing head injury (Lantz et al. 2004; Lueder et al. 2006). RHs are not found in cases of mild accidental head injury but may occur in an occasional case of severe accidental trauma such as vehicular accidents (Duhaime et al. 1992; Johnson et al. 1993). RHs may occur in a variety of conditions and disorders, and some of these conditions produce characteristic findings in the retinal pathology. Disorders associated with RHs include sepsis, meningitis, bleeding disorders, vasculopathies, some genetic disorders, increased intracranial pressure, some newborns, and others (Douherty and Trubeck 1931; Emerson et al. 2001; Fraser et al. 1995; Wilbur 1992). Resuscitation has been cited as a cause of RHs; however, Gilliland and Luckenbach found no evidence that resuscitation causes retinal hemorrhages (Gilliland and Luckenbach 1993).

The examination of the eyes at autopsy is a part of the forensic autopsy, and a forensic pathologist is perfectly capable of undertaking the examination of the eyes. In all cases of suspected or known abuse, the eyes should be removed. The eyes with the optic nerves attached should be removed by taking off the bone of the orbital plates and lifting out the globes and nerves with

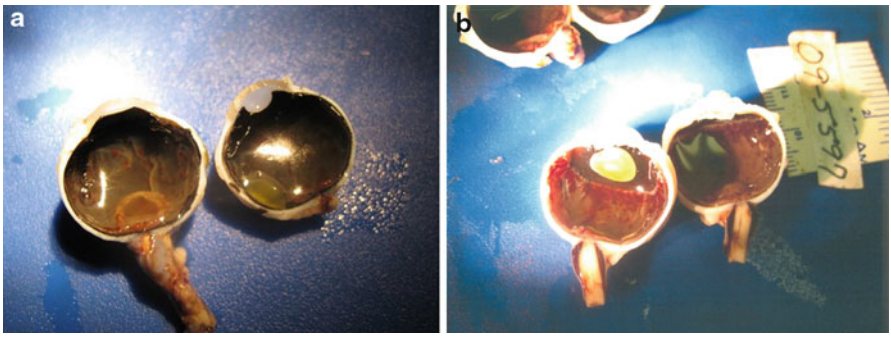

Fig. 17.11 Cross section of eye from infant with AHT showing large retinoschisis cavity in (**a**). (**b**) Shows cross sections of eye of infant with AHT showing very numerous retinal hemorrhages extending to the ora serrata and hemorrhage can be seen in the optic nerve sheath

the adjacent fatty tissue. These specimens are fixed in formaldehyde for at least 2 weeks. Once fixed, the external features of the eyes are described, and the presence of blood in the optic nerve sheath should be noted and documented. Each eye is then opened by making an incision from the pupil to the optic nerve so that the interior of the eye is exposed (Fig. 17.11a, b). The interior of the eye is closely inspected, and transillumination is helpful to visualize any abnormalities. The presence of RHs is usually very evident as red dots or streaks. Other findings that may be seen readily include retinoschisis, retinal folds, and vitreous hemorrhage. These can be described and documented by photography. Microscopic sections are taken even from eyes that appear to have no findings grossly. The author has seen one case where no RHs were visible grossly, but retinal hemorrhages in small numbers were seen microscopically. The gross examination should include the presence, size, and numbers (few, many) of RHs; their distribution within the retina (posterior, midretina, peripheral retina to the ora serrata); the presence of retinoschisis cavities and retinal folds; and any blood within the optic nerve sheath. The microscopic examination should describe the numbers of RHs (few, many), the distribution of the hemorrhages within the layers of the retina, and the distribution within the retina (posterior, middle, periphery). Retinal folds that radiate outward from the optic nerve head in vertical lines may be postmortem artifacts and should be distinguished from actual perimacular folds which appear as circumlinear retinal pleats that surround retinoschisis cavities. These are findings that appear in the gross examination of the eye (Levin 2011; Massicotte et al. 1991). Optic nerve sheath hemorrhage is highly associated with RHs in association with AHT. It is not pathognomonic for AHT and may be seen in other circumstances on rare occasion. The author has seen a 4-month-old infant who was strangled and survived 2 days brain-dead and at autopsy had bilateral optic nerve sheath hemorrhages presumably secondary to raised intracranial pressure.

Neuropathology of Traumatic Head Injury in Children

Traumatic Diffuse Axonal Injury

Severe inertial brain injury resulting from rotational angular acceleration–deceleration forces causes diffuse or widespread shearing injury to axons and small blood vessels and may even cause tears of the brain tissues. The inertial brain movement causes the periphery of the brain to move away from the skull, and greater force causes greater movement extending deep into the brain, the adnexal bridging veins are torn at the brain surface, and axons are damaged beginning at the periphery of the brain and extending through the central white matter, corpus callosum, deep gray matter, and into the brainstem. Within the brain, there are variations in tissue consistency and architecture at junctions between different tissue types such as those between the cortex and subcortical white matter, and these are the sites where axons are particularly vulnerable to shearing injury (Adams et al. 1980, 1982). Traumatic diffuse axonal injury (tDAI) can be classified into three grades in the Adams et al. system (Adams et al. 1989): Grade 1, microscopic damage to axons without gross hemorrhage; Grade 2, microscopic damage to axons with hemorrhage in the corpus callosum; and Grade 3, microscopic damage to axons with hemorrhage in the dorsal aspect of the brainstem.

The hemorrhages described in tDAI occur immediately adjacent to the areas of damaged axons and appear grossly as streak or punctate hemorrhages. These begin as small hemorrhages 1 mm or so and in cases of survival for several days, these may enlarge greatly (Adams et al. 1982). In young children, hemorrhages are rarely seen in association with axonal damage so that the classification of Adams is not particularly useful.

In tDAI, damaged axons become visible on light microscopy within 18–24 h. On H & E staining, a damaged axon is a retraction bulb where axoplasm has poured out of a damaged axon. Damaged axons are difficult to see in young children because of the small size of the axons. Immunohistochemical staining for β-amyloid precursor protein (βAPP) offers a great advantage in visualizing damaged axons over older staining techniques. Damaged axons may be detectable using βAPP staining within 2 h of injury and sometimes less (Sheriff et al. 1994). The axonal damage is nonspecific as to what type of damage is present, and there are differences in the patterns seen for damage to axons caused by trauma (traumatic diffuse axonal injury or tDAI), for hypoxic–ischemic (vascular axonal injury, or VAI), and for metabolic axonal injury (MAI). To make an appropriate distinction among these patterns requires protocols for sampling large numbers of sections of the brain including the cortex, white matter, basal ganglia, corpus callosum, brainstem, and cerebellum in multiple sites (Dolinak and Reichard 2006; Reichard et al. 2003). The VAI pattern appears as broad geographic zones of βAPP expression, often associated with vascular structures, tends to have a so-called zigzag appearance, and is often very extensive in the brainstem. The tDAI pattern appears as small scattered groups or individual fibers of βAPP-positive expression and is especially found in the

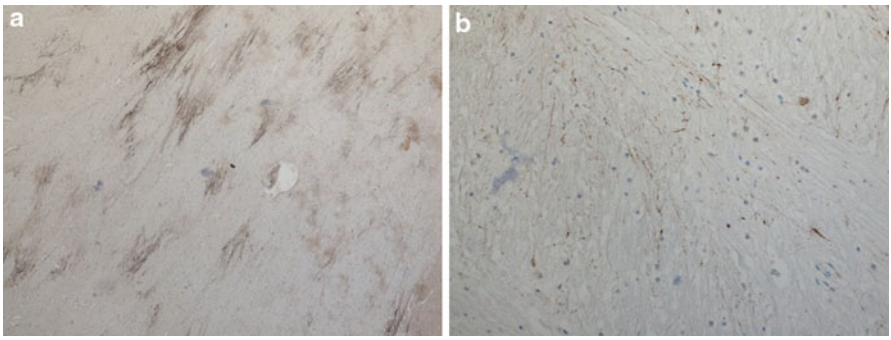

Fig. 17.12 (**a**) βAPP immunohistochemical stain showing VAI with broad areas of βAPP expression (β-amyloid precursor protein (βAPP) × 40). (**b**) tDAI with individual scattered βAPP-positive axons (βAPP × 40)

corpus callosum, corpus striatum, and medulla (Fig. 17.12a, b). The metabolic pattern resembles the tDAI pattern with scattered βAPP reactive fibers or bulbs and has been detected in cases of hypoglycemia although the underlying cause may not be identified and could be global hypoxia–ischemia also (Reichard et al. 2003).

The utility of using βAPP stains to assist in determining the cause and manner of pediatric deaths has been recently studied by Johnson et al. who found that three independent reviewers, blinded to all other information, were able to unanimously identify five of seven cases of inflicted head trauma (Johnson et al. 2011). These authors also studied in a blinded manner 7 control cases from deaths from nontraumatic mechanisms (other than sudden infant death syndrome, or SIDS) and 10 cases of SIDS. In two of the nonhomicidal cases, patterns of axonal staining were seen that could not be distinguished from traumatic patterns of βAPP-positive expression. The authors noted from their experience that βAPP studies are only one piece of the information necessary to consider in determining the cause and manner of pediatric deaths. An interesting finding in one of the nonhomicidal cases, a 2-year-old child who drowned and underwent resuscitation and survived in a hypoxic–ischemic state for 21 h, was that frequent βAPP-positive axons were found in the cervicomedullary junction.

The neuropathology of AHT in young children is not well studied. This is partly true due to the fact that most autopsies on cases of AHT are carried out by forensic pathologists who are not familiar with neuropathological techniques such as βAPP staining or with the interpretation of such stains. The brains in cases of AHT are often not examined with the neuropathological expertise necessary to fully elucidate the neuropathological findings.

Geddes et al. looked at 53 cases of AHT using the βAPP technique (Geddes et al. 2001a, b). Of the 53 children, 37 were under 9 months and 16 were between 13 months and 8 years. Of these children, 51 % had injuries in addition to the head injury

including new or old fractures, abdominal injuries, burns, or extensive bruising. Impacts to the head were evident in 85 % by either scalp bruising or skull fracture. Cortical contusions were present in five cases. The most common microscopic finding noted was global neuronal hypoxia–ischemia which was noted in 84 % of infants and 63 % of older children. This study found only 3 of 53 cases had evidence of tDAI. They found focal axonal damage to axons in the corticospinal tracts in eight cases and postulated that such damage was the result of stretch injury from cervical hyperextension–flexion. An important finding from this study was that the control group of nonhead-injured infants who had suffered respiratory abnormalities and would be expected to show VAI from the hypoxic encephalopathy did not show the same evidence of VAI as did the group with AHT.

The author carried out a study very similar to the Geddes studies using similar protocols for sampling and using βAPP staining (Case 2008). In this, there were 34 cases of AHT with 18 under 12 months and 16 from 13 months to 8 years. There were 19 control cases of nonhead-injured children from 5 weeks to 10 years old. In addition to the head injuries, the AHT cases showed multiple bruises in 50 %, burns 5 %, rib fractures 20 %, laceration of liver 5 %, torn frenulum 5 %, laceration of mesentery 2 %, healing or healed skull fracture 5 %, healed clavicle fracture 8 %, and long bone fractures 29 %. Of these cases, 76 % had subgaleal contusions and 20 % had skull fractures. Subdural hemorrhage was present in 91 %, and multiple extensive retinal hemorrhages were present in 80 %. Of this group, VAI was present in 27 % and tDAI in 73 %. Contusion tears were found in two cases. In 72 % of the cases which had spinal cords available for examination, there was βAPP expression in the cervical cord or cervicomedullary junction. Similar to the Geddes findings is that in the control group which had uniformly hypoxic brain damage, the VAI pattern of βAPP expression differs from that seen in the group with AHT. In the control group with hypoxic brain damage from nonhead injury causes, there are small amounts of βAPP expression in some cases and none in some cases. In cases where it is present, it does not occur with the abundance and in the large areas as seen in the AHT group but occurs in small clusters most frequently in the brainstem. This is an area that requires greater study. Another finding of interest from this study is that the incidence of tDAI seems to depend upon the length of survival. All AHT cases that are lethal have respiratory difficulties and will become hypoxic. In those cases where survival is shorter, these appear to have a greater incidence of tDAI. This may indicate that once hypoxia becomes extreme and VAI is extreme, any tDAI may be overshadowed by the pervasive VAI expression on βAPP staining.

The discussion of whether the neuropathological basis of AHT is tDAI or hypoxia remains open for debate. In porcine models of inertial nonimpact head trauma, both in neonatal pigs to model infants and toddler-age pigs to model older children, the pathology is SDH/SAH and axonal injury indicating that the underlying neuropathological basis of these head injuries is tDAI with the markers of SDH/SAH. These pigs show concussion and brief spells of apnea in response to their injuries (Raghupathi and Margulies 2002; Raghupathi et al. 2002; Ibrahim et al. 2010).

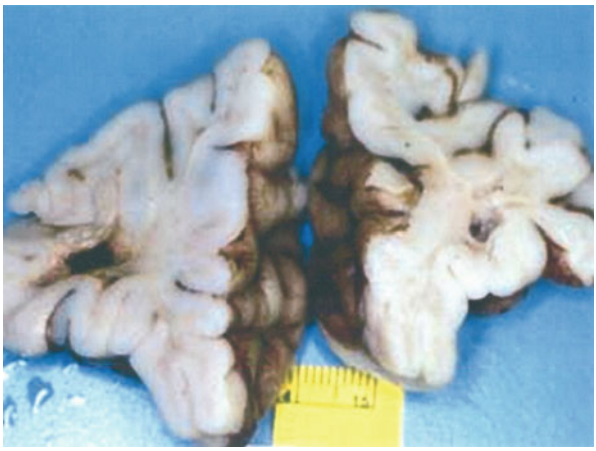

Fig. 17.13 A 7-month-old infant with AHT showing contusion tear within the corpus callosum

Brain Contusions and Lacerations

Contusion in infants and young children was previously addressed in the section on "Accidental Traumatic Head Injury in Children" and will not be repeated here. A unique lesion seen on rare occasions in AHT is the contusion tear. The contusion tear described by Lindenberg and Freytag is a lesion seen most often in infants under 5 months old although the author has seen some in infants up to 8 months old (Lindenberg and Freytag 1969). Contusion tears appear as slits or tears in the subcortical white matter, within the lamina of the cortex or within the corpus callosum. Contusion tears are associated with small amounts of hemorrhage at the site of the tear (Fig. 17.13). In acute contusion tears, the hemorrhage is also acute, and in a surviving infant, the hemorrhage will be resorbed over time leaving remnants of hemosiderin. Artifacts that resemble contusion tears may be produced in merely handling the brain which can cause small tears. Caution should be taken in diagnosing contusion tears. The lesion needs to be seen grossly and confirmed microscopically and not found incidentally microscopically.

Brain Swelling

Brain swelling or cerebral edema is common in many cases of AHT. This is particularly true in cases of AHT that survive unconscious with hypoxic encephalopathy or brain death. In cases of AHT that die very early, swelling may be very minimal. Brain swelling can be identified by the flattening of the gyral surfaces and narrowing of the sulci. The brain weight may be a good indicator of swelling if the weight is greater than 10–15 % of the expected weight for age. In infants, it is very rare to see evidence of tentorial herniation as identified by uncal markings and necrosis as an indicator of increased intracranial pressure because the sutures are open and diastasis of the sutures will occur with brain swelling (Fig. 17.14).

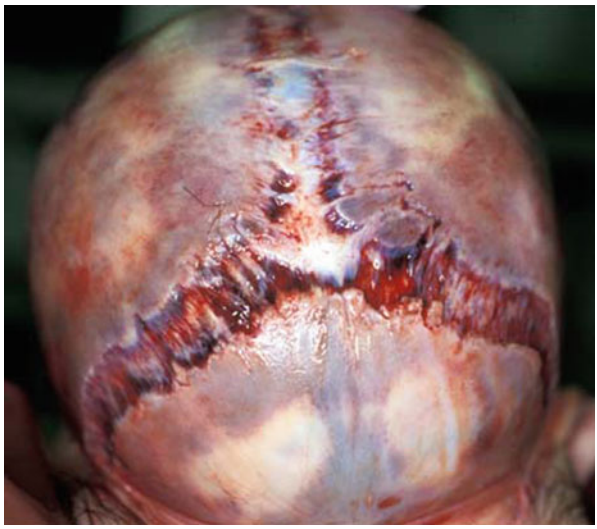

Fig. 17.14 A 4-month-old infant victim of strangulation with 2-day survival with severe hypoxic encephalopathy showing marked diastasis of sutures from brain swelling

Between 12 and 18 months, the sutures will become fused and will no longer separate with brain swelling. This diastasis of the sutures due to brain swelling should not be identified as diastatic fracture. Secondary brainstem hemorrhages or Duret hemorrhages typically associated with tentorial herniation do not occur in infants, so any hemorrhage present in the brainstem of an infant is likely to be from actual trauma. Duret hemorrhages are hemorrhages that occur commonly in the midline of the midbrain and pons but do not occur in the medulla. Brainstem hemorrhages due to traumatic axonal injury appear grossly as streak hemorrhages in the midbrain, pons, and medulla. These are easily distinguished from hemorrhagic strokes associated with hypertension which occur as large hemorrhages in the basilar pons, and embolic hemorrhagic foci appear as small hemorrhages at the cortico–white matter junction. Because the posterior cranial fossa of the infant is relatively small, it is not unusual for the brainstem and cerebellum to be swollen with increased intracranial pressure, and often there is prominence of the tonsils although simple prominence does not uniformly imply that there is cerebellar tonsillar herniation. In cases of brain death, there will be very early softening and dissolution of the tonsillar tissues.

Hypoxic Brain Swelling as a Cause of the Findings in Traumatic Head Injuries in Children

Geddes et al. in 2003 proposed a "unified hypothesis" to explain the pathological findings in some infants with fatal head injury (Geddes et al. 2003). This hypothesis arose from several observations made by Geddes and her fellow researchers. The first set of observations were from the neuropathology studies of 53 cases of AHT in

which they noted few of the cases showed tDAI and a third of the cases showed evidence of craniocervical damage (Geddes et al. 2001b). They noted that the most common neuropathological finding was hypoxic brain damage. These cases of AHT did show SDH and RHs in the majority of cases. They proposed that the injury at the craniocervical junction caused by stretch resulted in hypoxia which then gave the neuropathological findings noted but did not explain the SDH and RHs. Geddes et al. made additional observations on studies carried out on the duras of pediatric autopsies of 50 cases from 18 to 41 weeks gestation of which there were 17 intrauterine deaths, 3 spontaneous abortions, 16 perinatal deaths (less than 7 days after birth), 5 neonatal deaths (within first month of life), and 9 deaths in infancy (within first year of life) (Geddes et al. 2003). None of these cases had suffered a head injury. At autopsy, strips of the dura were studied. Duras from three infants with head injury believed to be AHT were also studied. Of the cases without head injury, the causes of death were infection (6), hypoxia (26), infection with hypoxia (8), and sudden infant death syndrome (SIDS) (4). Six deaths were unexplained. The only significant pathological finding in the duras in 36/50 was bleeding in the strips of dura referred to as intradural hemorrhage (IDH). The bleeding was fresh with no hemosiderin suggesting the bleeding occurred less than 2–3 days before death. IDH was present in 11/17 of the intrauterine deaths so could not be attributed to the birth process. In one case, a 25-week-gestation female born with fulminant Enterobacter septicemia, there was subdural bleeding. The three cases of AHT all showed IDH in their duras. Geddes at al. then "hypothesized" that hypoxia-related leakage of blood from veins both inside the dura and in the subdural space was the source of SDH rather than tearing of the bridging veins in the AHT cases. They further "hypothesized" that in the nonhead-injured cases, hypoxia alone or in combination with infection alters vascular permeability and causes extravasation of blood within and under the dura. They proposed the three factors of cerebral venous hypertension and congestion, arterial hypertension and brain swelling, and immaturity and hypoxia-related vascular fragility provide an alternative explanation for the subdural bleeding in shaken baby syndrome (SBS). They further expanded this proposal to include a physiological explanation for the RHs seen in AHT although no studies were ever done on the eyes of nonhead-injured infants. This thinking became the "unified hypothesis." This hypothesis has been the subject of considerable debate and court censure, and Geddes at al. subsequently noted that they never intended this "hypothesis" to be factual but only to stimulate discussion (Punt et al. 2004; Richards et al. 2006; Supreme Court of Judicature 2005).

Byard et al. carried out a multicenter study on 82 fetuses, infants, and toddlers with hypoxic–ischemic encephalopathy and without head injury, and in not a single case did they find SDH (Byard et al. 2007). Cohen and Scheimberg examined the duras of 25 fetuses (26–41/40 weeks' gestation) and 30 neonates (1 h–19 days' survival) (Cohen and Scheimberg 2009). These fetuses and neonates had grossly evident IDH and hypoxia. Subdural hemorrhage was seen in 16 fetuses and 20 neonates, and they concluded that there was a common association between IDH and SDH. The SDHs found in these

cases are not SDH over the cerebral convexities but are a thin film of subdural blood on the occipital region of the brain or in the posterior fossa. Interestingly, these SDHs occur in the same locations as those SDHs seen in the 20–30 % of births of normal neonates without hypoxia as noted earlier in this chapter.

Some additional comment might be relative to the unified hypothesis. Geddes et al. notes that their neuropathology studies find damage to the craniocervical area and postulate that this damage causes respiratory abnormalities and hypoxia at that same time noting that there is not significant axonal damage elsewhere in the brain except in a few cases. The idea that isolated damage in the medulla and upper cervical spine as a cause of concussion was looked at by Denny-Brown with negative results (Denny-Brown and Russell 1941). The introduction of contusion into the medulla and upper cervical cord does not produce an immediate disturbance of consciousness. To produce respiratory depression at the respiratory center requires rather an extreme crushing or penetrating injury and would not be expected with a mere stretch injury.

Damage to the Craniocervical Region

Studies of the neuropathology of infants and young children with AHT frequently find evidence of injury in the area of the craniocervical junction (Geddes et al. 2001a, b; Case 2008). The mechanism of these injuries has been postulated by Geddes as due to stretching at that point with damage to axons. It has been postulated that damage to the axons at that region might be a cause for respiratory impairment leading to hypoxia–ischemia of the brain and brain swelling (Geddes et al. 2001b). In a study carried out on the utility of βAPP staining in traumatic and nontraumatic deaths of infants and young children, Johnson et al. found that one of their cases, a 2-year-old drowning victim, had positive βAPP expression in axons of the dorsal and lateral white matter of the cervicomedullary junction (Johnson et al. 2011). Thus, in a case in which there was no head trauma, damage to the craniocervical region was found, so the meaning of this damage is unclear.

Matshes and colleagues carried out studies in which the entire cervical spinal column was removed from 12 infants and young children who were suspected or confirmed by history and circumstances to have been subjected to hyperextension and hyperflexion forces either by accidental or homicidal means. These authors found that all cases showed unilateral or bilateral intraneural and/or perineural hemorrhage of the nerve roots of C3–C5 (Matshes et al. 2011). They hypothesized that trauma resulting from the hyperextension/hyperflexion of the neck injured the third to fifth cervical spinal nerve roots, thereby disrupting innervations of the diaphragm and leading to respiratory compromise. They further proposed that the resulting anoxic brain damage was the basis of the SBS rather than mechanical brain damage.

Concussion and Second-Impact Syndrome

Cerebral concussion has been classically described as a reversible syndrome without detectable pathology (Denny-Brown and Russell 1941). In the section of this chapter on "Mechanisms of Traumatic Brain Injury," reference is made to inertial brain motion as a cause of bridging-vein failure and tDAI. Inertial loading of the head from acceleration–deceleration produced by either impact or impulse also causes the syndrome of concussion. The term concussion comes from the Latin "concussus" which implies to shake violently. Ommaya and Gennarell established that translational acceleration in which the head is moved from posterior to anterior along a straight line did not produce concussion, although when the head was moved with a center of rotation in the lower cervical spine to cause rotational or angular acceleration, concussion was readily produced (Ommaya and Gennarelli 1974).

Mild concussion occurs when consciousness is not lost, but there is confusion and disorientation. This is a common occurrence in many contact sporting activities. Players while confused may continue to play and after the game may initially remember events of the injury, but after 5–10 min, there is no memory of the events. As the severity of the concussion increases, there is confusion and amnesia from the time of injury. The classic concussion syndrome is loss of consciousness and some degree of retrograde (events prior to injury) and posttraumatic (events following the injury) amnesia. Physiological responses of bradycardia, hypertension, apnea, papillary dilatation, and flaccidity also occur at the time of unconsciousness (Blumbergs et al. 2008).

The concept that concussion is a transient physiological disturbance without detectable pathology has been replaced by evidence that concussion creates complex physiological derangements that last as long as a week in even a mild concussion, and in some concussions there is structural damage with loss of neurons. The clinical appearance of concussion may be appreciated by considering two of the systems used to grade concussion. Table 17.1 (Cantu 1986) and Table 17.2 (Ommaya 1985) illustrate systems for grading concussion, and both focus on loss or retention of consciousness and/or amnesia. Symptoms that occur with concussion include a sensation of being stunned, seeing bright lights, lightheadedness, vertigo, headache, and blurred vision. Postconcussive symptoms may persist for weeks or months and include headache, vertigo, labyrinthine disturbance, and cognitive disturbance (Alves et al. 1993). Because patients with concussion are not examined neuropathologically, not much is known of the pathology. Blumbergs et al. described multifocal axonal injury in five mildly head-injured patients who died from other causes 2–99 days after injury using βAPP staining (Blumbergs et al. 1994).

Concussion initiates a complex sequence of ionic and metabolic events. In a very simplified version of a very complex sequence of events, following concussion, there is an efflux of K+ from neurons due to mechanical membrane disruption, stretching of axons, and opening of voltage-dependent potassium channels. To restore membrane potential, the Na+, K+ -ATPase must work overtime and consumes large amounts of ATP. To meet the demands for the increased ATP, there is

Table 17.1 Cantu system for grading concussion

Grade 1. No loss of consciousness: posttraumatic amnesia less than 30 min
Grade 2. Loss of consciousness less than 5 min or posttraumatic amnesia longer than 30 min but less than 24 h
Grade 3. Loss of consciousness for more than 5 min or posttraumatic amnesia longer than 24 h.

Table 17.2 Ommaya system for grading concussion

Grade 1. Confusion without amnesia (stunned)
Grade 2. Amnesia without loss of consciousness
Grade 3. Unconsciousness less than 6 h (includes classical concussion from minor and moderate head injuries)
Grade 4. Unconsciousness lasting 6–24 h (severe head injuries)
Grade 5. Unconsciousness more than 24 h (severe head injuries)
Grade 6. Unconsciousness, death within 24 h (fatal head injuries)

greatly increased cellular glycolysis. At the same time, there is an increase in lactate production. There is also Ca+ influx which may lead to further dysfunction (Takahaski et al. 1981). The cerebral blood flow is closely coupled to cerebral glucose metabolism. Injured brain may greatly increase the utilization of glucose to meet the demands for ATP being used up. This increased period of hyperglycolysis may represent a period of increased vulnerability of the brain to a second insult.

In 1983, Saunders and Harbaugh described the second-impact syndrome as occurring when an athlete sustains a head injury which is often a concussion or worse and then sustains a second head injury before the symptoms of the first head injury have cleared (Saunders and Harbaugh 1984). The postconcussive symptoms that might be seen after the first injury include headache, labyrinthine dysfunction, visual disturbance, and cognitive dysfunction especially memory. The second impact may be quite minimal and may be simply jarring of the body or a blow to the chest. In a brief period of 15–60 s, there is collapse followed by rapid dilatation of the pupils, loss of eye movements, and respiratory failure. There is about a 50 % mortality in these cases. The pathophysiology is thought to be loss of autoregulation of cerebral blood flow leading to rapid hyperemia and malignant brain swelling with increased intracranial pressure and herniation. The pathology of these cases is not well studied as they are relatively rare, but some of the cases have subdural hematomas; these are small and not clinically significant. The primary problem is the massive brain edema. The cases of second impact described have been in teenagers and athletes in early adulthood who were involved in sporting events which subjected them to significant acceleration–deceleration head trauma (Cantu and Voy 1995; Cantu 2000). The question of whether such injuries occur in infants and young children has been asked by some, and the answer is not known; however, infants and young children do not

participate in the types of sporting events in which second impact has been known to occur. Minor trauma would not be expected to set up the metabolic sequence that leads to hyperglycolysis and creates the vulnerability for second-impact syndrome.

Spinal Trauma in Children

Unique Features of the Spine in the Young Child

Just as the young child's head and brain have unique anatomic and developmental features and undergo a long period of growth and maturation, the spine of the infant and young child is unique in its anatomical and developmental characteristics and has a long period of maturational growth. There is very great flexibility in the young spine. The vertebral column is predominantly cartilage and later ossifies. The uncinate articulations are poorly developed. The vertebral bodies are wedge-shaped, the articulating facets are angled horizontally, and there is a tendency for the vertebral bodies to slide forward with flexion. The end plates, interspinous ligaments, and joint capsules are more elastic and lax in the young human. These differences are reflected in the injuries that occur in the spine in young children. Because of the greater flexibility of the spine, there are fewer spinal fractures in children under age 10 years than in older individuals. After age 9 years, the vertebrae begin to ossify, the vertebrae become more rectangular in shape, the facets become more horizontal, and the articular processes begin to protrude (Fesmire and Luten 1989).

Spinal Trauma in Children

In young children, if a cervical fracture occurs, it is more likely to be an upper cervical fracture. Adults have more fractures in the middle and lower cervical spines. Spinal cord injury is unusual in the pediatric group; only 5 % of all spinal cord injuries occur in this group. Children sustain a larger proportion of nonfracture ligamentous spinal injuries in comparison to adolescents or adults. Fractures of the atlas and axis are rare in children. Under the age of 8 years, spinal injuries usually manifest as radiological abnormalities, SCIWORA (spinal cord injury without radiological abnormality), subluxations, or fracture–subluxations. Atlanto-occipital dislocation is more common in children than in adults. In young children, the craniocerebral junction is inherently less stable than later in life due to the relatively small occipital condyles and the horizontal orientation of the articulation between the cranium and the atlas. With age, this articulation becomes more vertical and the condyles become more deeply and firmly seated in the fossa with the superior facet of the atlas. Occipital dislocations in children can occur in falls, vehicular collisions, wrestling, and other such activities. MRI may demonstrate EH over the clivus and odontoid in such dislocations (Mizushima et al. 1998).

Although spinal cord injury is relatively uncommon in children under age 12 years, when it occurs in these early ages, cord injury tends to have more severe consequences than similar injuries in adults (Ruge et al. 1988; Scher 1976; Bondurant and Oro 1993). This is true because in the younger child, the cord injury is often at a higher level resulting in more severe disability, it may show a delayed onset, disruption in the vertebral bone is more often at the cartilaginous endplate causing deformity to be more threatening, and because there may be no radiological evidence of injury (SCIWORA). SCIWORA occurs because the distinctive characteristics of the infant and young child's spine allow the spine to be deformed to the point that cord injury can occur without fracture or rupture of ligaments. Despite no radiological evidence of the injury, MRI can demonstrate these injuries by demonstrating edema and hemorrhage within the cord which is not able to be visualized by radiology.

Spinal Trauma in Inflicted Injuries in Children

Spinal injuries in cases of child abuse are not common and are seen in fewer than 3 % of child abuse cases (Diamond et al. 1994). The small numbers may reflect a relative lack of diagnosis in actual cases. Vertebral injuries may be asymptomatic, and the young child may not experience the same type of chronic pain syndromes seen in adults. Investigation of spinal injuries may only be undertaken if there is neurological deficit or spinal deformity. When spinal injury occurs as an abusive injury, it tends to be in the younger child with an average age of 22 months.

The mechanisms which are particularly apt to damage a child's spine by abusive injury are as follows:

1. Hyperextension–flexion – created by forces such as seen in AHT or shaking
2. Traction–distraction – the head is held and the body is shaken
3. Rotary distortion – lateral bending of the neck

Other types of spinal injuries seen in association with abusive actions are

1. Compression fractures – of the vertebral bodies usually thoracolumbar from forceful compacting movement such as slamming a child onto the buttocks
2. Fractures of spinous processes from direct impact
3. Anterior notching of vertebral bodies – due to disruptions of the endplate which leads to loss of bone and deformity

Distraction Injury of the Cervical Spine

A rare cause of inflicted trauma is the distraction injury of the cervical spine. Priatt described a case of a 15-month-old who presented with quadriplegia after reportedly falling from a couch (Priatt 1995). The child was in the care of the mother's boyfriend who did not see her fall but said he heard a cry and found her on the floor. Two months earlier this child had received care for facial burns when she was said to have put her face into a bowl of soup while in the care of the same boyfriend.

On presentation, the child had a small laceration of the tip of the tongue, an abrasion to the upper lip, red linear contusions on the skin in front of the ear and along the jaw on the right, and showers of petechial hemorrhages heaviest over the left side of the neck but also over the right arm and over the upper chest. There were yellow–green brown ecchymoses at the lateral margins of both orbits, on the medial aspect of both arms, on the dorsal surface of the left forearm, and on the medial surface of the right thigh. Older healed skin lesions consistent with the history of facial burns were noted on the left cheek and nose. The child was awake and alert, but there was a flaccid quadriplegia with complete anesthesia below the neck. Radiographs of the spine were normal. An MRI of the cervical spine demonstrated fusiform swelling of the cord in the midcervical region with hematomyelia. A bone scan suggested a fracture of the right clavicle, and an old fracture was confirmed on radiographs. Skull radiographs were normal. Abusive injury was supported by statements of the child's grandmother and statements of the boyfriend. After 2 months, follow-up MRI of the cervical spine showed atrophy of the cord in the region previously swollen. In this report, the author notes that the mechanism of injury was obscure. The bruises over the arms suggested that possibly the child had been grasped by the arms and shaken. The facial petechiae and ecchymoses below the jaw raised the question of the perpetrator grasping the child by the neck and whiplashing the body rather than the head.

Parrish wrote a letter to the editor in response to the above case of the 15-month-old with quadriplegia and hematomyelia of the cervical spine to report a similar case that he had prosecuted (Parrish 1996). This child was a 2-month-old infant who had contusion of the upper cervical spinal cord and lower medulla and died. At autopsy, the eyes were studied and found to have anterior chamber bleeding bilaterally, a dislocated left lens, and vitreous hemorrhage. There were no RHs. The eye injuries were studied by Robert Folberg, MD, and his opinion of the mechanism of injury was that the optic injuries were due to direct compressional forces being applied to the front of the eyes. The only theory that could account for both the eye injuries and the cervical spine injury was that the perpetrator picked up the child by his head with the thumbs over the eyes and violently shook the body while the head was held relatively stable.

The author has seen three cases of cervical spinal cord injury with features that suggest a distraction mechanism of injury to the lower medulla and upper cervical cord region with similarities to the above two cases (Case et al. 1996). Two of the cases were siblings. The first sibling, a 3-month-old infant, was injured by the father who described that he grasped her by the head and shook the body. That child survived with a central cord syndrome. The second sibling was found dead at age 3 months. Autopsy demonstrated petechial hemorrhages of the right bulbar conjunctiva and hematomyelia of the medulla and upper cervical cord. For this child, the father described several abusive actions such a pushing on her back but no details to explain the cord injury. The third case died at the age of 25 days after he was found unresponsive after crying all night. He was pronounced dead on arrival in the emergency department. His autopsy showed contusions of the right jaw,

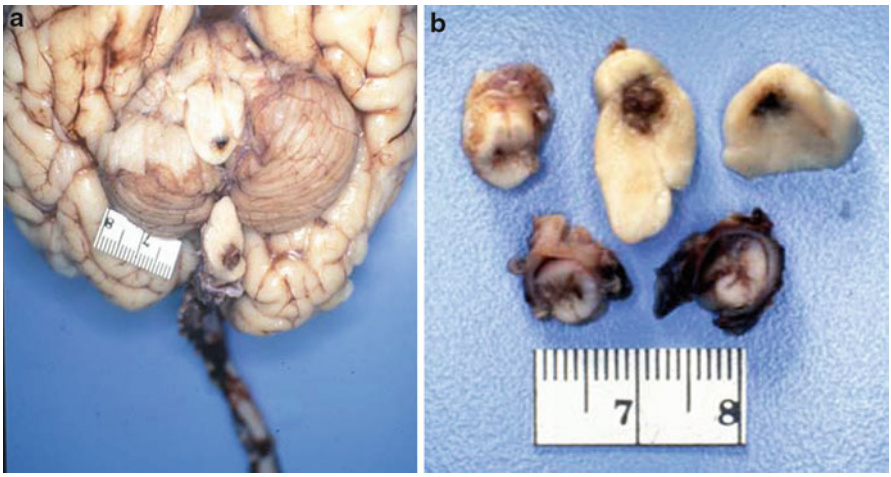

Fig. 17.15 A 25-day-old infant with distraction injury of medulla and upper cervical cord. (**a**) A cross section between medulla and cervical cord showing hematomyelia. (**b**) Multiple cut sections of lower medulla and upper cervical cord showing the central area of hemorrhage (hematomyelia)

beneath the left lower lip, right shoulder, left abdomen, posterior left arm, and both legs. The contusions on the legs looked like gripping marks. There were petechial hemorrhages of the right preauricular area, left lateral forehead, and the bulbar and palpebral conjunctivae. There was a single small RH. There was fracture of the right clavicle with early callus. There was separation of the C3-C4 intervertebral disc and hematomyelia of the upper cervical cord and lower medulla (Fig. 17.15a, b).

The injuries and findings of these children suggest that the children were grasped by the head and violently shaken. Such an action creates distraction of the upper cervical spine/lower brainstem region while the body is suspended and unsupported. The action of shaking while in this position creates further distracting forces. The petechial hemorrhages noted in these cases are similar to petechial hemorrhages seen in other children who are grasped firmly on the face or neck.

Artifactual Cervical Cord Hemorrhage from Brain Death

The hematomyelia described in the above distraction injury consists of hemorrhage within the central portion of the spinal cord which resembles a contusion of the cord made by direct impact to the cord by fracture of the spine or by penetrating injury. There is an artifactual lesion that is seen in cases of brain death that also resembles a cord contusion and which needs to be distinguished from a true traumatic injury. In brain death, the brain becomes very soft after the first day or two of survival in

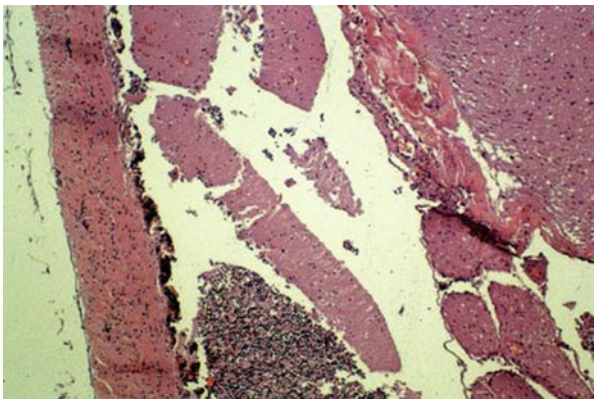

Fig. 17.16 Photomicrograph of cervical cord showing fragments of cerebellum in subarachnoid space which have descended from above disintegrating cerebellar tonsils in brain death (Hematoxylin and Eosin, H&E ×40)

that extremely hypoxic state. The earliest and greatest softening of the brain occurs within the cerebellar tonsils which may begin to fragment. As the tonsils disintegrate, fragments of the cerebellar tissue fall into the subarachnoid space and may travel downward into the cervical region subarachnoid space. The material may compress small pial blood vessels and cause cervical cord ischemia. The result is ischemic necrosis of the cervical cord which is a centrally placed hemorrhagic lesion which resembles a cord contusion. Microscopically, the fragments of cerebellum can be observed in the subarachnoid space around the cervical cord (Fig. 17.16). Experimental brain death in animals produces an identical lesion (Matakas et al. 1973). Because these two lesions look virtually identical, it would be very challenging to identify the hematomyelia of the distraction injury in a brain-dead infant, so great care is advised.

Epidural Hemorrhage of the Cervical/Thoracic in Infants: Artifact or Trauma?

In 1967, Towbin studied five children who died suddenly and unexpectedly and found EDH in the cervical spine of these children (Towbin 1967). Towbin suggested from these observations that the spinal findings might be traumatic and might be related to the cause of death through mechanical damage to the cord. In 1969, Harris and Adelson studied 19 infants under 1 year old who died suddenly and unexpectedly (Harris and Adelson 1969). Of these 19 infants, 5 died from natural causes noted at autopsy, and 14 were unexplained by autopsy findings and were felt to be sudden infant death syndrome deaths. Of these 19 infants, 18 had EDH within the spinal region which varied from venous congestion to hemorrhage within the adjacent soft tissues and was greatest in the lower cervical region. These authors concluded that the EDHs were not traumatic, the epidural blood was not damaging to the cord, and the hemorrhage was related to hemodynamic forces.

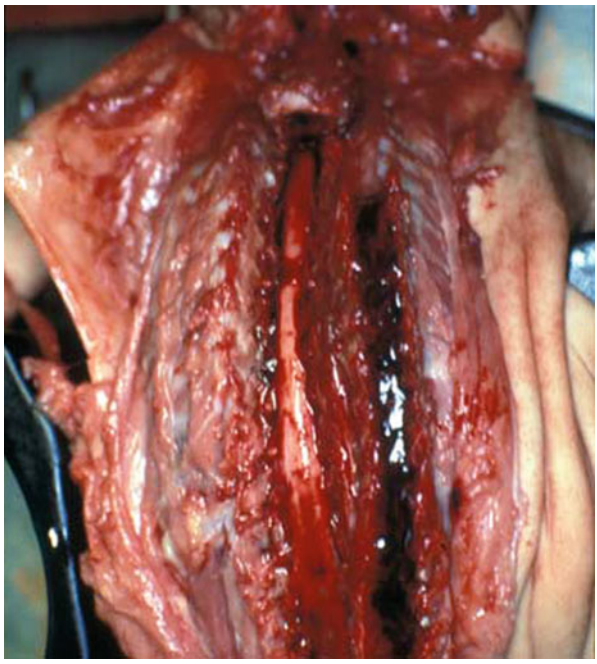

Fig. 17.17 Posterior dissection of spine demonstrating nontraumatic EDH in the spinal region

In 1989, a paper by Hadley et al. described 13 infants who were diagnosed as shaken infants (Hadley et al. 1989). Of these 13 infants, 8 died and 6 were autopsied. The autopsy findings in these 6 were as follows: 5/6 had EDHs in the cervical spine, 4/6 had SDH in the cervical spine, 4/6 had contusions of the high cervical cord, and only 1 had none of these findings. This paper is of interest in several aspects. The presence of subdural blood in the cervical spine region in the 4/6 who showed this finding is not unexpected as noted in the section above on SDH. Subdural blood in the posterior fossa can descend by gravity into the cervical spinal region, and young children with AHT often have subdural blood in the cranial fossae. The EDH in the 5/6 infants who showed that finding is a subject that had been investigated by Harris and Adelson in 1969, with the conclusion that such hemorrhages were nontraumatic and of hemodynamic origin (Harris and Adelson 1969). However, those studies were carried out before AHT was readily diagnosed. There had not been a study which specifically examined young children with AHT to see if they showed EDH. A study carried out by the author looked at a series of children under age 3 years with AHT as well as controls for the presence of EDH in the spinal area (Case 1993). After examining 50 children, it was found that both AHT and control groups frequently had EDH in the spinal areas (Fig. 17.17). Lastly, there is not any description of the contusions in the four cases in which contusions were noted, so it is not possible to know if these were distraction injuries as described in the section above or if they were

some other type of lesion. The spinal region should always be examined in any child under 3 years of age when there is AHT or any possibility of other abusive injury or suspicious finding.

Conclusion

Head injuries in infants and young children are common injuries that will simply by numbers become cases for almost every forensic pathologist, pediatrician, neurosurgeon, and radiologist. Physicians who need to distinguish how these head injuries occur need a great depth of knowledge of basic head trauma as well as knowledge of the specialized area of head injuries in these young children. This knowledge requires pursuit of the literature as well as training and education. A number of areas of research exist that need to have investigation carried out. In particular, the neuropathology of abusive head injury needs more detailed studies using the special technique of the βAPP stains to more fully understand the patterns of VAI and tDAI in young children. To fully understand these patterns requires that studies also be performed on nonhead-injured children with hypoxic–ischemic encephalopathy. A fruitful area of investigation is the vasculature of the young brain to learn whether stretching injury of the vessels is a part of shearing injury of tDAI.

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Biomechanics of Pediatric Head Injury

18

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Contents

Abstract

Biomechanical modeling is very useful in the ongoing advancement of our knowledge of human infant head injuries. The current models are limited by a paucity of basic science data on the biomechanics of human infant tissues at

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various stages of development. Overall, the current state of biomechanical modeling does not justify reaching forensic or legal conclusions regarding the head injuries of infants and young children. This chapter discusses the various aspects of biomechanical head injuries in infants and young children.

Biomechanical Terms and Concepts

Force acting on a free body will accelerate or decelerate it. *Acceleration* and *deceleration* represent identical phenomena differing only in direction (Spivack 2006). The force (F) required to accelerate an object through a specified change in velocity (Δv) over a specified period of time (Δt) is defined by the equation $F = m$ ($\Delta v/\Delta t$) where (m) represents the object's mass. During cranial impact with the ground, more severe cranial deceleration will occur if impact velocity (Δv) is very high (e.g., a fall from a significant height) and/or impact duration (Δv) is very short (e.g., a fall onto a rigid, non deformable surface).

Load is an engineering term that describes a physical excess or burden. Mechanical loading in cranial injuries can be classified according to its dependence on time. *Static* loading implies that forces are applied slowly or gradually (e.g., head squeezing or crushing). In *dynamic* loading, the mechanical input is time-dependent and is rapid (usually <200 ms). Dynamic loading can be of two types. *Impact loading* necessarily indicates contact (i.e., cranial collision), whereas *impulsive loading* can occur when the head is accelerated or decelerated without contact by forces transmitted through the neck.

A tissue can resist an applied impact or impulsive mechanical load by building up internal forces (*stresses*) or by deforming (*strains*) and thus reorienting internally. When a mechanical load is applied rapidly (short Δt), living tissues demonstrate increased resistance to deformation (more stiffness) that lessens deeper injury risk despite increased stress magnitude. In contrast, when a mechanical load is applied slowly (prolonged Δt), living tissues demonstrate less resistance to deformation (less stiffness), and there is more time for accommodative tissue strain, thereby increasing deeper tissue injury risk even at relatively lower resultant stress magnitudes. This time-dependent response of living tissues to mechanical loading is called *viscoelasticity*.

A tissue's elastic modulus (or modulus of elasticity) describes its tendency to be deformed elastically (i.e., nonpermanently) when a force is applied to it. A stiffer tissue will have a higher elastic modulus. Ultimate stress defines the maximal load that a tissue can bear at the point of failure.

Kinetic energy ($1/2\ mv^2$) is related to mass and velocity and (as in all other forms of energy) can neither be created nor destroyed but can change form. When a cranium decelerates against a rigid, unmoving object (e.g., a concrete surface), no work can be performed on that object. Therefore, most of the impact kinetic energy is transferred to potential energy that is stored within the cranium by deforming (and potentially damaging) it. This deformation can be described as *strain*, a term used to describe the difference between the undeformed and

deformed state of a body. There are three types of strain: (1) *compressive*, tending to decrease the length of an element; (2) *tensile*, tending to increase the length of an element; and (3) *shear*, tending to cause angular distortion or sliding between elements.

If and when a moving impactor strikes a stationary cranium, some of the impactor's kinetic energy can be stored within the cranium by deforming it. However, if the cranium is free to move in the direction of the applied force, some of the impactor's kinetic energy can be transformed into kinetic energy that accelerates the cranium. Assuming impact force is sufficient, biomechanical factors that favor whole-head cranial acceleration are cranial freedom to move and a relatively large surface area of contact (i.e., distributed loading). Biomechanical factors that favor cranial deformation (rather than acceleration) include restriction of cranial motion (i.e., fixity) and a small surface area of contact (i.e., nondistributed loading).

Two types of cranial acceleration are possible. *Translational* acceleration occurs when the head's center of gravity moves in a straight line. *Rotational* (or *angular*) acceleration occurs when the head turns about its center of gravity without the center of gravity moving. Many impacts induce a combination of translational and rotational cranial acceleration.

Cranial injuries are frequently classified as contact or inertial. *Contact* injury requires that the head strike or be struck by an object. Contact injuries can be viewed as the deformational injuries that result from cranial impact if the head is prevented from moving. *Inertial* injuries result from cranial acceleration (or deceleration), irrespective of whether that acceleration was triggered by direct cranial impact (or impulsively). When cranial impact induces both contact and inertial injuries, the inertial injuries can be viewed as those injuries that would not have occurred if the head had been fixed at impact.

The compressive, tensile, and/or shearing strains induced in the cranium by contact or inertial loading are the cause of *primary* traumatic cranial injuries. *Secondary* hypoxia and/or ischemia due to apnea, altered autoregulation of cerebral blood flow, venous vasospasm, space-occupying intracranial hemorrhage, acquired coagulopathy, the generation of free radicals, calcium influx into cells, and/or brain swelling also contribute dramatically to brain-cell injury and/or death.

Contact forces cause focal strains particularly at the site of impact, resulting frequently in scalp injury and skull fracture. Contact injuries underlying skull fracture or the site of impact can include hemorrhage (e.g., epidural, subdural, or subarachnoid) and/or parenchymal disruptions (e.g., contusion or laceration). Contact injury mechanisms can sometimes cause injuries distant from the site of impact (e.g., basilar skull fracture and contrecoup contusions).

Inertial strains created by cranial acceleration cause injuries in one of two distinctive ways: (1) The brain may move relative to the skull and dura, producing rupture of bridging veins, and (2) acceleration may create strains within the brain itself, particularly where brain tissues of different densities interface, where brain tissue abuts against more rigid intracranial structures, and/or where brain tissues bridge intracranial compartments.

Fatal head injuries in children are most often the result of primary *inertial* strains – not *contact* strains. And yet, caregiver explanations relating pure inertial injury mechanisms are rare. Instead, most caregivers of young children with fatal head trauma attribute their child's cranial injuries to an accidental cranial impact. Only two general scenarios for accidental cranial impact are possible. Either *the head was struck* by a moving impactor or *the head struck* a stationary surface (or object resting on a stationary surface). And yet, in the normal (indoor) world where infants and young children typically reside, (1) the vast majority of moving objects possess insufficient mass, velocity, kinetic energy, and/or force to significantly accelerate the stationary cranium of an infant or young child and (2) the vast majority of pediatric falls from a standing height or from an indoor surface fail to induce clinically significant cranial deceleration.

Embodied in these final statements is *the* essential contradiction that so often demands thoughtful and objective forensic consideration: Does the caregiver's account of the child's accidental cranial impact reasonably explain severe or fatal cranial acceleration or deceleration? If not, homicide must be considered.

Biomechanical Properties of Tissues

One of the challenges of using biomechanics in pediatric cases is the paucity of normative data on the biomechanical properties of human children and adolescents. Obtaining this data is complicated by child growth – the anthropometric parameters of their bodies change on a month-to-month and year-to-year basis. Not only does anthropometry differ with age, but the anatomy and material property of tissues differs as well.

Most of the data on the mechanical properties of human tissue are derived from cadaver and volunteer tests (Beusenberg et al. 1993). Very few cadavers of infants and small children are available for research purposes. In addition, children are generally not appropriate subjects for experimental research because of problems with risk of harm and informed consent. Most biomechanical data on tissues of the young are studied in quasistatic loading, so the results might not be relevant to what actually happens under dynamic loading circumstances. Few total-body cadaver tests have been done on infants and young children to determine body-part responses (Kalieris et al. 1976). Most injury threshold data for infants and children are derived from the scaling of adult and animal responses and tolerances. This is problematic since the geometry, elasticity, and other tissue properties are usually very different between adults and the very young.

Skull: The biomechanical properties of the infant skull differ from those of the adult skull. Infants have thin skull plates of membranous bones connected by sutures and fontanelles. The infant skull has a single bony layer as opposed to the layered skull of the adult.

Coats and Margulies (2006) studied skull response at varying strain rates in pediatric skull and suture over a range of ages. Between 21 weeks' gestation and 13 months of age, bending modulus and ultimate stress significantly increased with the

age of the donor. McPherson and Kriewall (1980) determined that differences exist between the elastic modulus of the infant skull depending upon which direction the skull tissue was stressed and concluded that the infant skull is anisotropic (differing with direction). They also determined that the elastic modulus of skulls of preterm infants was significantly lower than that of the term infant. Margulies and Thibault (2000) found that in slow "crushing events," the age of the infant affected the elastic modulus of the skull and that the pediatric skull elastic modulus was much lower than that of the adult skull. Age-specific data should be used in computational models investigating pediatric head injury.

Parietal bone was found to be stiffer and have a higher ultimate stress than occipital bone in these infant skulls (Coats and Margulies 2006). Occipital bone is more rigid because it is much thicker than parietal bone. Based on Coats' data, impact to the occipital bone will likely lead to fracture and absorb energy before deformation, while the parietal bone may be more likely to distribute energy to the surrounding sutures before distorting significantly and deforming the underlying bone. Therefore, location of impact will influence whether the skull actually fractures in falls from low heights.

McPerson and Kriewall (1980) found when skull fibers were parallel to the long axis of their specimens, the elastic modulus was higher. They concluded that differences in material properties between pediatric and adult skulls are due to structural changes in the skull. Fiber patterns of immature cranial bone emanate radially from ossification centers and are easily seen. Adult skulls are highly rate dependent and have no visual pattern of fiber orientation; testing orientation does not affect results with adult skulls. Suture has a much lower elastic modulus than bone and can absorb more energy than bone. Pediatric cranial bone is 35 times stiffer than suture (Coats and Margulies 2006). Large strains in pediatric bone and suture result in a skull case that can undergo dramatic shape changes before fracture, which might cause substantial deformation in the brain. In Coat's study (Coats and Margulies 2006), suture experienced strains over 100 % before failing, 30 times more than bone. Pediatric skull deforms more during impact, while adult skulls deform very little prior to fracture. Dura is four times stiffer than human suture (McElhaney et al. 1970).

Brain: Most estimates of pediatric head injury tolerances and criteria are based on the scaling of adult values to the size of the pediatric brain (Prange and Margulies 2002). Since the properties of infant brain are very different from adults, these scaling results are suspect. Infant brain is poorly myelinated and has high water content. Infant brains also have a very different response to injury. Serum markers of neuronal death and apoptosis have been found to be more elevated after infant head trauma than after adult head trauma (Kochanek et al. 2010). It is possible that the normal developmental propensity of infants toward apoptosis or "pruning" of many neurons influences cell death mechanisms (Kochanek et al. 2010).

No pediatric threshold data exist relating to infant head injury risk criteria. The prediction of injury in the pediatric population using adult data and scaling based on the mass of the brain is complicated by the lack of information that

accurately can support the scaling of injury thresholds from adults to children (Thibault and Margulies 1998). Material properties of the brain are age dependent, and current literature lacks adequate data on the material properties of the pediatric brain. Thibault and Margulies (1998) showed that the shear modulus of porcine brain tissue was quite different in adult and infant pigs, with the shear modulus increasing with age. Their work predicted a lower scaled rotational acceleration threshold for children than that based on brain mass alone.

Neck: There is limited biomechanical data available on the pediatric neck. Most of the studies have been done on embalmed postmortem tissues. In addition, testing has been done on necks after the soft tissue and muscle layers have been removed, which makes the cervical spine more vulnerable. Luck et al. (2008) found that pediatric cervical-spine stiffness and strength increased with the age of the child. There is little data on the tension, compression, and bending properties of the infant neck (Coats and Margulies 2008). Passive head range of motion has been studied in 38 infants 2–10 months old (Ohman and Beckung 2008). Infants under a year of age had greater than 100° of axial rotation and greater than 65° coronal rotation.

Spinal vertebrae synchondroses close in a "caudocephalad" sequence over the early years of life, with the lower vertebrae calcifying before the upper vertebrae. Yoganandan and colleagues found 50 % of pediatric patients will fuse the posterior synchondroses of C1 at 7 years of age, C2 at 5 years of age, and C3 at 2 years of age (Yoganandan et al. 2011). The maturation of spinal tissues results in significant changes in failure load and stiffness of the cervical spine. This correlates clinically with the higher incidence of injuries to the upper cervical spine in infants and very young children (McGrory et al. 1993).

Thorax: The rib cage stiffness and geometry are very different in infants and young children compared with adults (Snyder et al. 1975, 1977). In addition, young humans have cartilage incorporated into the posterior ribs as well as in the anterior ribs. Infant ribs are far more flexible than ribs of older children and adults.

Bones: In the young, mineral content and strength of bone progressively increase until maturity (Kleerekooper et al. 1986). The presence of epiphyseal growth plates in children's bones also changes the responses of bones to loading. Bones of children are more vulnerable to plastic deformation than bones of adults (Currey and Butler 1975). Most of the work on biomechanics of children's bones has been done on femurs, and normative data is not as readily available for other bones. Little data exists on the compressive failure strength of cancellous bone in children (Yamada 1970).

Tendons and ligaments: Tendons and ligaments become stiffer and less resilient as humans age (Hubbard and Soutas-Little 1984). In infants and young children, bone fractures are more likely to occur than joint sprains or dislocations because the bones are generally more vulnerable to injury than the joints and ligaments. Most of the data on age changes in ligaments have been obtained in primates instead of humans (Noyes and Grood 1976).

Skin: The tensile strength of human skin increases during the first years of life. From birth to age 35, the thickness of skin doubles (Sturtz 1980). The slope of the stress–strain curve of human skin decreases throughout maturation, reaching

a minimum between 15 and 25 years of age, and then increases with advancing age (Alexander and Cook 2006).

Applying Biomechanics When Analyzing Injuries

Contact injuries: Child head injuries can be caused by the head making contact with a surface. Contact injuries are listed in Table 18.1, Row 1, Column 2, and in general, the severity and type of injury is a function of the difference in velocity between the head and the contact surface at the time of contact, the stiffness of the contact surface compared to that of the head, and the size of the impacting surface compared to that of the skull.

In case a weight is dropped on the head, the type and severity of injury depends on the weight dropped in addition to the factors listed above.

In both cases, severity of injury will generally be higher if the head is restrained and prevented from moving freely. This type of loading is shown in Fig. 18.3.

Figures 18.1, 18.2, and 18.3 illustrate occipital impacts; however, the principles described apply to impacts to other parts of the head. Similarly, Fig. 18.4 illustrates shaking/whiplash in the sagittal plane.

Blunt impact: Figure 18.1 illustrates impact between a head and large plate which can be categorized as blunt impact. In these cases, either the plate can contact the head or the head can be dropped onto the floor or other stiff surfaces. Note that the head is free to move.

Focal impact: Impact between the head and an impactor is termed a focal impact when the size of the impactor is smaller than that of the head. This is shown in Figure 18.2. Note that the head is free to move.

In blunt, focal, and dynamic–restrained impact, injury severity is directly related to mass of impactor, velocity of impactor, and stiffness of impactor. In clamped loading, injury severity is directly related to stiffness of loading system (*red* rectangle in Fig. 18.3), the degree of fixity of the head (stiffness of restraining system – *blue* rectangle in Fig. 18.3), and the load applied.

Inertial injuries: Shearing inertial injuries are caused when the head is exposed to angular acceleration by shaking. This type of loading is illustrated in Fig. 18.4. Severity of injury under purely inertial loading (Fig. 18.4) is directly related to the level of acceleration, viz., the higher the angular acceleration, the higher the injury severity.

In very broad terms, qualitative biomechanical analysis of pediatric head trauma directs the forensic pathologist to work backward – from injury to required history – by answering the following sequential questions: (1) What are/were the child's specific primary cranial injuries? (2) What specific injury mechanism(s) are required to explain each of these primary cranial injuries? and, (3) Are these required injury mechanisms clearly or reasonably evident in the caregiver's account of the child's head-injury event? If not, fatal abusive trauma (or homicide) must be considered.

Begin your analysis by reviewing the relevant clinical and historical data. Conduct a comprehensive forensic autopsy using age-appropriate protocols.

Table 18.1 Primary injury classification based on injury mechanisms

Category	Injuries	Cause
Primary *non-penetrating* cranial injuries requiring *contact* mechanisms of injury illustrated in Figs. 18.1, 18.2, and 18.3	• Facial and scalp soft tissue injuries • Subgaleal hematoma • Cephalohematoma • Skull fracture(s) • Epidural hematoma • SDH, SAH, or focal brain distortions or injuries more likely resulting from skull deformation than from cranial acceleration or deceleration (e.g., localized or focal SDH, SAH, or brain distortions underlying the impact site or skull fracture)	• Blunt or focal impacts to head at low impact velocity (Figs. 18.1 and 18.2) with impactor stiffer than head. Either impactor hits the head or the head hits a stiffer object • Or crushing or clamping of head (Fig. 18.3)
Primary cranial injuries requiring *inertial* mechanisms of injury illustrated in Fig. 18.4	• Acute encephalopathy or LOC resulting in brief concussion • Acute encephalopathy or LOC resulting in more prolonged loss of consciousness or traumatic coma • Diffuse primary brain injuries (e.g., diffuse axonal injury) • SDH, SAH, or focal brain distortions more likely resulting from cranial acceleration than from skull deformation (e.g., SDH from torn bridging vein(s), craniocervical injuries with associated acute cardiorespiratory compromise)	• Linear or angular acceleration of the head caused by whiplash or shaking (Fig. 18.4). Head makes no contact with external object
Combined *contact* and *inertial* injuries	• A combination of injuries in Rows 1 and 2	• Blunt or focal impacts to the head at high velocity (Figs. 18.1 and 18.2) with impactor stiffer than the head. Either impactor hits the head or the head hits a stiffer object like the floor • Shaking or whiplash with impact (Fig. 18.4) • Head free to move

SDH subdural hematoma, *SAH* subarachnoid hemorrhage, *LOC* loss of consciousness

Compile a complete list of the child's primary cranial injuries. Thereafter, refer to Table 18.1, Rows 1 and 2, Column 2, which list primary cranial injuries resulting from contact and inertial [non contact] events. As this table indicates, injuries caused by head contact are different from those caused by inertial effects. This process will result in one of three "biomechanical" possibilities: (1) The child's primary injuries demonstrate that he/she likely experienced *isolated contact* injury mechanisms illustrated in Figs. 18.1, 18.2, and 18.3; (2) the child's primary injuries

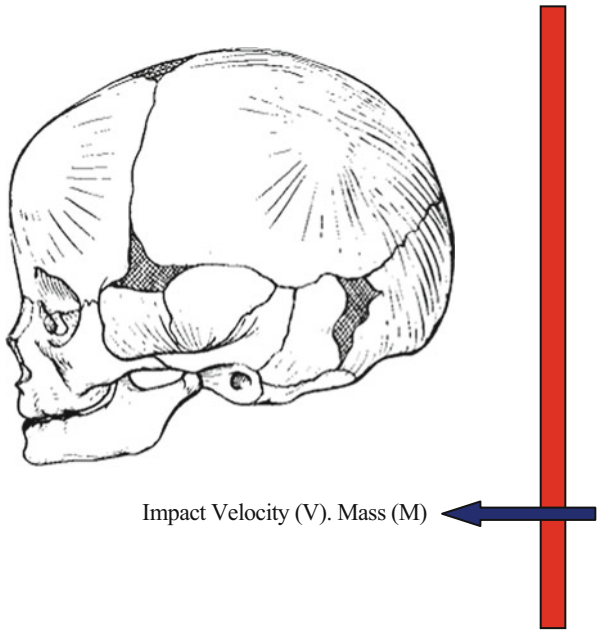

Fig. 18.1 Blunt impact (between a plate (*red rectangle*) and head)

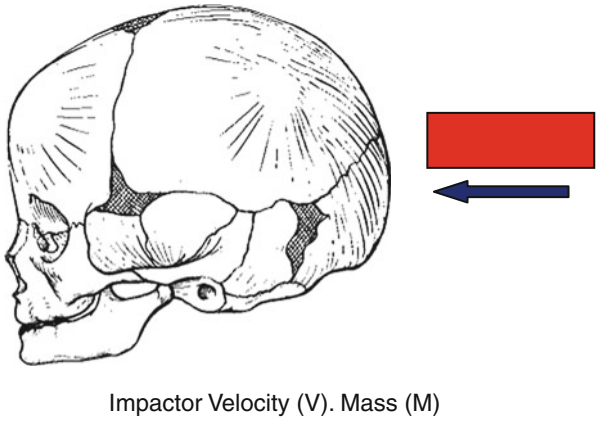

Fig. 18.2 Focal impact between head and impactor (*red rectangle*)

demonstrate that he/she likely experienced *isolated inertial* injury mechanisms, illustrated in Fig. 18.4; or (3) the child's primary injuries demonstrate that he/she likely experienced *combined* contact and inertial injury mechanisms.

Having sorted your case into one of these three "biomechanical" categories, refer to Column 3 of Table 18.1 to identify the specific loading or impact

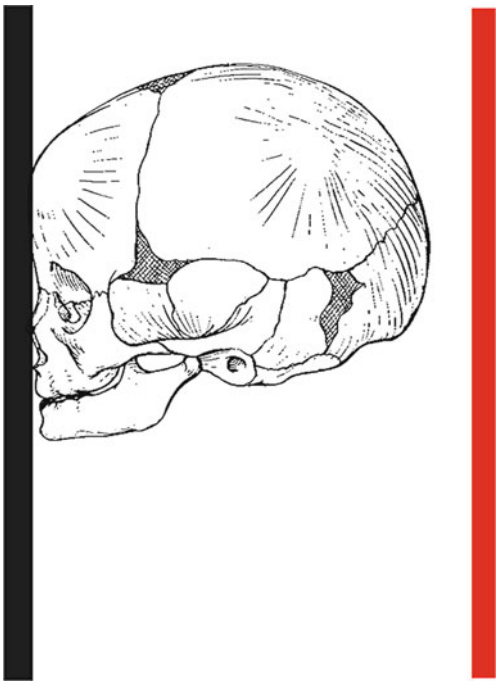

Fig. 18.3 Dynamic-restrained impact when head is restrained (by *black rectangle*) and impacted by impactor (*red rectangle*) or clamped when impactor velocity is zero

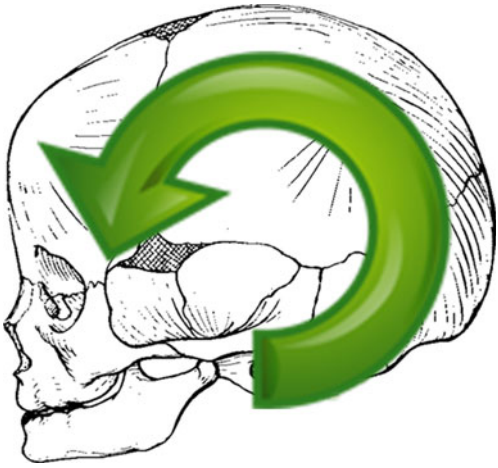

Fig. 18.4 Purely inertial loading through shaking (*green arrow*) or whiplash

circumstances required to produce your victim's isolated contact, isolated inertial, or combined (contact and inertial) injury mechanisms. Finally, interpret the plausibility of the caregiver's account of the child's head-injury event in light of these specific, required biomechanical circumstances.

Are the required biomechanical circumstances and injury mechanism(s) clearly or reasonably evident in the caregiver's account of the child's head-injury event? If not, fatal abusive trauma – or homicide – must be considered.

Use of Biomechanical Models to Assess Injury

There are two important tools that biomechanical engineers use to understand problems of impact. The first is the use of cadavers (whole cadavers or isolated tissues) to develop data on injury-tolerance data and injury risk. Cadaver tests provide the primary data from which all dummies and models are developed. The second is the development and use of biofidelic dummies which respond dynamically in a "human-like" fashion to impact. Paralleling the efforts to develop dummies are efforts to develop biofidelic mathematical models, either finite element (FE) or lumped mass models.

Child Cadaver Testing

Cadaver tests allow engineers to seek answers to questions about injury tolerances. Examples of such questions include the following: "From what height will a child of a given age and weight fall before sustaining a skull fracture?" Or "What kind of shaking or impact will cause brain injuries?" Ethical and societal concerns inhibit the availability of child cadavers and tissues. This means that biomechanical engineers cannot develop relationships between insults (such as the height of fall or frequency of shaking) with injuries (such as skull fracture or brain injury) to quantify the risk of injury.

Up until now, only two series of cadaver tests have been conducted, one by Weber (1985) and one by Prange et al. (2004). Weber dropped 50 child cadavers ranging in age from newborn to about 8 months from a fixed height of 82 cm onto various types of surfaces such as tiled floor and carpeted floor. He observed linear fractures, some of which crossed suture lines, in all cadaver heads dropped onto tile floors and in a majority of heads dropped onto thinly carpeted rigid floors. Weber did not publish a number of experimental details, including how long the cadavers were stored or how they were stored. In addition, the cadavers in his tests were not instrumented. While the experiments indicated that dropping a child cadaver onto a stiff surface can cause a linear skull fracture, they could not indicate if the injury would have been life-threatening to a living child or what fall heights would cause a child to sustain a serious head injury. Because of a lack of instrumentation, these tests did not quantify the response of the cadavers.

Prange et al. dropped the heads of three neonates (newborn to 11 days old) onto rigid plates from 15 cm and 30 cm and recorded the acceleration response of the heads (Prange et al. 2004). The authors chose these two drop heights so as not to

cause fracture. Thus, while these tests quantified very useful information, they did not provide injury-tolerance information since no fractures were produced.

It has not been possible to conduct tissue tests in numbers large enough to develop an understanding of the material properties of tissues of infants and small children. Cadaver and tissue tests are vital to the success of efforts to build dummies or mathematical models. Detailed data from whole-cadaver tests are used to validate dummy and model response and judge their biofidelity or the degree of human-like response. Data from tissue tests are vital to the design of parts of both dummies and models. Given this, it is clear that biomechanical engineers are greatly limited in their efforts to understand child skull and brain injury to date.

Child Dummy and Model Design

Construction of a biofidelic child dummy requires several types of data, including data on anthropometry of children (sizes and shapes at each age), mass of body segments, moments of inertia of body segments, location of center of gravity of body segments, impact response of body segments, material properties of various parts of the body, fracture tolerance, and brain injury criteria. Much of this data is not known for infants and children. This has made it difficult to build biofidelic child/infant dummies or FE models, although several such dummies and models are available. Problems with these models are listed below:

1. FE models have been created using *estimated* values of child-tissue properties even though the process for estimating these properties is evolving. These models have generally been designed by academics as research tools.
2. Models have been used to simulate known automobile accidents where children were injured. This information has then been used to develop estimates of injury thresholds (Desantis Klinich et al. 2002). Automotive accidents are complicated events, however, and it is inadvisable to use simulation to provide anything but a tenuous guideline to the relationship between input variables and injuries. Authors of these papers generally advise against using the threshold and injury risks developed by them, but many expert witnesses choose to disregard these cautionary notes. It was not possible to compare these model results with cadaver test data because none are available.
3. Researchers have developed infant dummies with "human-like" response properties, but there are no human response properties available to compare with the response of these dummies (Coats and Margulies 2008). The response of these dummies has been related to Weber's cadaver tests, and some conclusions have been drawn about injury thresholds. It is unknown, however, if the dummies' heads are human-like in response.
4. In the 1990s, child dummies were developed to evaluate the safety of child seats, and these dummies may or may not include all anatomically important parts. Injury thresholds for these dummies were scaled down from adult dummy threshold values, but the validity of the scaling procedures is in doubt.

Is It Reasonable to Use a Crash Test Dummy to Model the Injuries Sustained When an Infant Is Shaken?

Before a dummy can be used in any test, the following conditions must be met:

1. Size, shape, total mass, mass distribution, and location of center of gravity of dummy segments (anthropometry) of the dummy should be close to the human it is supposed to model.
2. The dummy should be capable of providing "human-like" response under the proposed experimental conditions. Ideally, the dummy should be calibrated such that its responses are close to the expected response for the proposed loading conditions. For example, Irwin and Mertz (Irwin et al. 1997) developed the CRABI 6 and CRABI 12 infant dummies to evaluate the interaction between infants seated in the front seats of cars and airbags deployed during car crashes. They mention that for their CRABI 6 and CRABI 12 infant dummies, their scaled data from adult dummies is to be used only for specific impact conditions. They point out that the CRABI head response is reasonably human-like only for impact with padded surfaces and may not be suitable for hard impact. Still, these dummies are frequently used in court cases to model injuries from fall to hard surfaces.
3. When a biofidelic dummy is developed, a set of "injury assessment reference values" (IARV) will also be developed for that dummy. The relationship between the test variables measured by the dummy and human injury must have been established for the proposed experimental protocol. Since human injury criteria have not generally been established for infants and young children, IARVs may not be accurate.

Some engineers have used the CRABI dummies to simulate injuries to infants caused by violent shaking (Lloyd et al. 2011). These dummies have been designed for use in controlled experiments to evaluate if a vehicle passes a given regulatory test. Various parts of the dummy have been designed to provide "human-like" responses for a limited number of test variables under specific conditions. They are not biofidelic under all test conditions and under all ranges of impacts. They are not a perfect model of a human.

In an adult dummy (the Hybrid III 50th male dummy), it has been shown that while the dummy accurately models the response of the human head and neck in frontal crashes, its response was not "human-like" under other test conditions such as rear-end crashes (Philippens et al. 2002). If one were to shake a Hybrid III dummy, the response of the head and neck system could be very different from that of a human of about the same anthropometry. Since the CRABI dummies have been scaled from the responses of the Hybrid III dummy, it can be argued that the CRABI dummies are likely to respond inappropriately in tests where the dummies are shaken.

In addition, some of the details of the construction of the CRABI dummy would prevent it from responding like a human baby when shaken. The dummy has a central cable in its neck that prevents the neck from stretching and limits its

rotational movement. The dummy has no atlanto-occipital (AO) joint. The head is bolted to the top of the neck, leading to an incorrect coupling of masses, an incorrect center of rotation for head/neck motion, and a very stiff neck.

Yoganandan et al. (2011) studied ossification patterns in infant spines. They found that cartilaginous joints (synchondroses) are often present in the top three vertebrae of infants and children. For example, there is a 50 % probability of finding one cartilaginous joint at C1 level at the age of 7.57 years. Vertebral ossification in the neck of a child and infant is directly related to strength and spinal stability. Ossification proceeds from the bottom up, and this means that the support provided to the head from the higher vertebra is not at full strength till the child is almost 8 years old. This ossification pattern has profound effect on the strength of an infant's neck and its ability to support the head when the head is moved rapidly.

Currently used child dummy necks are designed using scaling strength requirements from adult dummies. Adult dummies represent adults whose neck vertebrae are fully ossified. So, the process of scaling strength requirements is liable to result in a child dummy neck which is considerably stiffer than a real child's neck. The stiff neck of the CRABI dummy does not reflect the reality of the construction of the necks of infants and young children. In addition, neck strength differs markedly between children of different ages, making it difficult to measure the strength of any individual child's neck using a dummy.

Is It Reasonable to Use a Crash Test Dummy to Model Head Injuries Resulting When Infants and Young Children Fall?

Crash test dummies are designed to be used as a "go-no go" tool in the automotive industry. Automobiles that fail crash test dummy tests are not allowed to be marketed. Crash test dummies are biofidelic around response levels at which they are calibrated. As an example, the Hybrid III 50th percentile male head is biofidelic in mass, moment of inertia, location of the center of gravity (CG), and impact response against a rigid surface when it is dropped onto a rigid plate from a distance of 367 mm. The linear acceleration at the CG of a calibrated head lies between 250 and 275 G. The human head exhibits linear fracture around this level of linear acceleration when impacted against a rigid surface. However, once the loading conditions cause much higher or lower linear accelerations, the dummy head may not be biofidelic. For various reasons the dummy head does not fracture like the human head. The process of fracture enables the head to release energy and also attenuate the acceleration response.

A crash test dummy, like a human body, consists of several segments which are connected together at the joints. But a dummy is a passive device and cannot be used to mimic any defensive action that a human will take to reduce injury while falling. Thus, a dummy falls like a dead weight. Even drops onto soft surfaces like carpet yield fairly high head angular accelerations, thus falsely indicating the probability of injury even from short falls. There are extensive indications from peer-reviewed articles that fatalities and severe injuries are

rarely seen as a consequence of short falls (Chadwick et al. 1991, 2008; Foust et al. 1977; Fujiwara et al. 2010; Haney et al. 2010; Lyons and Oates 1993; Plunkett 2001; Reiber 1993; Tarantino et al. 1999; Thompson et al. 2011; Wang et al. 2001; Williams 1991).

There is no prescribed IARV for head angular rotation for the CRABI or any other dummy for shaking or impact. In 2003, Prange and colleagues wrote, "Although the anthropometric dummy test data are useful to evaluate the rotational response of the head caused by falls and inflicted injury events, the results of the dummy tests cannot be used to predict whether such rotations are sufficient to cause injury. Regional tissue thresholds specific to the infant would be required to predict injury on the basis of local intracranial stresses or strains produced by the rapid rotations. These thresholds are currently unavailable for the pediatric population" (Prange et al. 2003).

Prange et al. (2004) conducted drop tests of human infant heads and CRABI 6-month heads onto rigid platforms and plotted resultant linear acceleration of the head of each infant head and the CRABI dummy. Dummy and infant heads were dropped from 15 cm and 30 cm heights. Their results indicate that the CRABI 6 head response was quite close to infant head response in occipital impacts but differed from the human infant response when the forehead or the vertex made first contact. In parietal impacts, the CRABI response was much stiffer than that of the human infant. So, if a CRABI 6 dummy is dropped and there is involvement of the parietal region, it is likely that the linear acceleration of the dummy will be much higher than what would be seen when an infant head is dropped from the same height. Therefore, it is hard to relate CRABI 12 responses to human responses without additional data.

While a dummy might look and sometimes feel like a human, it is a passive device designed to be used under well-defined conditions. Response of a dummy in well-controlled tests can be related to human injury for regulatory purposes where a safety device or a vehicle is said to either pass or fail a test. While it seems to make intuitive sense, it is very difficult to relate CRABI dummy response to human injury. A considerable amount of human impact data are needed to relate the response of dummy heads to injuries.

An Evaluation of the Literature Dealing with Injury Potential When Shaking an Infant

Duhaime et al. (1987) concluded that shaking alone in an otherwise normal baby is unlikely to cause the "shaken baby syndrome." The authors compared the angular acceleration response of their model with the response obtained in animal experiments. Threshold values for angular acceleration and other responses of the animal model were scaled to adult and pediatric human population using mass scaling alone. In the animal experiments the authors used for comparison, the test subjects were exposed to a single, short-duration, whiplash-like impulsive loading. This type of loading is self-evidently very different from the repetitive, long-duration, impulsive loading seen in shaking.

Ommaya et al. (2002) reviewed the 1997 report of Pounder (1997) and wrote, "The reality of fatal brain damage by repeated shaking of the larger adult brain and sustained over repetitive significant periods has been well documented recently in an adult Palestinian who died after repeated and sustained violent shaking in 12 sequential sessions by Israeli interrogators of the Shin Bet without (*external*) evidence of head injury. Autopsy findings discovered acute subdural haematoma, retinal haemorrhages and extensive soft tissue bruises in the shoulders and pectoral muscles. Similar severity and repeated episodes of shaking in children could also result in fatality with similar neuropathology lesions, e.g., acute SDH and retinal haemorrhage with soft tissue bruises, as well as skeletal injuries at higher levels of shaking force based on the inverse relation to the head mass. Damage to the neck and the spinal cord analogous to our experimental findings is also to be expected." It is possible that the last conclusion about neck injury may be related to the authors' opinion that very high head angular accelerations are needed to cause injuries to brains from shaking. However, it is possible that the Palestinian man in this case may not have been shaken hard enough to cause very high head angular accelerations, and sequential, repetitive episodes of shaking might have caused the injuries observed. This view is supported by Ommaya's own conclusion regarding the need for larger animal models.

Ommaya et al. (2002) also discuss the experiments of Smith et al. (1998) who tried to develop animal models for SBS using rats. Smith could produce SBS-like symptoms in rats that had been severely shaken only if hypoxia was introduced by hanging the rats upside down. Ommaya indicated that a large animal model is needed to correlate biomechanical test parameters and pathology caused by repetitive and prolonged shaking. Such a model is also required to evaluate the cumulative effects of repeated shaking episodes over time.

Since Duhaime published her work (Duhaime et al. 1987), other researchers have evaluated the validity of her model. In 2003, Cory and Jones (2003) attempted to reproduce Duhaime's results. They reported that the dummy used by Duhaime was not biofidelic in that it did not include features such as an atlanto-occipital joint where the neck is connected to the head and which allows a great deal of free motion of the head in infants. They constructed an adjustable dummy with a higher center of gravity, padded back and chest, and a hinge neck. The model was not biofidelic, but it showed that minor changes in the anthropometry and response characteristics of the model could cause major changes in the measured angular accelerations.

The human body is a very complex system consisting of geometric features and materials whose response and tolerance limits might depend on interior geometry, loading rate, and loading duration. The work of Thibault and Margulies (1998) indicates scaling based on brain mass alone might not be appropriate. They conducted tests on porcine brain tissue and found that elastic and viscous behavior of porcine cerebral tissue changed markedly with age. Based on their findings, the authors suggest that age-specific and loading-specific head injury thresholds need to be developed to quantify the injury threshold of infants with their compliant skull. It is also noteworthy that geometric differences between the infant and adult skull and contents might also necessitate development of age-specific tolerance limits.

In her Ph.D. dissertation, Coats reported on drop tests conducted with a biofidelic dummy representing a 1.5-month-old infant (Coats 2007). The dummy was dropped onto concrete, carpeted surfaces, and a mattress from heights of 0.3, 0.6, and 0.9 m. She found that the peak angular acceleration and peak-to-peak change in angular velocity decreased significantly when compared with responses previously reported by Prange et al. (2003). Coats reported that peak angular acceleration and peak-to-peak angular velocity decreased (36 % and 88 %) and time duration increased between 13 % and 77 % when compared to the results of Prange's experiments for AP direction. She based the differences between her results and those of Prange on several factors. The dummy neck in her study was hypermobile and capable of motion in all three planes. The dummy that Prange used had a hinged neck. The neck of the dummy she used was less stiff than Prange's. The head of Coats' dummy was more deformable than the head of the dummy used by Prange. The extremities of her dummy were more realistic in the distribution of body weight.

In her study, Coats compared dummy-head angular accelerations with available data from adult primate and human studies (Coats 2007). She scaled head angular acceleration and angular velocity of nonhuman primate studies to a 6-week-old infant with a brain mass of 430 g. The highest resultant angular acceleration of all the dummy drops onto all surfaces from all heights was 20 % lower than the lowest angular acceleration causing concussion and over 50 % lower than the lowest angular acceleration causing diffuse axonal injury or acute subdural hematomas. She cautioned that since no nonhuman primate studies have been conducted at the *low* angular accelerations seen in her study, she was unable to determine if drops similar to the dummy drop tests would cause concussion, diffuse axonal injury, or acute subdural hematoma. She cautioned against using the data from her tests to develop injury measures and threshold corridors because of paucity of biomechanical data on infants and young children.

Conclusion

In summary, biomechanical modeling is very useful in the ongoing advancement of our knowledge of human infant head injuries. The current models are limited by a paucity of basic science data on the biomechanics of human infant tissues at various stages of development. Overall, the current state of biomechanical modeling does not justify reaching forensic or legal conclusions regarding the head injuries of infants and young children.

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Ocular Findings in Pediatric Inflicted Injury 19

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Abstract

The ocular findings in abusive head trauma are well-documented and recorded in the literature. Increasingly, the examining ophthalmologist has come under scrutiny to defend the nature and pathophysiology of these retinal findings in a legal setting.

This chapter provides an overview of the epidemiology and associations of the retinal hemorrhages (RHs) observed and their pattern of distribution, nature, and morphology. A specific type of hemorrhage, the retinoschisis lesion, which is recorded more often in abusive head trauma than in any other scenario, is discussed in greater detail. Possible etiologies and theories as to the underlying pathophysiology are discussed with a comprehensive review of the scientific literature. Differential diagnoses are also outlined.

A comprehensive guide to examination and recording of the presence of retinal hemorrhages is provided, along with a discussion of various grading systems used for these hemorrhages in the literature.

Introduction

Pediatric abusive head trauma (AHT) is a significant social problem and was first highlighted in the scientific literature in the 1960s (Kempe et al. 1962), although one of the first descriptions harks back to the 1920s (Alkman 1928). In 1971, Guthkelch described a form of pediatric head trauma as a syndrome characterized by intracranial hemorrhage and intraocular bleeding together with characteristic findings and deemed this was due to repetitive acceleration–deceleration forces, with or without blunt head impact. Caffey later coined the term "Whiplash shaken impact syndrome" (Caffey 1972, 1974) to refer to this scenario, which became known as the shaken baby syndrome. Isolated cases in the literature prior to this date suggest that this was not

a new syndrome, but the recognition of the constellation of signs and symptoms that had previously gone unrecognized. A paper by Hollenhorst et al. in 1958 clearly describes these signs in 47 infants with an average age of 6 months (Hollenhorst and Stein 1958). Symptoms included convulsions, vomiting, an enlarging head, paralysis, spasticity, and stupor. A history of trauma (not described) was given in only 23 cases. "Intraocular bleeding frequently was massive." "An intracranial procedure" found subdural bleeding or "hygroma" in 37 cases, and "examination of the cerebrospinal fluid" found subarachnoid hemorrhage in 10. Seven died. No skeletal surveys and no autopsies were reported. The description mirrors the many cases of inflicted head injury published in the last 25 years. Had Hollenhorst and coauthors access to current technology, it is highly likely that many of these infants would have been found to have been the victims of child abuse.

Since the publication of Caffey's papers (Caffey 1972, 1974), a solid evidence base has been created examining the likely associations, exclusions, differential diagnoses, and postulated mechanisms underlying the association of retinal hemorrhages (RH) in abusive head trauma. Outliers do exist, and these will also be discussed.

Terminology

The term "shaken baby syndrome" (SBS) has been and continues to be frequently used, particularly in the ophthalmic literature, but will not be used in this chapter as it may be suggested that this entity does not exist. This suggestion is centered on two pieces of evidence. Firstly, in many (if not most) cases of AHT, evidence of impact to the head may be found, and secondly, that the biomechanical forces generated by impact are significantly greater than the forces predicted to result from shaking alone (Duhaime et al. 1987; Prange et al. 2003). These pieces of evidence stand in contrast to the data from perpetrator confessions which suggest that shaking alone can indeed cause the injuries seen in AHT (Biron and Shelton 2005; Starling et al. 2004), although these data have been challenged (Leestma 2005, 2006). As sufficient evidence suggests that shaking is not the only mechanism capable of causing such RH, and that impact alone may suffice, the possibility of impact can never be excluded in a case of so-called SBS. It is therefore preferable to use a term which does not limit the diagnosis of non accidental injury to one particular mechanism. Preferred terminology includes abusive head trauma (AHT), inflicted traumatic brain injury (ITBI), or non accidental injury or head injury (NAI/NAHI) (Reece 2008).

Epidemiology

In the United States (USA), it is estimated that child abuse victims constitute 1.7 % of all children hospitalized for physical injury (Bullock et al. 2009). Of these, it is thought that 1,200–1,400 are victims of abusive head trauma due to repeated acceleration/deceleration with or without head injury (Newton and Vandeven 2005).

In New Zealand, AHT has an estimated annual incidence of 15–20 per 100,000, with a higher incidence reported in the indigenous population, the Maori, up to 33–39 per 100,000 (Kelly and Farrant 2008; Kelly et al. 2009). In Scotland, a prospective population-based study estimated an annual incidence of AHT of 24.6 per 100,000 children younger than 1 year (median age 2.2 months) (Barlow and Minns 2000).

An American study demonstrated the three strongest demographic predictors of coded child abuse were as follows: age younger than 1 year (Adjusted relative risk (RR) 11.46), age 1 to younger than 2 years (RR 3.07), and Medicaid as primary payer (RR 1.99) (Bullock et al. 2009). This study also showed a higher presentation during winter and on weekdays. The Scottish study demonstrated that AHT was more common in urban regions and also during autumn and winter months (Barlow and Minns 2000). Some of the most recognized risk factors for abuse are poverty and stress (Kotch et al. 1995); AHT is increased following natural disasters (Keenan et al. 2004) and is associated with combat-related deployment in military families (Gibbs et al. 2007). A recent study looked at unemployment rates and demonstrated that the rate of AHT increased from 8.9 per 100,000 prerecession to 14.7 per 100,000 during the recession (Berger et al. 2011). These findings add credence to our understanding of the effects of stress on violence.

Clinical Features

The appearance of RH in AHT in children is often characteristic and best observed through dilated fundal examination. The hemorrhages are typically too numerous to count, and they are present in multiple layers of the retina (preretinal, intraretinal, subretinal). The layer in which the hemorrhage occurs generally determines its morphology – dot, deep blot, flame (Fig. 19.1).

Blood within the retinal layers (intraretinal) can be further categorized as superficial and deep. Blood in the superficial layers streams between the individual ganglion cell nerve fibers of the nerve-fiber layer giving the characteristic "flame" hemorrhages. Deeper within the retina, the hemorrhages form dots or larger blots. More superficial RH obscure the retinal blood vessels, while deeper RH can be seen underneath the retinal vessels.

Subretinal blood lies under the retina. Preretinal or subhyaloid hemorrhage is in front of the internal limiting membrane, that is, in front of the retina, but behind the vitreous gel (hyaloid) (Levin 2010) (Figs. 19.1, 19.2, and 19.3).

The RH in AHT often extend to the periphery, which anatomically is the ora serrata, usually visualized by indentation (Fig. 19.4). This pattern and distribution of RH is described as occurring in 51–100 % of AHT (Bhardwaj et al. 2010a) and in an average of 75 % and 82 % of autopsy cases (Bhardwaj et al. 2010a). The findings may be asymmetrical (Figs. 19.5 and 19.6) and even unilateral in 20 % (Arlotti et al. 2007) (Fig. 19.7), but with the described characteristics, they are highly specific for AHT. However, RH do not exist in isolation but in conjunction with other signs in a clinical context (Figs. 19.8 and 19.9).

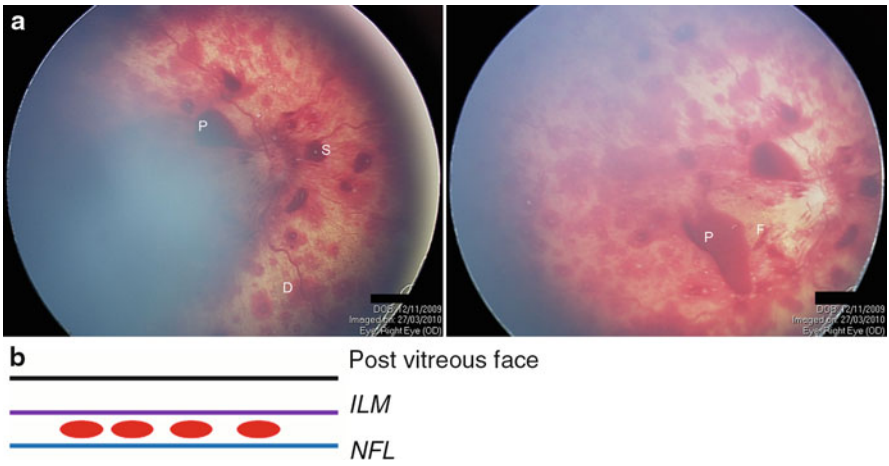

Fig. 19.1 (**a**) Bilateral retinal hemorrhages (RHs) in AHT involving all layers of the retina, *P* preretinal, *S* superficial, *D* deep, *F* flame. (**b**) Diagram demonstrating the relationship between the posterior vitreous face, which in infants is firmly adherent to the inner limiting membrane (*ILM*), which in turn overlies the retinal nerve fiber layer (*NFL*). The *red ovals* here demonstrate the position of blood as would be seen in hemorrhagic retinoschisis

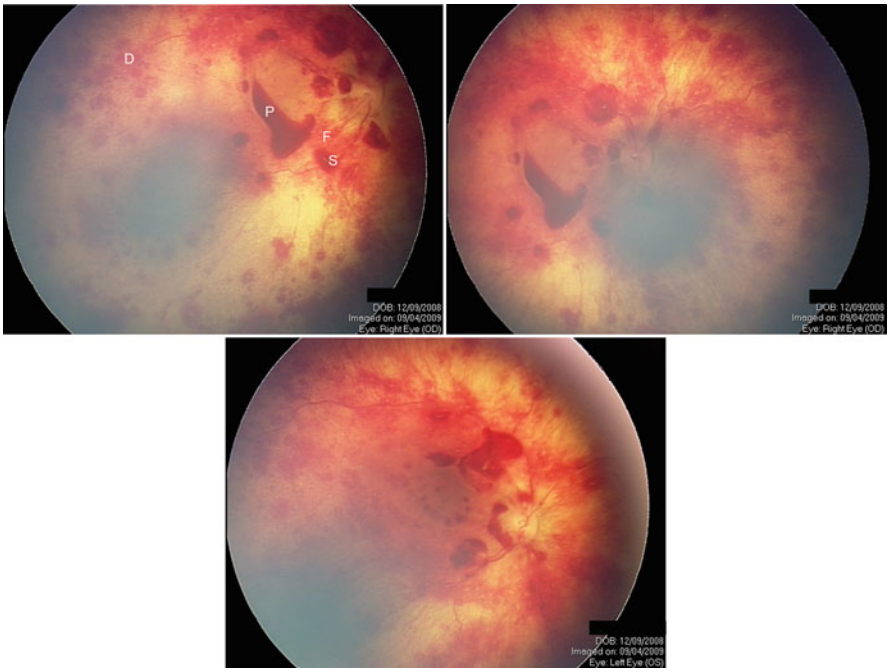

Fig. 19.2 Bilateral RHs in AHT involving all layers of the retina, two images of right eye, and one of left eye. Deep hemorrhages have retinal blood vessels overlying them, although these blood vessels are obscured by more superficial hemorrhages. *P* preretinal, *S* superficial, *D* deep, *F* flame

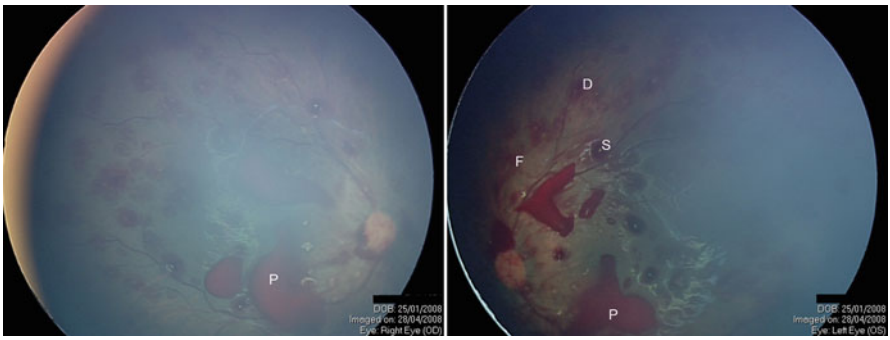

Fig. 19.3 Bilateral RHs in AHT involving all layers of the retina. *P* preretinal, *S* superficial, *D* deep, *F* flame

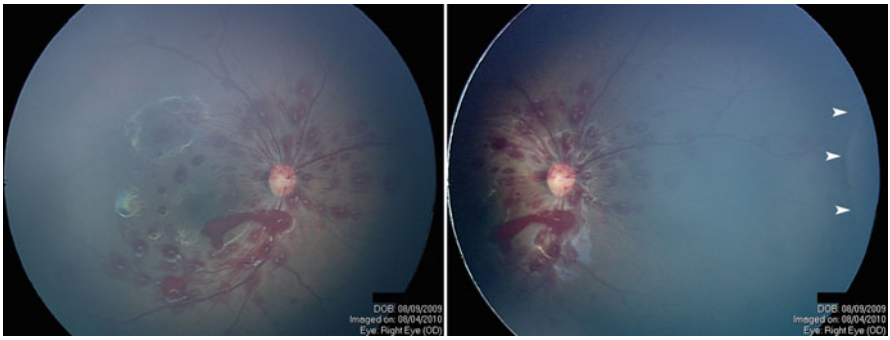

Fig. 19.4 Two images of the right eye, with one showing the periphery with indentation (*arrowheads*). Although on the first photograph it would appear the RH are limited to the posterior pole, it is clear they extend to the periphery

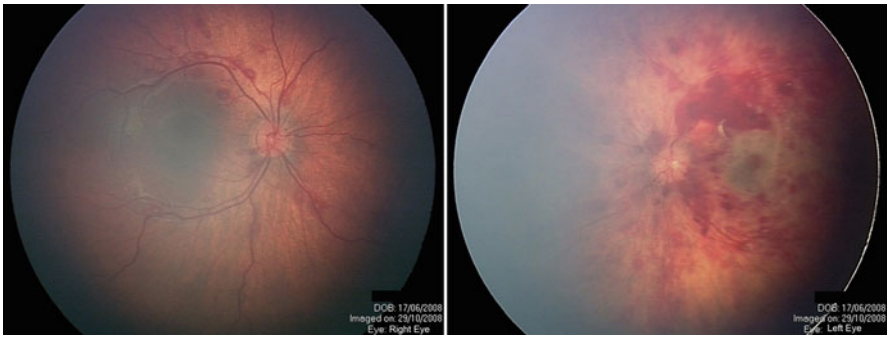

Fig. 19.5 Bilateral RH, showing asymmetry with the left eye more severely affected than the right eye

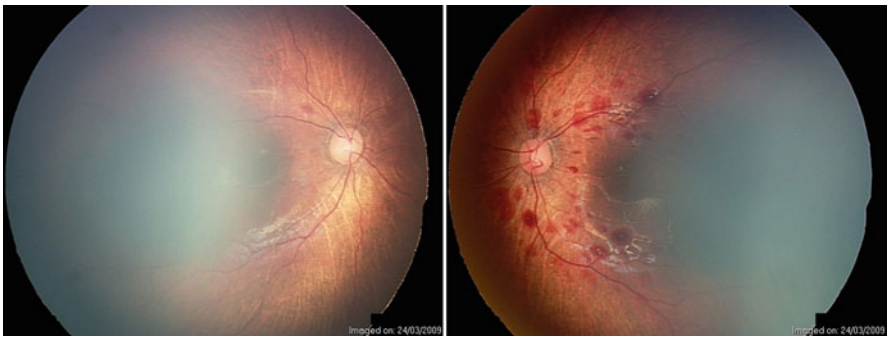

Fig. 19.6 Bilateral RH, showing asymmetry with the left eye more severely affected than the right eye

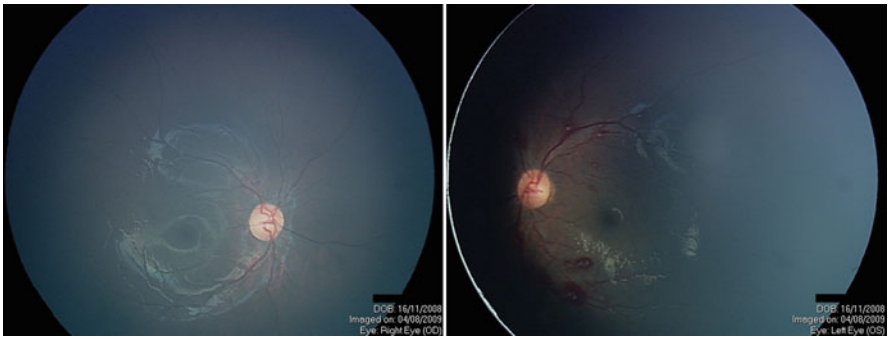

Fig. 19.7 Unilateral RH, no RH are present in the right eye

Evidence of external injury is often absent (Bechtel et al. 2004; Feldman et al. 2001; Jenny et al. 1999). Characteristically there is no evidence of direct ocular trauma – that is, no periorbital bruising, lid swelling, or lacerations; the eyes are white, and the anterior segment examination unremarkable.

Another form of RH highly characteristic of AHT is macular retinoschisis (splitting of the retinal layers), which results in a dome-shaped hemorrhage at the macula, sometimes associated with traumatic macular folds (Figs. 19.10 and 19.11). Recent reports suggest that this lesion may rarely result from crush and other severe injuries (Lantz et al. 2004; Lueder et al. 2006; Reddie et al. 2010; Watts and Obi 2008); however, the common denominator is likely to be a significant force impacting directly or indirectly on the infant retina. Retinoschisis is discussed in further detail below.

In reported cases of confirmed child abuse where the perpetrator confessed (Biron and Shelton 2005; Starling et al. 2004), the retinal findings are consistent with the findings described above.

The other non ocular findings observed in AHT are beyond the scope of this chapter, but it cannot be overemphasized that RH do not exist in isolation but in

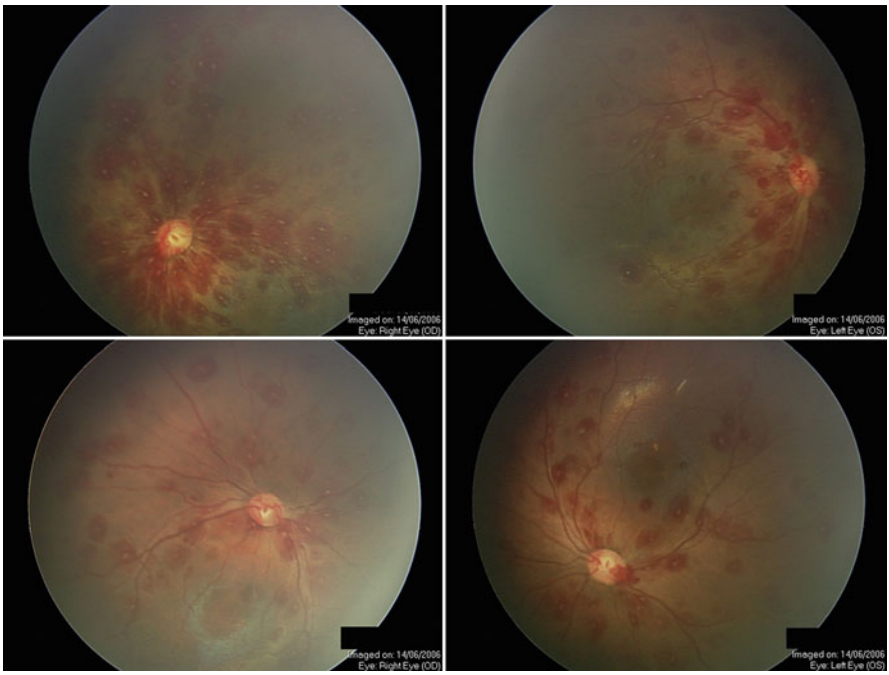

Fig. 19.8 Bilateral RH in twins; twin 1 above, twin 2 below. Both twins died at age 3 months of their injuries which included rib fractures and brain injury

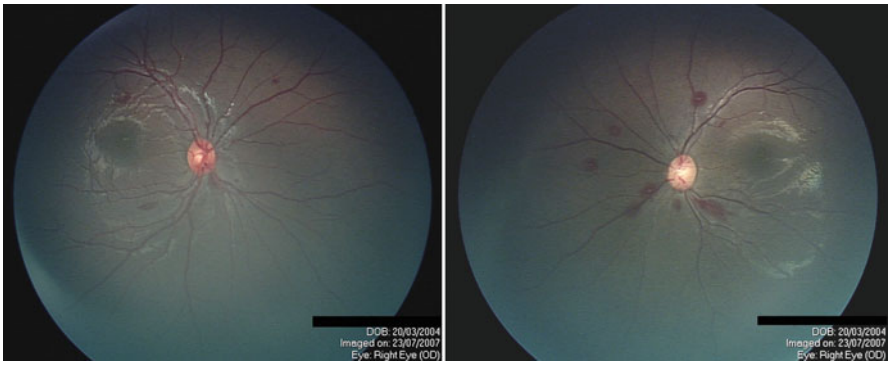

Fig. 19.9 Bilateral RH in a 3-year-old who died from her injuries, which included extensive systemic evidence of abuse. The RH seen in a 3-year-old may differ from an infant as the elastic fibers in the sclera are much more modifiable from 5 months of gestation to the age of 3 years, permitting more deformation with acceleration

a context. The major non ocular feature is intracranial injury, resulting in subdural hemorrhage (SDH) and/or cerebral edema. It is thought that this bleeding comes from tearing of bridging veins as they cross from the brain to the dura, precipitated by very forceful acceleration and deceleration of the head (Case 2008).

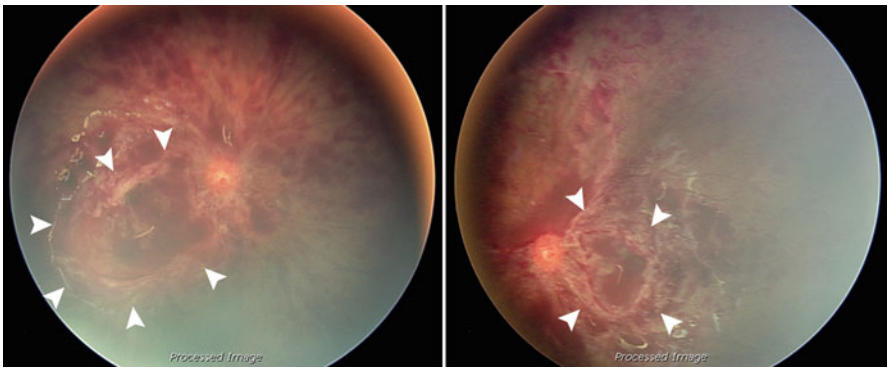

Fig. 19.10 Bilateral traumatic macular retinoschisis (delineated by *arrowheads*)

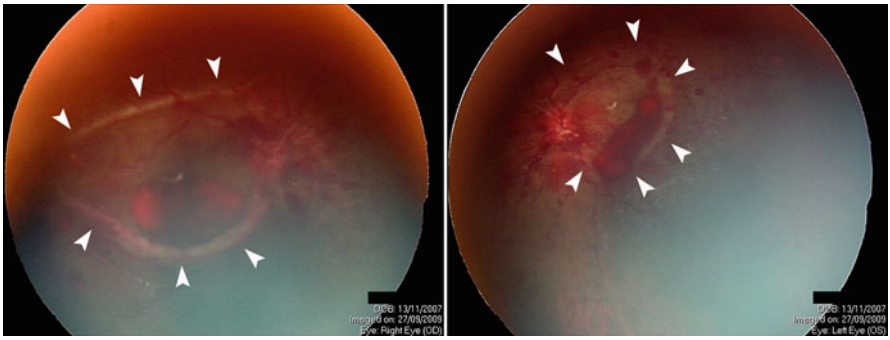

Fig. 19.11 Bilateral traumatic macular folds (delineated by *arrowheads*)

In many cases, the subdural bleeding consists of a thin layer, often bilateral, which does not in itself have a mass effect on the underlying brain. It is recently suggested that in young infants with non traumatic subdural bleeding, the source may be the highly vascular dural plexus. It is unclear what, if any, relevance this has for the subdural bleeding seen in AHT.

A characteristic feature of AHT is the associated brain injury. AHT has a higher mortality and a higher morbidity than accidental head injuries associated with subdural bleeding (DiScala et al. 2000; Duhaime et al. 1992; Ewing-Cobbs et al. 1998; Hymel et al. 2007; Kelly and Hayes 2004; Reece and Sege 2000; Tzioumi 1998; Vinchon et al. 2005).

Up to 30 % of victims with AHT die, and of those that survive, more than 80 % demonstrate signs of significant and permanent neurological deficits including intellectual deficits, visual deficits and blindness, and motor impairment (Newton and Vandeven 2005; Barlow et al. 2005; Keenan et al. 2003). The reason for this difference in outcome is debated, and it is likely that hypoxia plays a significant role (Geddes et al. 2001). Some reports suggest a correlation between

the severity of acute neurological injury and the severity of RH (Morad et al. 2002; Wilkinson et al. 1989).

There may also be other characteristic features of child abuse such as old fractures detected on a skeletal survey, although often the injuries are restricted to the head alone. It is always important for the ophthalmologist to work in conjunction with the rest of the clinical team involved with the child. If possible, this should at least involve a pediatrician with expertise in child protection and in the differential diagnosis of AHT. Other important personnel might include a neurosurgeon, an intensivist, a pediatric radiologist with expertise in pediatric head injuries, a social worker with child protection expertise, and, in the event of death, the examining pathologist (Ewing-Cobbs et al. 1998). In this fashion, the presence, type, and distribution of the RH can be placed in the context of the other injuries present and a collaborative decision made as to whether the nature of the described trauma is or is not consistent with the injuries.

Examination Requirements and Techniques

When asked to examine a child with suspected AHT, it is vital to have a systematic approach with meticulous documentation of your clinical findings. Treat every case of suspected AHT as if you will be summoned to present your findings to a courtroom. To this end, the importance of clear and detailed documentation cannot be overemphasized.

The study of rate of disappearance of birth trauma–related retinal hemorrhages indicates that some superficial retinal hemorrhages can resolve after only a few days, while deeper hemorrhages may take many weeks to resolve (Baum and Bulpitt 1970; Kaur and Taylor 1992; Sezen 1971). Serial imaging of the retina in AHT has shown that severe RH can resolve over a period of a week (Vinchon et al. 2002).

For this reason, the child should be examined by an ophthalmologist as soon as possible after presentation and ideally within the first 24 h (Levin and Christian 2010). This should primarily be performed by a suitably experienced ophthalmologist, for example, any consultant ophthalmologist or experienced trainee ophthalmologist; however, the presence of RH requires corroboration, ideally by a consultant pediatric ophthalmologist, in view of the likely judicial involvement. If corroboration by a second examiner is not possible, fundal photography may be substituted.

Begin your examination by general examination of the ocular adnexae for signs of direct ocular trauma.

- Is there any bruising/edema/laceration to the eyelids?
- Look for subconjunctival hemorrhage and conjunctival edema (chemosis), bearing in mind that this can occur in ventilated patients due to exposure keratopathy. In the awake child, try to determine visual function.
- Can the child fix and follow an object? Do they object to occlusion of either eye or both eyes equally?

- Assess whether extraocular movements are normal.
  For all children, perform a comprehensive ocular examination.
- Examine the pupillary light responses for the presence of a relative afferent pupillary defect.
- Look for any corneal epithelial defects; for example, cigarette burns result in a well-circumscribed circular corneal burn; however, inferior epithelial defects and stromal opacification can occur due to exposure keratopathy in sedated/ventilated patients.
- Is there any evidence of intraocular injury such as hyphema, irregular pupil (such as in traumatic iridodialysis), inflammatory cells in the anterior chamber, phacodonesis/lens subluxation, or cataract?

Finally, complete fundal examination is performed, preferably with the binocular indirect ophthalmoscope (BIO), as the direct ophthalmoscope cannot visualize the peripheral retina. Either a 20 Dioptre (D) or 28D lens may be used, although a 28D lens will give a better view in the smaller infant. Pharmacological pupil dilation is preferred unless, in a severely injured child, the pupils are already fixed and dilated. Adequate pupillary dilation is usually achieved with 0.5 % cyclopentolate together with 2.5 % phenylephrine drops. Pupils must be well dilated; therefore, drops should be repeated if not adequately dilated. This is often necessary for pigmented irides. Problems arise when the care of the child requires pupil examination as part of their neurological observations. Although not ideal, in this situation it may be possible to dilate one pupil at time, with examination of the second eye the following day. It may also be possible to use a shorter-acting mydriatic agent such as phenylephrine without cyclopentolate. Fundal examination through the undilated pupil may be possible with the small pupil setting on the binocular indirect ophthalmoscope, although this will not allow visualization of the peripheral retina so is the least preferable option. In this situation, a further examination should be performed at the earliest time possible once pupillary dilation will not compromise critical care of the child.

As the RH of AHT are typically described in the posterior pole and peripheral retina, examination of the peripheral retina is vital (Bhardwaj et al. 2010a). This can be achieved in a conscious child by getting the child to look at an object in different positions of gaze. In an uncooperative child, swaddling can be used to restrain hands, and with the aid of a lid speculum to hold open the eye, an indenter/eye depressor may be used to rotate the eye in order to achieve adequate visualization (Fig. 19.4). This can also be employed for the sedated/ventilated child. If using either a speculum or indenter/depressor, it is vital that local anesthetic drops are first instilled.

- A clear view indicates that the ocular media are clear, while a hazy view could indicate pathology in either the cornea, anterior chamber (hyphema), or vitreous (vitreous hemorrhage).
- Examine the optic disk for evidence of edema.
- Look for the presence of pre-/intra-/subretinal hemorrhages, retinal folds, and macular schisis.

If RHs are found, a detailed and accurate record of the type, location, and number of hemorrhages must be made in the notes in the form of a diagram.

If available, photography with the RetCam (Clarity Medical Systems, Pleasanton, CA) is a useful adjuvant and will provide corroboration of the clinical findings. This is particularly useful if court proceedings are likely. With a well-dilated pupil and clear ocular media, excellent wide-field images can be achieved using either the 120° or 130° lens. Although images obtained using the RetCam provide irrevocable evidence of the presence and extent of the RH, its use should not be a substitute for examination with the binocular indirect ophthalmoscope, as it does not visualize the ora serrata, nor provide depth perception.

Inconsistencies in the reporting and documentation of RH may occur when a child is examined at multiple sites due to transfer between hospitals, particularly if the peripheral hospital does not have a subspeciality-trained ophthalmologist.

A study by Morad et al. (2003) showed that non ophthalmologists did not attempt to (36 %) or were "unable to" (19 %) examine the fundus in 72 children with shaken baby syndrome. When the retina was examined, non ophthalmologists were accurate in recognizing the absence or presence of RH in 87 %. However, false-negative examinations occurred in 13 %. Similarly, Kivlin et al. reported that non ophthalmologists missed the hemorrhages in 29 % of affected patients (Kivlin et al. 2000).

For example, if RH are not seen on admission but are described later by an ophthalmologist, the experience and technique of the original examiner is most likely the reason rather than subsequent bleeding while hospitalized. It is difficult to ensure that all cases of suspected AHT are examined within minutes or hours of admission, and no published studies have described repeated ocular examination in the first few days in hospital. All that can be definitively stated is that there is no good evidence that significant evolution of RH over time occurs. Gardner (2007) published one case report suggesting this occurred, but some issues with that case report make it difficult to draw a conclusion (Gardner 2007; Chadwick 2008; Glick and Staley 2007; Greeley 2008). There are no retinal photographs but only drawings of the retinal lesions, there is a discrepancy between the clinical description and the drawings, and there are also concerns about the reliability of the witness (Glick and Staley 2007). Theoretically there is potential that RH might extend, for example, if the child had a severe coagulopathy. An extensive literature search has identified one case reported by Gilles et al. (2003) – this patient, who was reportedly strangled, shaken, and thrown onto a coffee table, sustaining a >4 cm occipital fracture in addition to other injuries, was reported to have had RH ipsilateral to the intracranial findings when first examined, but 24 h later had bilateral RH. Presumably the images shown in this paper are from the second examination, as the figure legend describes three RH in the left eye, but there are obvious RH in the right eye. Looking at the photograph, in this case, it is very difficult to visualize the described hemorrhages, and as the first examination may not have included photography, they would be difficult to see. The mechanism and sequelae of the child's abuse, which included an occipital fracture and neck bruising, is somewhat more severe than usually described in AHT.

In anticoagulated patients on warfarin, RH were observed in 3 %, none of which caused any significant visual symptoms (Superstein et al. 2000). Similarly, although RH can occur in coagulation disorders, this is an infrequent occurrence (Spraul and Grossniklaus 1997) with no report of extension of an existing RH found. Extension is theoretically unlikely, given the tamponade effect from retinal tissues and intraocular pressure, the unique clotting abilities of the retinal milieu (Spraul and Grossniklaus 1997), as well as the absence of abnormal vasculature or fragile neovascularisation, particularly in AHT.

The utility of a detailed ophthalmic examination in all children suspected of being subject to physical abuse has been questioned. Thackeray et al. retrospectively analyzed the data of 282 children under 2 years of age evaluated for physical abuse, but with no evidence of AHT on neuroimaging (Thackeray et al. 2010). Only nine children had RH, of which only two (0.7 %) were considered characteristic, and both of these children had sustained obvious injury to the face and head.

The importance of having a protocolized system in place, ideally established in conjunction with the pediatricians and neurosurgeons, cannot be overemphasized – the aim is to perform a consistent, timely dilated ophthalmic examination in all cases of head trauma, particularly when AHT is suspected.

Circularity Bias

One criticism of the ophthalmic literature is the bias of ascertainment and circular reasoning – that is, if only children who are suspected of being victims of AHT have a retinal examination, and the presence of RH in the clinical setting is highly suggestive of AHT, then the presence of RH automatically implies abuse. This circularity argument implies that children with accidental head trauma do not get eye examinations, or those without the classic constellation of symptoms do not get eye examinations. One of the difficulties is, of course, knowing whether the child has truly been abused, and if so what the mechanism of abuse was, unless the perpetrator confesses.

Retinoschisis

One particular feature of AHT that has a high positive predictive value is the lesion termed hemorrhagic macular retinoschisis. This is typically a dome-shaped hemorrhage often surrounded by traumatic macular folds, although the folds may exist without the schisis (Figs. 19.10, 19.11, 19.12, 19.13, and 19.14). A number of other terms are used to describe this lesion including hemorrhagic macular cyst, or sub internal limiting membrane (ILM) hemorrhage. The location of this lesion occurs underneath the ILM. In infants, the ILM overlying the retinal nerve-fiber layer (RNFL) is firmly adherent to the overlying posterior hyaloid face – the posterior aspect of the vitreous and the hemorrhage

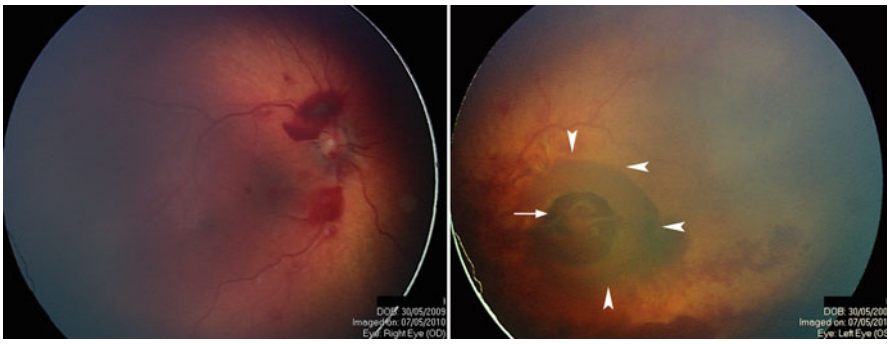

Fig. 19.12 Unilateral left traumatic macular retinoschisis (delineated by *arrowheads*), with blood leaking into preretinal and vitreal space (*arrow*)

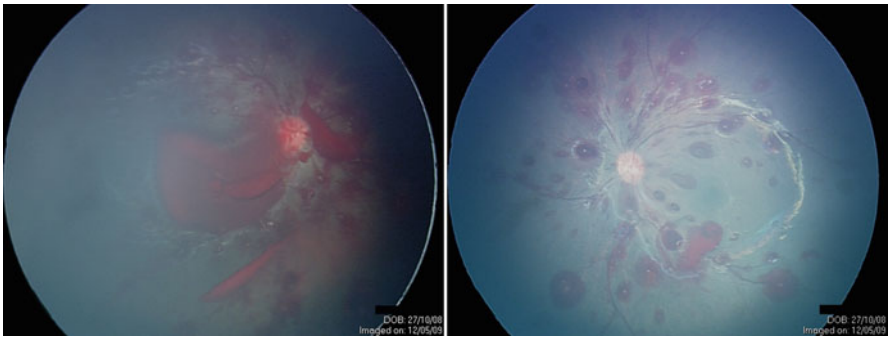

Fig. 19.13 Right traumatic macular retinoschisis with overlying preretinal blood

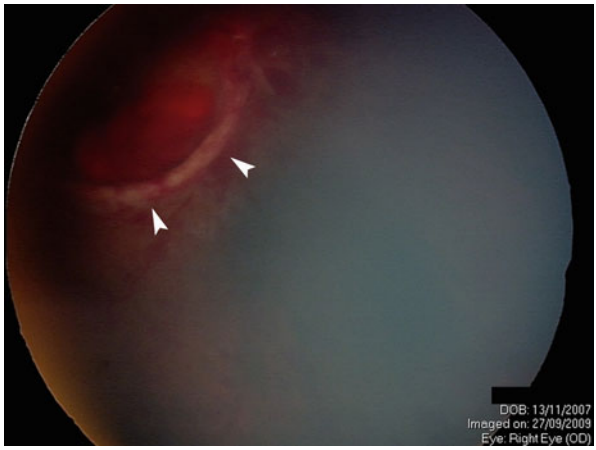

Fig. 19.14 Traumatic macular fold in greater detail (*arrowheads*) showing the blood vessels coursing over the surface where the retina is tented up. No hemorrhagic retinoschisis is associated with this retinal fold

caused by separation of the ILM. Even deeper retinoschisis is also documented (Morad et al. 2002; Kivlin et al. 2000; De Maeyer et al. 2007; Kivlin 2001; Meier et al. 2005).

The blood contained within the retinoschisis cavity can gradually leak into the overlying vitreous cavity within hours up to days following the initial injury (Fig. 19.12). For this reason, it is imperative that sequential examination and monitoring is performed as vitreous hemorrhage may compromise vision if it does not resorb (Eisenbrey 1979). In general, the actual retinoschisis lesion would not appear to affect vision in the long term (Levin 2010).

The frequency of retinoschisis and traumatic macular folds has been reported in 8–14 % of all AHT (Bhardwaj et al. 2010a), although in postmortem series it is reported at a higher rate of 23 % (Eisenbrey 1979; Rao et al. 1988). One series reported the presence of retinoschisis correlating with a fatal outcome (Mills 1998). Other series have included retinoschisis as part of a "severe" or grade 3 retinopathy, which in turn correlated with severity of the brain injury (Morad et al. 2002). It is likely that it is the associated brain injury that is responsible for the reported incidence of long-term visual impairment in 75 % of long-term survivors of AHT with retinoschisis (Escardo-Paton et al. 2011).

Recently, retinoschisis has been demonstrated to occur in major crush injuries to the infant head. Three cases have been reported since 2004 (Lantz et al. 2004; Lueder et al. 2006; Watts and Obi 2008), thereby generating an increased awareness in the ophthalmic literature. These three specific cases of crush injury involved the following:

1. A television falling onto a child's head (Lantz et al. 2004).
2. A 63 kg person falling onto a 4-month-old infant (Lueder et al. 2006).
3. A mother holding a 10-week infant in a front-holding papoose, who tripped and fell forward crushing the infant's head between a wooden barrier and the mother's chest (Watts and Obi 2008). All three cases had massive head injuries with skull fractures. Two of the infants died.

To further investigate the significance and frequency of these findings, a subsequent retrospective and pathological review of crush injuries in children was undertaken by Gnanaraj et al. (2007). This study consisted of two cohorts – one group who had been subject to crush injuries from falling televisions ($n = 16$) and for the second group the autopsy findings were reviewed in nine children who died with crush and skull fractures. The specific outcome was the nature and distribution of RH associated with these injuries. They concluded that intraretinal and preretinal hemorrhages, particularly in the posterior pole, could occur in crush injury in the pediatric head. Hemorrhages under the ILM or extending to the ora serrata were only seen in situations where crush injury was part of a fatal-trauma scenario related to motor vehicles. Retinal folds and the typical macular schisis associated with AHT were not observed.

Therefore, while retinoschisis hemorrhages have been observed in crush injuries, they are extremely rare. These cases illustrate the importance of placing the retinal findings in the context of the given history. In most cases of AHT, the history of alleged mechanism of injury is that of a minor fall, often from a height of 1 m or less such as from a change table, without the massive force which existed in these three cases.

Recently a further case documented the presence of bilateral macular retinoschisis associated with preretinal, intraretinal, and subretinal hemorrhages in a 2-year-old child who fell 11 m onto concrete (Reddie et al. 2010). She sustained significant head trauma including multiple skull fractures, acute SDH, and cerebral edema, requiring a decompressive craniotomy.

Postmortem findings in ten children fatally injured in motor vehicle crashes have also documented RH in eight children, of whom three had elevated circular retinal folds, and six had dome-shaped hemorrhages just below the ILM (Kivlin et al. 2008). These findings would be consistent with retinoschisis, and as the significant trauma and subsequent death resulted from sudden acceleration/deceleration forces, are in keeping with the proposed mechanism of RH in AHT.

A further case of a sub-ILM hemorrhage associated with perimacular folds is described in a 14-year-old boy with acute myeloid leukemia (Bhatnagar et al. 2009). Not only was his age outside that of the normal distribution for AHT, but a known condition was present that predisposed to RH. It is postulated in this case that the reduced platelet count caused extravasation of blood from retinal vessels, resulting in rapid accumulation of blood in the sub-ILM space, raising the ILM from the inner retina and creating a perimacular fold at the edge where the ILM remained attached. The authors rightly point out that perimacular folds associated with large sub-ILM hemorrhages can occur in a non abusive setting and that hematological disease must be excluded in all cases (Bhatnagar et al. 2009).

Bhardwaj et al. undertook a critical literature review of the ocular findings associated with AHT (Bhardwaj et al. 2010a) and discussed the high specificity of retinal folds or traumatic retinoschisis in AHT. Brown wrote an excellent response to that article, rephrasing the interpretation of the findings (Brown 2011). She highlighted that, based on the Bhardwaj article, even without retinoschisis or retinal folds being present, RH is characteristic of AHT, as it is rarely seen in other forms of mild and moderate accidental head trauma. Therefore, RH has a high (but not 100 %) positive predictive value for an ultimate diagnosis of AHT. When the presence of retinal folds and retinoschisis is taken into consideration, they are described in two main patterns of injury: multiple skull fractures caused by a head crush or high fall and acceleration/deceleration (with or without impact) due to AHT or a motor vehicle accident (MVA). Brown concludes that based on the literature, retinoschisis and retinal folds have a positive predictive value for AHT of 100 % in any child who has not been involved in an MVA and who does not have multiple skull fractures (Brown 2011). Any outlier from this scenario, however, must be subject to thorough investigation to ensure that the underlying cause was truly accidental (Levin 2006).

Classification Systems

A number of authors have created classification systems in order to quantify and qualitatively record the “severity” of RH. The methods used vary, and a resultant severity score is created which can then be assessed in terms of its association

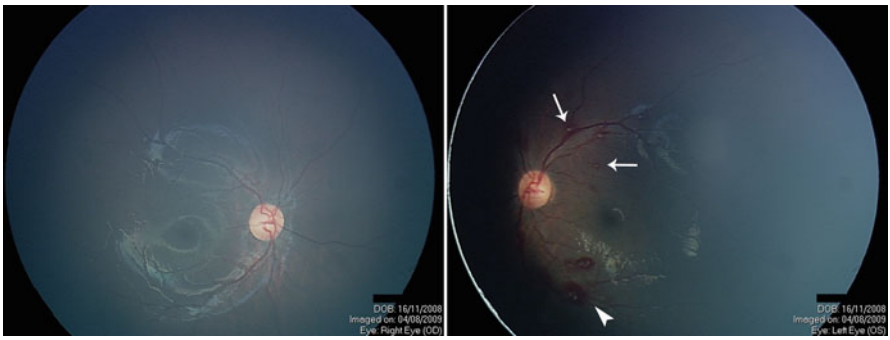

Fig. 19.15 Unilateral mild (Grade 1) RH left eye as per Vinchon (Vinchon et al. 2002, 2005, 2010) – intraretinal dot (*arrows*) and blot-shaped (*arrowhead*) RH

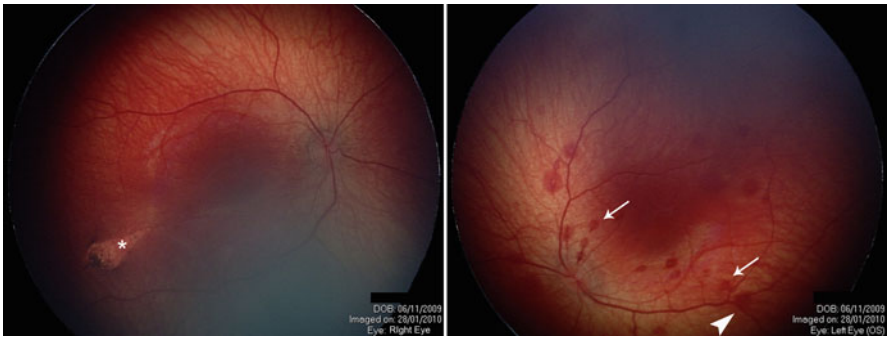

Fig. 19.16 Unilateral mild (Grade 1) RH left eye as per Vinchon (Vinchon et al. 2002, 2005, 2010) – intraretinal dot (*arrows*) and blot-shaped (*arrowhead*) RH. An incidental finding was a presumed toxoplasmosis scar in the right eye (*asterisk*)

with the degree of brain injury or likelihood that the observed injuries are caused by AHT.

Vinchon et al. have utilized a grading system in a number of papers (Vinchon et al. 2002, 2005, 2010). RH were graded as absent (0); mild (1) consisting of preretinal: superficial, splinter, or flame shaped: or intraretinal, dot, or blot shaped (Figs. 19.15 and 19.16); moderate (2) defined as preretinal, pearl shaped with a diameter less than twice the papilla (Fig. 19.6); or severe (3) consisting of large preretinal, associated with other types, diffuse with or without retinoschisis (Figs. 19.17 and 19.18).

In the most recent of these studies from Vinchon's group, fundoscopy was performed systematically by an ophthalmologist for all cases of trauma. In cases where RH were present, repeated examination and imaging were undertaken by a trained neuroophthalmologist (Vinchon et al. 2010). The aim of this paper was to determine if the nature and extent of RH differed between accidental trauma (AT) and AHT; it looked at a cohort of 45 cases of confessed AHT and 39 cases of AT

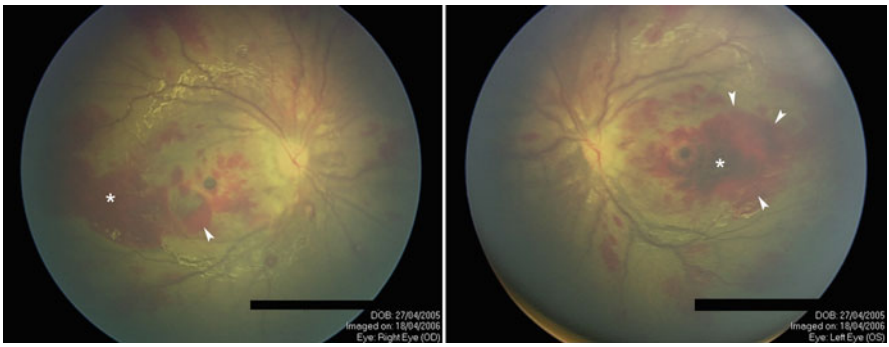

Fig. 19.17 Bilateral severe (Grade 3) RH (as per Vinchon (Vinchon et al. 2002, 2005, 2010)) – large preretinal RH (*asterix*), associated with blot and flame RH, diffuse with retinoschisis (*arrowheads*)

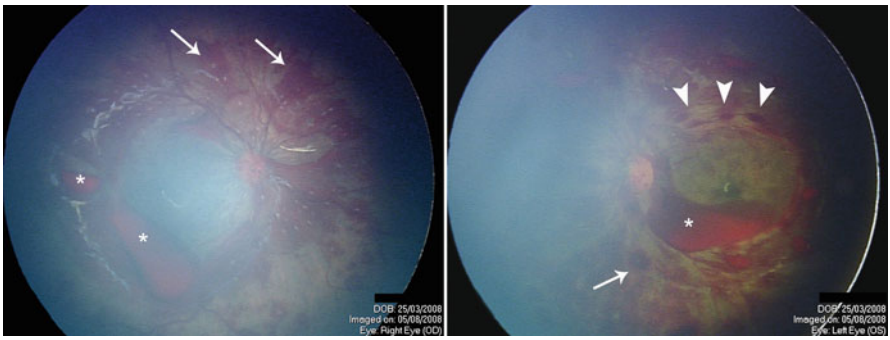

Fig. 19.18 Bilateral severe (Grade 3) RH as per Vinchon (Vinchon et al. 2002, 2005, 2010) with preretinal RH (*asterix*), superficial RH (*arrowheads*), and deep blot hemorrhages (*arrows*), extensive, too numerous to count

which occurred in a public (and therefore witnessed) place. RH was observed in 84.1 % of AHT compared with 17.1 % of AT. The nature of the RH was significantly different however. In the six cases of AT where RH was observed, they were mild in five and described as being flame shaped. Only one child with AT had severe RH and also had significant facial trauma suggesting impact on the globe. In the confessed AHT group, 56.8 % were severe, 20.5 % moderate, and 6.8 % mild. Vinchon et al. felt their four-tier grading system could be validated in this particular study as all cases of AHT were confessed, thereby avoiding the circularity bias discussed earlier. Severe RH were found in the majority of cases of AHT, and so it was concluded that severe RH in the absence of facial trauma are specific for AHT. Vinchon et al. had previously demonstrated that RH caused by AHT were severe, and those caused by AT were mild, but because of the circularity bias this finding is difficult to validate (Vinchon et al. 2002, 2005). In a cohort of 18 cases of infants with SDH due to traffic accidents, fundoscopy was performed in

Table 19.1 Classification system developed by Morad et al. to correlate the presence and severity of retinal hemorrhages with degree of brain injury (From Morad et al. 2002)

Retinal hemorrhage score	
Number of hemorrhages	
<10	1
>10	2
Extent of hemorrhages	
One zone	1
Two zones	2
Three zones	3
Type of hemorrhages	
Preretinal	1
Intraretinal	1
Subretinal	1

16 (89 %), and 3 had definite fundus RH (Vinchon et al. 2002). In all cases, the RH were flame shaped and located at the posterior pole, which is consistent with a grading of mild. All of these RH occurred in association with intracranial hypertension.

In a previous prospective series, fundoscopy was recorded on all children admitted over a 3-year period with head injury, with the authors aiming to determine the predictive value of RH in assisting with the diagnosis of AHT (Vinchon et al. 2005). Of 129 cases where fundoscopy data were available, RH was found in 36.4 % (47/129). Of these, RH was present in 42 of 56 AHT cases (75 %) compared with 5 of 73 AT (6.8 %). The severity of the RH also differed between the two cohorts – all of the AT was classified as mild, compared with AHT where 5 were mild, 10 were moderate, and 27 were severe. The authors calculated that the sensitivity of RH is 75 % and a specificity of 93.2 % for a diagnosis of AHT. They also estimated that the sensitivity and specificity of RH grade 2 or 3 for AHT diagnosis were 66.1 % and 100 %, respectively, and the predictive positive and negative values were 100 % and 79.3 %, respectively.

A slightly different classification system developed by Morad et al. was utilized to correlate the pattern and severity of the RH with the degree of brain injury (Morad et al. 2002). In this schema, RH are graded according to three parameters – number of hemorrhages, extent of hemorrhages using the retinopathy of prematurity retinal zone method (zones I, II, and III.), and type of hemorrhages. A score is given for each parameter with a maximum possible score of 12. Each eye is scored separately, and the final score given is a sum of the scores for the two eyes (Table 19.1).

In Modrad et al.'s study, the cohort consisted of 75 children diagnosed as victims of AHT, and 84 % had RH, of which 16 % were unilateral. The majority had multiple-confluent RH, found at all three levels in 74 %; 16 % had 10 or less RH. Retinoschisis was observed in 32 % and was predominantly unilateral (63 %). This study also graded the extent of severity of the brain injury. Analysis showed no correlation with laterality or asymmetry but demonstrated a correlation between the severity of the head injury and the severity of the RH ($p = 0.032$). An earlier

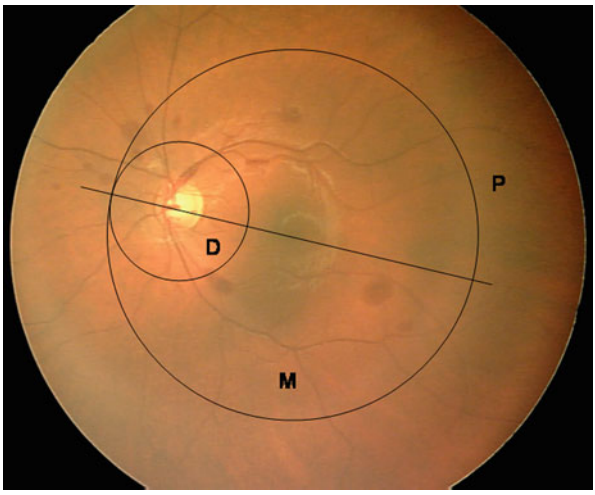

Fig. 19.19 Fundal image with the retinal zones superimposed. Zone D – circle with diameter of three times the optic disk diameter, centered on the center of the optic disk. Zone M – circle with a radius of four times diameter of the optic disk, centered on a line bisecting the retinal arcade and optic disk. Zone P – the peripheral area outside zone M (Reproduced from the BJO, Fleck WB, 94;886–890, 2010, with permission from the BMJ Publishing Group Ltd)

analysis of 14 children by Wilkinson et al. (1989) showed diffuse fundus involvement, vitreous hemorrhage, or large subhyaloid hemorrhages were also associated with more severe acute neurological injury.

More recently, Fleck et al. have devised a "zonal" classification system (Fleck et al. 2010) with the underlying aim of facilitating a consistent terminology and meaningful descriptive grading system based on photography which can be used for clinical, legal, and research purposes. When developing this system, it was taken into consideration that many of the normal retinal landmarks could not routinely be visualized, but usually the optic disk and temporal arcades were able to be located. The zonal system was divided into Zone D – the peripapillary circle, with a diameter three times that of the optic disk, centered on the optic disk; Zone M – the posterior pole, which is an area contained within a circle with a radius four times that of the optic disk diameter. The center of the circle is on a line bisecting the retinal arcades, and the nasal edge of the zone M circle is tangential to circle D. The remainder of the image is considered to be Zone P, the peripheral zone, that is, anything outside Zone M (Fig. 19.19).

To validate this scoring system, two clear transparent acetate templates were used to overlay each image and perform the analysis. They demonstrated interobserver agreement as being "almost perfect" with interobserver agreement of 0.86–0.92 for all pair combinations, and the interobserver agreement for multiple interraters was also "almost perfect" measuring 0.8841. Although developed for images taken with a RetCam 120° lens, the authors state that the graticules developed are easily utilized with other photography systems and even the

narrow-field, high-magnification lens on the RetCam. There are however no further studies validating the utility of this system, and so it is not known whether a certain zonal classification is more indicative of AHT as the underlying cause or if there is a severity correlation with head injury to allow discrimination between AHT and AT. The classification also takes no account of the presence or absence of macular retinoschisis.

Pathogenesis of Retinal Injuries

The gold standard of a randomized controlled trial in which infants are subject to the presumed shaking forces thought to cause AHT, with examination for RH, can of course never be undertaken. A fully adequate animal model of the relationship between RH and trauma has not yet been described, although some existing animal data provide insights into the mechanisms. Many theories as to the mechanism have been mooted, particularly in the courtroom setting, including hypoxia, increased intrathoracic pressure, and raised intracranial pressure. Counterevidence to these is provided in a later section.

Much of the body of evidence now suggests that the strength of the attachment between the formed vitreous and the ILM of the retina in the infant is a major determinant in the pathophysiology of RH, in association with specific effects of repeated acceleration/deceleration forces. A favored theory in the literature is that acceleration/deceleration forces create relative motion between adjacent tissues of different densities. Shearing (tangential) forces are thought to be particularly significant at the vitreoretinal interface due to the layered structure of the retina. These forces cause the vitreous to pull on the retina, possibly damaging retinal vessels with subsequent hemorrhage, or cause changes in vascular autoregulation (Coats et al. 2010; Wygnanski-Jaffe et al. 2006). The globe in the infant under the age of 3 is also more deformable than an older child's or adult's eye. The elastic fibers in the infant human sclera, compared with a woodpecker's eye, are capable of being stretched beyond their level of elasticity, particularly when not fully supported within the orbit. This increased tendency to deformity is likely to permit more relative motion of the intraocular contents when subject to acceleration forces (Wygnanski-Jaffe et al. 2007).

The infant orbit also contains a significant amount of orbital soft tissue allowing motion of the globe when subject to acceleration/deceleration forces. The optic nerve and other structures are tethered to bony structures and sclera, such that translational forces may cause traction and hemorrhage at these fixation points (Wygnanski-Jaffe et al. 2007). This is consistent with the finding that postmortem analysis of AHT victims has demonstrated hemorrhage at the optic nerve–scleral junction, intradural optic nerve sheath hemorrhage, and orbital apex fat hemorrhage (Wygnanski-Jaffe et al. 2006; Gilliland et al. 1994). A comparison with the woodpecker eye, which is subject to repeated acceleration/deceleration associated with pecking, shows it to be anatomically different from the infant eye, and it is postulated that this is protective against shaking-impact-related eye trauma (Wygnanski-Jaffe et al. 2007).

Woodpeckers have a reinforced sclera with firm fascial connections between the globe and the smaller, tighter-fitting orbit, with redundancy in the optic nerve. In particular, the retina lacks any attachment to the posterior vitreous (Wygnanski-Jaffe et al. 2007). A recent study subjected neonatal piglets to a single rapid head rotation and demonstrated that RH were predominantly located in areas of firm vitreous attachment to the retina, in addition to the optic nerve sheath (Coats et al. 2010), consistent with the theory of vitreoretinal traction in AHT.

Massicotte et al. have previously demonstrated a persistent attachment of the vitreous to the ILM at the apices of the perimacular folds. Therefore, they suggested that this finding might be significant in violent shaking (Massicotte et al. 1991). Imaging developments with optical coherence tomography (OCT) have added a further dimension to our understanding of pathogenesis by permitting in vivo imaging of the retina. OCT is noncontact and noninvasive, using scanning inferometry to create high-resolution cross-sectional images of retinal layers. Sturm et al. demonstrated clear vitreomacular traction in three cases of AHT and hemorrhagic macular retinoschisis. Persistent attachment of the vitreous was observed at the apices of the perimacular folds in macular retinoschisis (Sturm et al. 2008, 2009) (Fig. 19.14). A subsequently developed handheld OCT has made the imaging even more possible in this pediatric population and also demonstrated focal posterior vitreous separation, multilayered tractional retinoschisis, disinsertion of the ILM (or inner retinoschisis), and preretinal hemorrhages (Muni et al. 2010). These findings add significant support to the evidence base that vitreoretinal traction due to repetitive shaking plays a significant role in the pathogenesis of hemorrhage and retinoschisis in AHT.

Other Proposed Mechanisms

Terson Syndrome

Terson syndrome (TS) was initially described in 1900 by Albert Terson specifically referring to vitreous hemorrhage occurring in a patient with subarachnoid hemorrhage (Terson 1900). The terminology TS is however attributable to Paunoff who coined the phrase in 1962 (Paunoff 1962).

Subsequent reports have failed to distinguish between vitreous hemorrhage and other RH, such as retinal and subhyaloid, therefore limiting interpretation of the associations and natural history of TS (McCarron et al. 2004). It is well documented that 10–40 % of adults with subarachnoid hemorrhage will present with intraocular hemorrhage including retinal, subhyaloid, and vitreous (Fahmy 1973). A proposed mechanism is the sudden rise in intracranial pressure. The relevance of this in children has been debated. One prospective study undertook dilated eye examination in 57 consecutive children with intracranial hemorrhage from non abuse causes (Schloff et al. 2002). Hemorrhage was observed in only two: one septic child had one RH associated with infectious white retinal lesions, and the other, injured in a motor vehicle accident, had three flame and two deeper dot intraretinal hemorrhages. In a review paper of TS, the median age of the individuals with SAH and

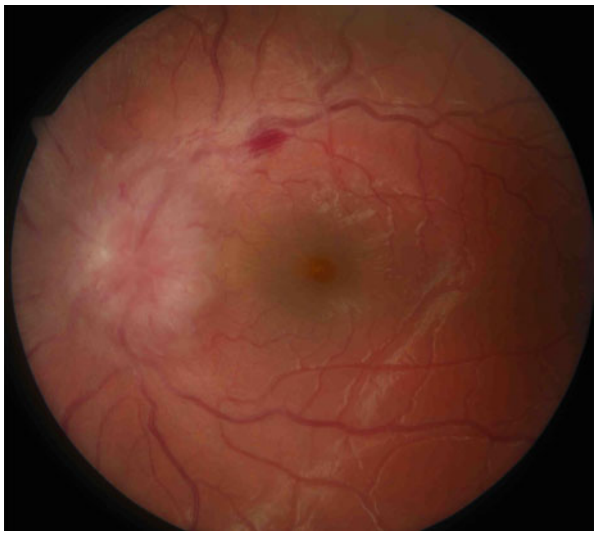

Fig. 19.20 Raised intracranial pressure manifesting with papilledema, with retinal nerve fiber layer swelling and a flame hemorrhage in the peripapillary region

vitreous hemorrhage was 55.2 years (range 36–74) (McCarron et al. 2004). Although cases of apparent TS have been described in children, they appear to be rare and likely to be associated with an aneurysmal event (Bhardwaj et al. 2010b; McLellan et al. 1986; Mena et al. 2011). The presence of an aneurysmal lesion would then seem to represent a known and documented etiology, which is not present in most cases of AHT.

Raised Intracranial Pressure

RH are occasionally observed in association with papilledema or optic nerve swelling (Fig. 19.20). The pattern, distribution, and nature of the RH in this setting are however distinctive from AHT (Parr 1989). This is also supported by series in the literature looking at the incidence and nature of papilledema post acute injury. One large study observed that papilledema in the acute head-injury setting is not common and was documented in only 3.5 % of patients (15/426) (Selhorst et al. 1985). However, the youngest age in this series was 5 years and the next youngest 9 years. These data are therefore probably not directly applicable to children as per Valsalva retinopathy and TS. The Selhorst paper also states, "papilledema was of a low grade in all patients," and that "retinal nerve fiber layer hemorrhages were not common and were not seen." Papilledema is reported in AHT occurring with a frequency of approximately 5 % of all cases, so it is unlikely to account for the RH observed in 83–85 % of those cases (Morad et al. 2002; Kivlin 2001). It may still be suggested that RH are caused by raised intracranial pressure, even if there is no evidence of papilledema on ophthalmologic examination. One study tried to examine the relationship of raised intracranial pressure and RH but was unable to establish any relationship of significance (Morad et al. 2002). Given that cerebral

edema is a common occurrence in an injured brain, it is difficult to explain why, if raised intracranial pressure is the causative factor, severe RH is almost never seen after serious or fatal accidental trauma (Vinchon et al. 2005). This issue was discussed in the High Court in the UK in 2005 in a legal review of cases of "shaken baby syndrome." The hypothesis under discussion at that time was the so-called Geddes hypothesis which, as one of its components, implicated raised intracranial pressure as a possible cause for RH in AHT (Geddes et al. 2003; Punt et al. 2004). In the High Court, one particular case was brought to the attention of Dr. Geddes as having no evidence of brain swelling at all on neuroimaging, yet still having bleeding in the form of an SDH along with RH. Dr. Geddes stated that she had no explanation for this and that her hypothesis was flawed (Supreme Court 2005).

Purtscher Retinopathy

The first description of Purtscher retinopathy is attributed to Purtscher in 1910. Retinal examination in a man who fell from a tree onto his head revealed multiple areas of retinal whitening and hemorrhage in both posterior poles (Purtscher 1910). Subsequently, a similar constellation of findings was described in a number of individuals with compressive chest injuries (Tietze 1911). The acute fundus abnormalities include *Purtscher flecken*, which consist of multiple discrete areas of retinal whitening in the superficial retina, and equate to infarcts of the retinal capillary bed (Agrawal and McKibbin 2006; Harrison et al. 2011). These *flecken* may be polygonal and of variable size – up to several disk areas. A clear zone usually exists between the affected retina and an adjacent arteriole, although it will extend right up to the edge of an adjacent venule. Additional findings include cotton-wool spots, retinal hemorrhage – usually flame shaped as well as dot and blot RH – as well as optic-disk swelling and hemorrhage.

Cardiopulmonary Resuscitation

A possible hypothesis is that chest compressions delivered as part of cardiopulmonary resuscitation (CPR) are the underlying cause of RH – almost a Purtscher retinopathy-type picture. One study looked at the postmortem eyes of 169 children who had CPR (Gilliland et al. 1994). The findings of the study did not support the theory that RH resulted from CPR.

Convulsions

Three studies have examined the eyes of children admitted to hospital following convulsions to determine whether convulsions alone may account for the presence

of RH (Curcoy et al. 2009; Sandramouli et al. 1997; Tyagi et al. 1998). Tyagi examined 32 children under the age of 2 years – none had RH. They conclude that the finding of RH in a child admitted with a history of convulsion should trigger a meticulous search for other causes of RH, particularly AHT (Tyagi et al. 1998). Similar findings were observed in the study of Sandramouli et al. where 33 children were examined following convulsions and none had RH (Sandramouli et al. 1997). Curcoy looked at children under 2 presenting to hospital with their first convulsion; of 389 seen in the emergency department, 182 were admitted, and 2 of these had RH. These two children were eventually diagnosed as AHT (Curcoy et al. 2009).

Valsalva Maneuver

A similar fundal picture is observed in adults with so-called Valsalva retinopathy. Evidence suggests that Valsalva retinopathy is a very rare event in infants. One study looked at 100 children with hypertrophic pyloric stenosis, which results in excessive vomiting, facial petechiae, and subconjunctival hemorrhage associated with the Valsalva maneuver (Herr et al. 2004). None of these children had any RH. Valsalva is, therefore, unlikely to be a causative factor in the majority of reported scenarios associated with AHT.

Incidence of RH in Accidental Trauma and Falls

A number of different studies have sought to overcome the circularity bias mentioned previously by: (1) submitting all children to an ophthalmic examination when seen through an emergency department with head injury from accidents or falls, (2) comparing the retinal findings in children in whom the perpetrator has confessed to those children at the other end of the spectrum in which the child was in an accident which was witnessed, and (3) excluding any retinal findings in children as a diagnostic discriminator in AHT in which the perpetrator confessed.

Accidental Head Trauma

RHs are exceedingly rare in accidental head trauma and when present, are usually only observed in severe life-threatening situations associated with evidence of extensive external injury, such as when a child is thrown from a car in a MVA. Specifically this evidence is backed by the following studies:

1. Billmire and Myers (1985) reviewed children less than 1 year of age, admitted with head injuries. RHs were observed in 89 % of 28 abused children and in none of 54 with accidental head injuries.

2. Duhaime et al. (1992) reviewed acute accidental head trauma in 100 children younger than 2 years of age, including those with skull fractures, falls from heights greater than 2 m, and falls down stairs and MVAs. RHs were seen in serious accidental head injury in only one child associated with a severe MVA but were most commonly encountered in inflicted injury. The authors concluded, based on history, that most household falls were neurologically benign.
3. Buys et al. (1992) reviewed 79 children under 3 years of age who presented with head injuries and had a full eye examination. Seventy-five had accidental injuries and had normal eyes. Three had non accidental injuries, and all had varying degrees of retinal hemorrhaging. One child had an injury of indeterminate cause and had a normal fundus. None with accidental trauma had RH.
4. Gilliland et al. (1994) prospectively studied the presence and location of ocular hemorrhages in 169 randomly selected child deaths referred to a medical examiner. RHs were identified in 70 cases: 62 head injuries, 4 central-nervous-system diseases (but not other natural diseases), and 4 deaths of undetermined cause. Among the head-injured with RHs, 9 had a history of severe traumatic event (e.g., an unrestrained rear-seat passenger in high-speed collision) and 53 were victims of inflicted injury (e.g., violent shaking).
5. DiScala et al. (2000) performed a comparative analysis of patients injured by child abuse ($n = 1{,}997$) with patients injured unintentionally ($n = 16{,}831$), newborn to 4 years of age, reported to the National Pediatric Trauma Registry (NPTR). 28.7 % of abused children had RH, compared to 0.07 % of those with non inflicted injuries. The authors concluded that: "RH, in the absence of documented history of major trauma ... should be considered as diagnostic of child abuse."
6. Vinchon et al. (2005) performed a prospective study of 150 cases of head trauma with 57 from AHT. Of the AHT group, 75 % had RH, compared with the accidental-trauma group – only 7 % of these had RH, all of which were mild or classified grade 1 (dot, blot, or flame at post pole). The clinical scenarios of these accidental trauma cases consisted of two children involved in MVAs, one child who fell down stairs, one child who fell with a walker, and the last child who fell from a chair on top of a table. Overall, Vinchon concluded that the presence of RH has a 93 % specificity for AHT. The severity of the RH is important though. There is a 66 % specificity for AHT if grade 2 RH (small dome- or pearl-shaped), compared with 100 % if grade 3 (large dome shaped to periphery and possible preretinal).

This list of the studies which have attempted to discern the frequency and type of RH in AHT and accidental trauma is not complete – other papers concur with the findings that in accidental trauma, RH is not common and is usually associated with significant force or external injury (Bechtel et al. 2004; Reece and Sege 2000; Plunkett 2001).

Short-Distance Falls

One of the most common arguments used against the specificity of RH in AHT is that they occur in short-distance falls. An article by Plunkett (2001) recorded US Consumer Safety Commission national injury information over 11.5 years and examined the records of 75,000 head and neck injuries from playground equipment, culminating in 18 deaths, of which 8 were under the age of 3 years – yet only 3 had retinal hemorrhages. Many of the falls were complex and involved swings or jungle gyms, and several were unwitnessed. The series included the case of a toddler videotaped falling from a plastic play gym, an event resulting in her death with subdural and retinal bleeding. Three cases (including this toddler) had RH, although the RH are poorly described. Thus, given the number of infants who fall in daily life, RH from low falls must be an exceedingly rare occurrence (Spivack 2001). A further case (described previously) in which a 5-year-old child reported an 11-month-old sibling falling back on to its head also had RH (Gardner 2007). There are no retinal photographs but only drawings of the retinal lesions. It is clear, however, from these drawings and the accompanying description that no retinoschisis cavity was present; in addition, there were concerns about the reliability of the witness (Glick and Staley 2007).

A second means of attempting to overcome the circularity argument is to compare the retinal findings in children in whom the perpetrator has confessed to those children at the other end of the spectrum in which the child was in an accident which was corroborated.

Vinchon et al. (2010) compared these two ends of the spectrum with RH found in only six cases of AT: (6/39-, flame-shaped (mild/grade 1) in five, and severe/grade 3 in only one patient who had facial trauma suggesting impact on the globe). This compared with 84.1 % in cases of confessed NAHI, of which 56 % were severe, and 20 % were moderate/grade 2. The authors concluded that overall, severe RH in the absence of direct impact appeared specific for AHT.

A further means of overcoming circularity bias is by excluding RH as a diagnostic criterion in AHT. A number of studies still show a distinct association between RH and AHT, even when RH are not used as a diagnostic factor (Bechtel et al. 2004; Duhaime et al. 1992; Critchley 1968). Margolin et al. (2010) retrospectively studied cases of AHT over a 5-year period to identify cases in which the perpetrator confessed (Margolin et al. 2010). The diagnosis of AHT was made on the confession of the perpetrator plus two other specific findings suspicious for abuse, but without RH as a qualifying criterion.

Of the 17 cases meeting entry criterion, retrospective audit of the notes revealed that 94 % (Kelly et al. 2009) had RH, 12 % would be deemed mild (less than 5 RH), and 3 % unilateral. On careful review of this study, however, it is not clear how the initial diagnosis of AHT was made, and if in fact RH were included for the initial diagnosis. Even if RH were subsequently included as a diagnostic criterion, the children had a retinal examination with a presumptive diagnosis made potentially

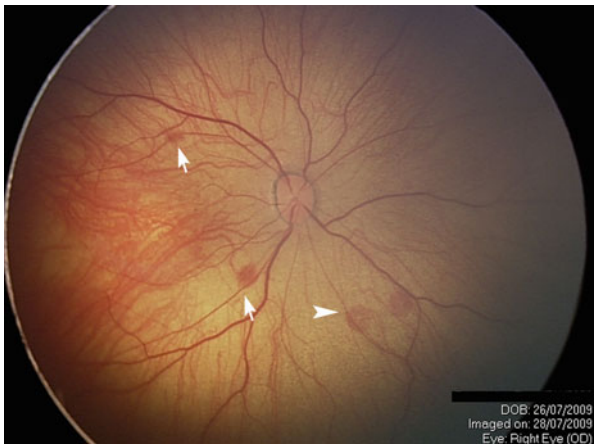

Fig. 19.21 RHs observed in a 3-day-old infant being investigated for an unrelated condition. Deep (*arrowheads*) and superficial intraretinal RH (*arrows*) are present

because the RH were present. Although the criteria was confession of the perpetrator, it is difficult to know how far into the investigation the confession was made – that is, were the clinical signs and symptoms, including the presence of RH, sufficient to have a high suspicion for AHT, and when this was put to the perpetrator, was a confession made?

Differential Diagnosis

Normal Deliveries

RHs in neonates following birth are common, reportedly occurring in 2.5–50 % of all births, although their etiology is unclear. They are typically clustered around the posterior pole as a mixture of "dot and blot" hemorrhages and "splinter" and "flame" hemorrhages and are usually intraretinal or occasionally preretinal but rarely subretinal (Fig. 19.21). They usually resolve within a week of birth, although larger hemorrhages may take up to 6 weeks to fully resolve (Kaur and Taylor 1992; Sezen 1971; Aryan et al. 2005; Critchley 1968; Giles 1960; Schoenfeld et al. 1985).

Coagulopathy

A number of different coagulopathies have been linked to RH in infants, including vitamin K deficiency, low fibrinogen levels, infantile giant-cell hepatitis, and type I von Willebrand disease (Guddat et al. 2011; Marshman et al. 1999; Rutty et al. 1999; Stray-Pedersen et al. 2010). Though type I von Willebrand disease is generally regarded as a mild coagulopathy, an 11-month-old girl with this disorder

was recently reported with a massive subdural hematoma and bilateral RHs following a minor fall (Stray-Pedersen et al. 2010). This suggests that even mild coagulopathies can be significant in the context of pediatric RH.

Anemia

There is a paucity of pediatric literature on this subject, but extrapolation of studies on adults suggests that the typical retinal findings observed in anemia consist of occasional small-dot or flame hemorrhages. These are however infrequent and uncommon. In one study of adult patients with mild and moderate anemia, only 5 % of patients demonstrated RH (Carraro et al. 2001). In severe anemia, RH were present in 83 % and were flame shaped in 41 %, discrete in 64 %, white centered in 3 %, and with a subhyaloid hemorrhage in one patient only. That report shows three representative photos, which all have less than 4 RH.

Hyperviscosity Syndromes

RH have a higher frequency with coexisting thrombocytopenia or platelet dysfunction. Retinal veins become dilated and tortuous, with multiple "dot" and "blot," and "flame" and "splinter" hemorrhages, which may have white centers. Cotton-wool spots and optic-disk edema may also develop. Hyperviscosity syndromes can also cause RH of all types and in all layers but without the white centers seen in anemia. In these cases, venous congestion and tortuosity is more marked (Allen and Straatsma 1961).

Leukemia

RH in any retinal layers are common in patients with leukemia. Although unusual, they may extend into the vitreous, with one reported case of a perimacular fold associated with a large subhyaloid hemorrhage as previously described (Bhatnagar et al. 2009). Usually occurring at the posterior pole, they are typically round or flame shaped and may have a white center consisting of leukemic cells and debris, platelet-fibrin aggregates, or septic emboli. Cotton-wool spots indicative of retinal infarcts secondary to anemia, hyperviscosity, or leukemic infiltration are also common (Bhatnagar et al. 2009; Allen and Straatsma 1961; Sharma et al. 2004).

Malaria

RH are found in 6–8 % of children admitted with cerebral malaria. They are usually intraretinal "dot," "blot," or "flame" hemorrhages, which can develop white centers (Looareesuwan et al. 1983).

Carbon Monoxide Poisoning

"Flame" and "dot" RH have been described in chronic carbon monoxide poisoning, in association with optic-disk edema and retinal venous tortuosity and congestion. The incidence of RH in this condition is not known (Bilchik et al. 1971).

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a form of cardiopulmonary bypass used in the management of respiratory failure. Retinal vascular changes including venous congestion and/or intraretinal hemorrhage(s) have been described in up to 13 % of infants undergoing ECMO and occur more commonly in the left eye (Pollack and Tychsen 1996; Young et al. 1997).

Osteogenesis Imperfecta

Multiple large intraretinal "dot," "blot," and "flame" hemorrhages, preretinal, and vitreous hemorrhages, in association with subdural hemorrhage, have been described in infants with osteogenesis imperfecta following minor trauma. There is only one case report of spontaneous RH in the form of a large subhyaloid hemorrhage, occurring in a 20-year-old (Ganesh et al. 2004; Khalil 1983).

Hypertensive Retinopathy

Retinal vascular changes, similar to those seen in adult hypertensive retinopathy, have been described in infants and neonates, with "splinter" hemorrhages present in 4 of 21 infants beyond 6 weeks of age, making them unlikely to be simple birth-related RHs. Blot hemorrhages were found in a further two infants (Skalina et al. 1983).

Meningitis

RHs have been described in several cases of fatal bacterial meningitis in infants. These can be extensive, "too numerous to count," intraretinal hemorrhages, which can extend to the ora serrata. A large subinternal limiting membrane was noted in one child. The hemorrhagic pattern is very similar to that seen in non accidental injury. It is not known whether the hemorrhages originate from retinal necrosis due to infection or vascular occlusion secondary to disseminated intravascular coagulation (Lopez et al. 2010; Ong et al. 2009).

Glutaric Aciduria Type 1

Glutaric aciduria type 1 is a rare autosomal recessive neurometabolic disorder. Multiple intraretinal and vitreous hemorrhages have been described in association with subdural effusions (Gago et al. 2003; Kafil-Hussain et al. 2000).

Subacute Bacterial Endocarditis (SBE)

SBE and other causes of sepsis are frequently associated with intraretinal hemorrhages which can have a white center – the so-called Roth spots. Histopathological studies have shown the white spots to be areas of capillary rupture, extravasation, and formation of a central fibrin-platelet plug (Duane et al. 1980).

Hyper/Hyponatremia

Multiple RHs have been reported in two cases of hyponatremic seizures in infants. One case was attributed to water intoxication while the other to non accidental injury; however, no other injury was found on magnetic resonance imaging (MRI) scan or skeletal survey. It is unclear whether the retinal hemorrhages were caused by the hyponatremia directly, the underlying cause of the hyponatremia (including possible subtle brain injury secondary to accidental/non accidental injury), or the seizures secondary to the hyponatremia, although as noted above, RH secondary to seizures alone have not been identified (Krugman et al. 2000; Rubin and Christian 2001). "Massive" RHs have also been described in one fatal case of hypernatremia, assumed to be secondary to dehydration. Histological examination revealed the hemorrhages to be in all retinal layers. Subarachnoid and subdural hemorrhage and diffuse cerebral edema were also present. The etiology of the RH was attributed to raised intracranial pressure secondary to the intracranial pathology; however, retinal vascular occlusion secondary to disseminated intravascular coagulation may also have contributed. Non accidental injury was excluded as a cause in this case (Fenton et al. 1999).

This list is not exhaustive, and other publications include tables of other diagnoses, which may be associated with RH (Levin 2010) (Table 19.2).

Ocular and Orbital Findings on Autopsy

In the event of death secondary to suspected AHT, an autopsy is vital in confirming and characterizing the nature of the abuse. If death has occurred shortly after presentation, an ophthalmologist may not have had an opportunity to examine the eyes. It is therefore vital that the examining pathologist approaches examination of the eyes in the same systematic approach taken in the live child – that is, starting with external examination of the eyes and adnexal tissues. A full description of the

Table 19.2 Differential diagnosis of RH. This list is not exhaustive

Accidental head trauma
Normal delivery
Coagulopathy
Anemia
Hyperviscosity syndromes
Hypertensive retinopathy
Terson syndrome
Raised intracranial pressure
Purtscher retinopathy
Cardiopulmonary resuscitation
Convulsions
Valsalva maneuver
Osteogenesis imperfecta
Meningitis
Glutaric aciduria type 1
Subacute bacterial endocarditis
Hyper/hyponatremia
Abusive head trauma (AHT)

recommended technique for removal of the globes can be found in Gilliland's paper (Gilliland et al. 2007). The en bloc ocular and orbital tissues should be fixed in formalin. After gross examination of the globe, optic nerve, and orbital tissues, the globe is sectioned in one of several accepted directions to allow visualization of the inner surface. The extent and type of RH are documented prior to sectioning of the eye for histology. This should ideally be done by photography, documenting the gross distribution pattern and number of the RH (Gilliland et al. 2007).

Microscopic sections of the eye are then taken in a pupil-optic nerve plane, taking care to include the optic nerve, and stained with hematoxylin and eosin. Prussian Blue can be used to stain iron in hemosiderin for the purpose of exclusion when macroscopic and microscopic evidence of RH are absent. On histopathological examination, as on clinical examination, RHs in AHT are found in any or all of the retinal layers but more commonly preretinal and intraretinal. Retinal folds are also more common in fatal AHT, with one study reporting their presence in 5 out of 12 cases examined (Munger et al. 1993). In addition, choroidal hemorrhage or engorgement has been observed in 30–50 % and optic nerve sheath hemorrhage in 65–100 % of eyes of victims of AHT at autopsy. The most common site of the optic nerve sheath hemorrhage is in the immediate retrobulbar portion of the optic nerve in the subdural sheath; however, hemorrhage has also been reported in the intradural space of the optic nerve sheath, in the orbital fat, and in the extraocular muscles. Orbital hemorrhages in accidental trauma were observed only when there was direct trauma to the orbit or severe repetitive acceleration–deceleration injury (Gilliland et al. 2007). Use of a standard protocol for the examination of the ocular and orbital structures in fatal cases of suspected AHT is therefore vital, as findings are likely to be the subject of scrutiny in the court setting.

Medicolegal Implications

Because of the implications of a diagnosis of child abuse, with criminal investigation of family members, caregivers, and other individuals in contact with the injured child, it is crucial the ophthalmologist works within a multidisciplinary team, and it is mandatory to conduct a thorough and clearly documented examination. Although less than half of these cases proceed to a criminal trial (Kelly and Farrant 2008), the observation of positive findings renders the ophthalmologist liable to appear as an expert witness in that trial, so clear documentation is essential. A key role of an expert witness is to be an impartial assistant to the court: in effect, to educate a lay audience as to the significance of the medical findings. A "Code of Conduct for Expert Witnesses" was adopted by the High Court of New Zealand in 2002 and is identical to that adopted in many jurisdictions internationally. According to this code, an expert witness has "an overriding duty to assist the Court impartially on relevant matters within the expert's area of expertise," and "an expert witness is not an advocate for the party who engages the witness."

While this code was developed originally for civil proceedings, it has been widely adopted, and a medical expert witness would be wise to be aware of its content and to practice in accord with it (Coates 2004).

Conclusion

AHT is a significant social issue, with implications for child safety, if the cause is unrecognized. As external signs are not always evident, this is a crucial diagnosis that cannot be missed, and the ophthalmologist plays an important role in the multidisciplinary approach to diagnosis and subsequent management. The orthodox scientific consensus view on the significance of RH in AHT is often challenged in criminal courts. Specifically it is the combination of the type, extent, and distribution of the retinal hemorrhages, in the context of the history and other findings in the case, which enables a diagnosis of AHT to be made. Alternative explanations should be appropriately investigated. The ophthalmologist functions as part of a team, which reaches a collaborative diagnosis based on the best evidence available.

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Neuroimaging of Pediatric Inflicted Injury 20

Donna R. Roberts

Contents

Abstract

Head imaging plays an essential role in the workup of an unstable child who presents with signs and symptoms of intracranial injury. Head imaging is important not only for detecting any potential neurosurgical emergency or need for immediate intervention but also in assessing for additional acute or remote intracranial injuries, particularly in children in whom there is a strong suspicion of child abuse. In addition to assisting in directing patient treatment plans, central nervous system (CNS) imaging is also important in aiding investigators in

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documenting as fully as possible the presence, extent, and timing of injury and to provide objective evidence of inflicted injury to prosecutors. Imaging provides essential data concerning the condition of the brain and spine in the living child, often immediately following the injury – data that cannot be acquired in the postmortem state. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are the main imaging modalities used clinically for detecting intracranial injury. Recent technological advances in neuroimaging have greatly enhanced our ability to identify subtle injuries that may have immediate and long-term consequences. Newer functional neuroimaging techniques (such as perfusion imaging, diffusion tractography, and MR spectroscopy) may lead to an improved understanding of the pathophysiology of nonaccidental intracranial trauma. This chapter will describe in detail each technique and give specific examples relevant to the neuroimaging of inflicted head injury.

Introduction

An unstable child who presents urgently with signs and symptoms of intracranial injury should be imaged as soon as possible with a head CT exam to detect any potential neurosurgical emergency or need for immediate intervention. Once a child has been stabilized and if there is continued clinical concern about intracranial injury, an MRI should be performed to further assess whether there are any acute or remote intracranial injuries. Head imaging should also be strongly considered and is recommended in the non symptomatic child in whom there is a strong suspicion of child abuse to detect any unsuspected acute or remote intracranial injury. As studies have shown that children, especially those younger than 12 months, may have significant intracranial injury without clinical signs or symptoms of head injury (Fig. 20.1), clinicians should have a low threshold for performing CT or MRI of the head in children with suspected abuse (Laskey et al. 2004; Meyer et al. 2009; Rubin et al. 2003). In addition to assisting in directing patient treatment plans, CNS imaging is also important in aiding investigators in documenting as fully as possible the presence, extent, and timing of injury and to provide objective evidence of inflicted injury to prosecutors. Imaging provides essential data concerning the condition of the brain and spine in the living child, often immediately following the injury – data that cannot be acquired in the postmortem state.

The American College of Radiology (ACR) publishes evidence-based guidelines to assist physicians in determining the appropriate use of medical imaging. These guidelines are developed by expert panels, including radiologists as well as physicians from other specialties, and are updated regularly. These are meant to assist practitioners in selecting appropriate imaging modalities for specific clinical situations. The ACR Appropriateness Criteria database can be found online at http://www.acr.org. The ACR Appropriateness Criteria for Suspected Physical Abuse – Child was last reviewed in 2009 (Meyer et al. 2009). Generally, the complexity and severity of a patient's clinical condition should guide the selection of appropriate imaging procedures which should be made by the attending physician in consultation with the

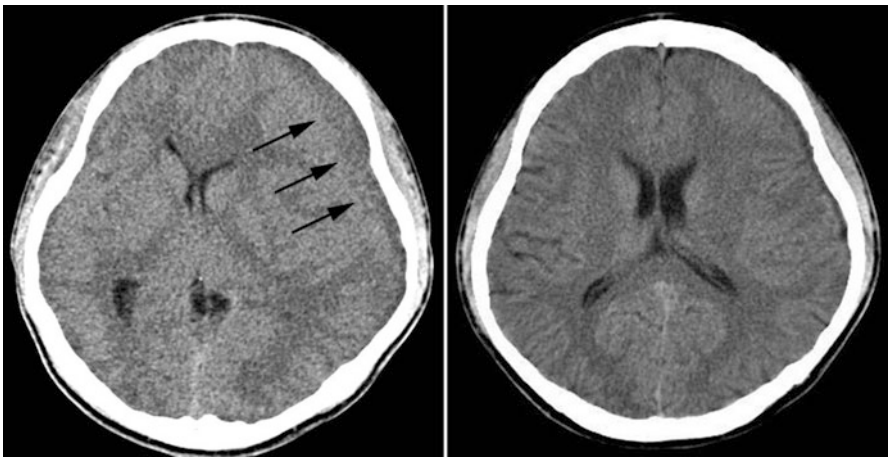

Fig. 20.1 Clinically occult intracranial injury. 15-year-old who complained of an ongoing headache for the preceding few days. There was no specific history of trauma or injury, although the patient was a soccer player and had participated in a soccer game 5 days previously. On physical examination, no focal neurological deficits or clinical signs of head injury were found; however, a CT was obtained due to the patient's complaint of ongoing headache. A noncontrast CT scan demonstrated an isodense subdural hematoma (SDH) (*black arrows*) indicating it was subacute in timing (see text below). The SDH had mass effect on the adjacent brain resulting in shift of the brain to the right. Also notice the displacement of the gray matter-white matter junction away from the inner table of the skull. A repeat CT scan following surgical drainage of the SDH showed resolution of the previously seen midline shift and a more symmetrical appearance of the lateral ventricles

radiologist. The ACR Appropriateness Criteria list CT scan of the head without contrast as most appropriate in a child less than 24 months old with a history of head trauma or if there is no history of head trauma but focal neurological signs and symptoms are present. In a child older than 24 months with focal neurological signs and symptoms, a head CT scan without contrast is also considered most appropriate. If the child has no history of head trauma or focal neurological signs and symptoms, the ACR still considers a CT scan of the head without contrast usually appropriate. According to the ACR, an MRI scan of the head may be appropriate in a child without focal neurological signs and symptoms if further evaluation is indicated after head CT scan has been performed. An MRI scan of the head is usually appropriate if focal neurological signs and symptoms are present. An MRI scan of the head may be useful whether or not the initial head CT scan is positive or negative. Importantly, a head CT scan should not be delayed for MRI scanning in a symptomatic child.

Imaging Modalities: CT and MRI

X-rays of the skull should be obtained as part of a skeletal survey and are discussed further in ▶ Chap. 15, "Evaluation of Pediatric Fractures at Autopsy" as well as the role of bone scintigraphy. Ultrasonography can also be useful in infants less than

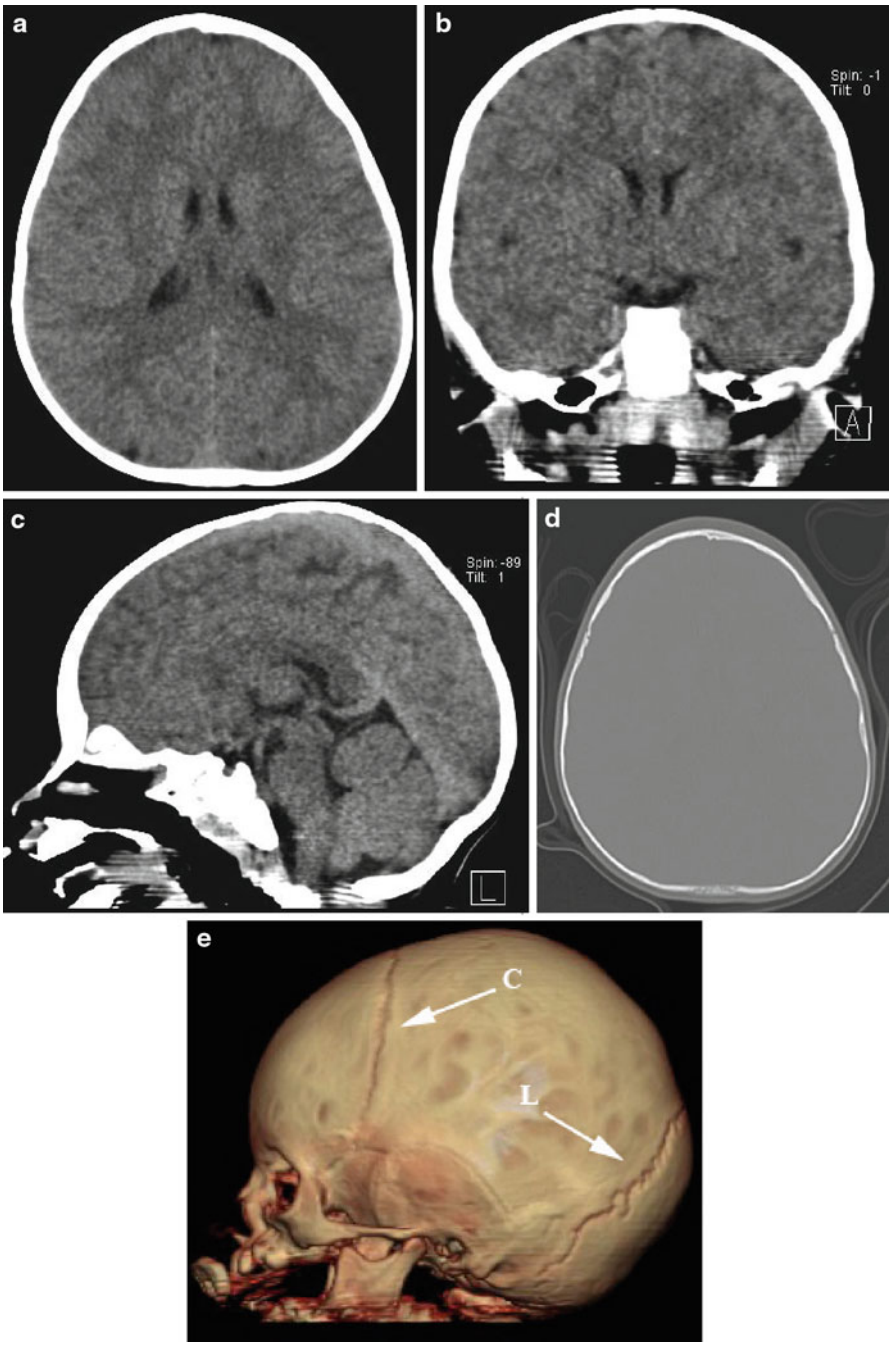

Fig. 20.2 (continued)

approximately 6–8 months of age before fontanelle closure. However, CT and MRI scans are the main imaging modalities used clinically for detecting intracranial injury. Recent technological advances in neuroimaging have greatly enhanced our ability to identify subtle injuries that may have immediate and long-term consequences. Newer functional neuroimaging techniques (such as perfusion imaging, diffusion tractography, and MR spectroscopy) may lead to an improved understanding of the pathophysiology of nonaccidental intracranial trauma. Software tools such as 3D reconstruction programs provide improved visualization of intracranial injury.

Computed Tomography (CT)

Computed tomography, commonly known as CT, became available clinically in the 1970s. CT is an imaging modality based on measuring the differential absorption of x-ray photons passing through tissues. During CT image acquisition, a source emits an x-ray beam which passes through a patient and is collected on the opposite side of the body by detectors. The x-ray beam is highly collimated and therefore exposes only a thin slab of tissue at a time. The x-ray source and detectors are located within a gantry which rotates around a stationary patient. A grayscale image is produced which is related to the degree of absorption of the x-ray beam by the tissue. A reconstruction computer algorithm is used to analyze the data and produce a CT image made up of multiple pixels whose intensity reflects the differential tissue absorption at each pixel location. Structures that are very dense, such as bone, have high intensity on the CT image and are bright. Structures such as soft tissue have intermediate intensity on the CT image, and gas-filled structures appear very dark. A CT scan through the head consists of multiple two-dimensional images or "slices" which extend through the entire head. Traditionally, CT slices were obtained one slice at a time and oriented in the axial plane. Modern CT scanners use spiral or helical technology in which the x-ray source and detectors rotate around the patient while the patient moves continuously through the x-ray beam. This creates a volume acquisition that can be reconstructed in any plane, for example, axial, coronal, sagittal, or oblique, thereby eliminating the multiplanar advantage that MRI previously had over CT (Fig. 20.2). Another recent advance in CT technology is the use of multi row detectors which greatly decreases the scanning time while improving image resolution. The decreased scan time also helps to improve image quality by resulting in fewer artifacts due to patient motion which is particularly important in the pediatric population. CT scans can be performed either without or following administration of iodine-based intravenous contrast material.

Fig. 20.2 Axial, coronal, and sagittal CT reconstructions. From a single CT acquisition, images can be reconstructed in any plane. Axial (**a**), coronal (**b**), and sagittal (**c**) noncontrast CT images are shown. The data can also be reconstructed in bone windows to highlight bony detail (**d**). Finally, the data can be used to create 3D reconstructions which are helpful in identifying fractures (**e**). Notice the normal coronal (*C*) and lambdoid (*L*) sutures

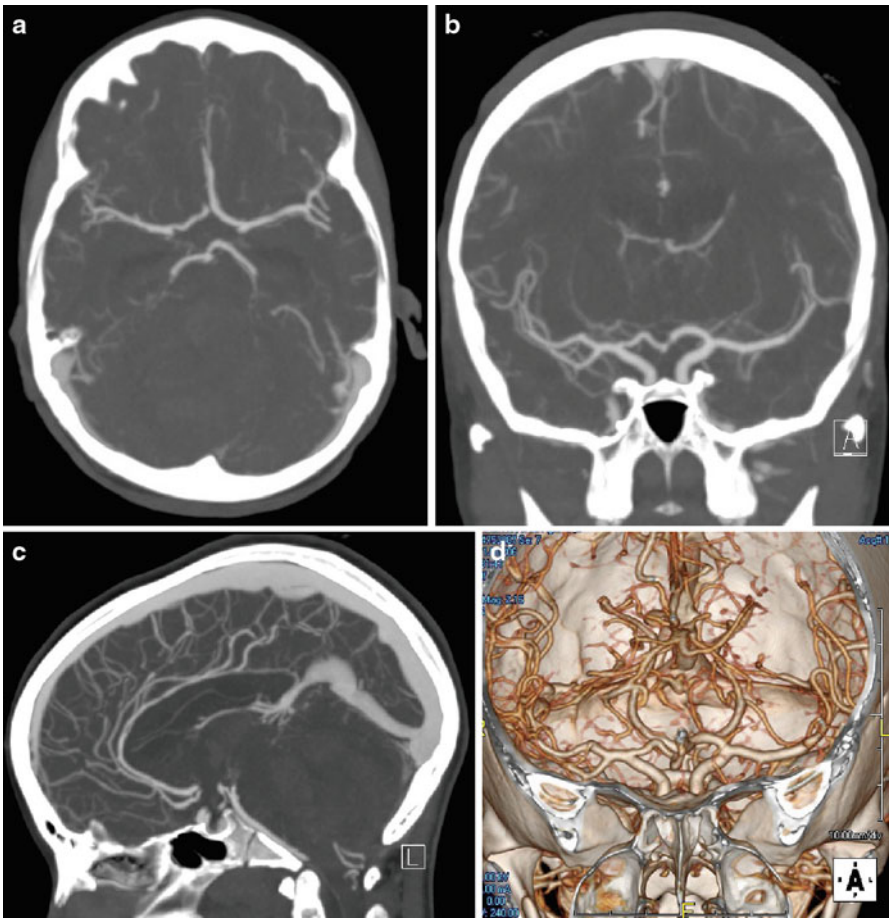

Fig. 20.3 CT angiogram. 9-year-old female with intracranial hemorrhage. These are images from a CT angiogram with contrast in the axial plane (**a**), coronal (**b**), and sagittal planes (**c**). 3D reconstructions of the vasculature can also be made from the original acquisition (**d**)

For the initial evaluation of suspected pediatric head and spine injury, CT imaging of the brain and spine is typically performed without intravenous contrast. The presence of contrast, which appears hyperdense on CT and therefore is bright, limits the detection of acute intracranial hemorrhage which is also hyperdense on CT. Additionally, intravenous contrast is not necessary to evaluate fractures of the skull, face, or spine. However, if injury to the intracranial or cervical vessels is suspected, then postcontrast images can also be acquired. Following the injection of intravenous contrast, imaging is acquired rapidly through the intracranial and cervical circulation during the arterial phase. This technique, known as CT angiography, is useful in evaluating the major vascular structures for dissection, occlusion, or active hemorrhage (Fig. 20.3). The data can be resliced in any orientation,

and 3D reconstructions can be performed to assess vessel caliber. A newer technique that may become important in the future in evaluating the acute-trauma patient is perfusion CT. Following a bolus of intravenous contrast, scanning is performed repeatedly through the brain as the contrast passes through the intracranial circulation. From these images, cerebral blood volume, mean transit time for the contrast to pass through the brain, and cerebral blood flow values can be calculated providing information concerning the state of cerebral vascular autoregulation, a process commonly disrupted in patients with acute brain injury (Fig. 20.4).

There are several advantages to CT as an imaging modality in the acute traumatic setting. Most importantly, a CT scan can be obtained within minutes and is relatively unencumbered by the presence of life-support equipment, making CT imaging useful for rapidly identifying life-threatening intracranial injuries. CT scans can then be used to triage those patients with a space-occupying lesion, such as a large extra-axial hematoma, for early neurosurgical intervention (Fig. 20.5). Most hospitals have CT-imaging capability readily available with easy access from the emergency department. CT imaging with a relatively open gantry allows greater access to patients during scanning, which can be a problem with MRI particularly for an unstable patient. A CT scan can be obtained rapidly, usually without the need for patient sedation or anesthesia. CT imaging, particularly with multiplanar reformat capability, is also the most sensitive imaging modality for identifying fractures. Acute traumatic pneumocephalus is easily seen on CT. In the same setting, CT imaging of the chest, abdomen, and pelvis can also be obtained. Also at the same time, CT angiography can be performed to evaluate traumatic vascular injury. A trauma protocol, including a CT scan of the patient from the head through the pelvis, along with vascular imaging, can be accomplished in less than 15 min. Finally, CT is useful in specific circumstances such as differentiating hemorrhage from calcification, which can at times be confusing on MRI.

Radiation dose should always be considered when performing CT imaging of a child. Children have a greater chance of experiencing radiation-associated cancers because they have a lifetime to manifest those changes. The ALARA (as low as reasonably achievable) principle should always be followed and includes limiting the scanning region to the smallest possible area, optimizing CT scanner setting for children based on their size and weight, using pediatric specific protocols to minimize dose, and determining appropriate scanner resolution such as using lower-resolution scans for repeated studies (Huda 2009).

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) became available for clinical use in the 1980s. MR imaging, unlike CT, does not use x-rays to produce images. Instead, MR image contrast is based on the response of body tissues to an externally applied magnetic field. An MR scanner is composed of a large magnet, typically a superconducting magnet, which creates a uniform magnetic field inside the bore of the scanner.

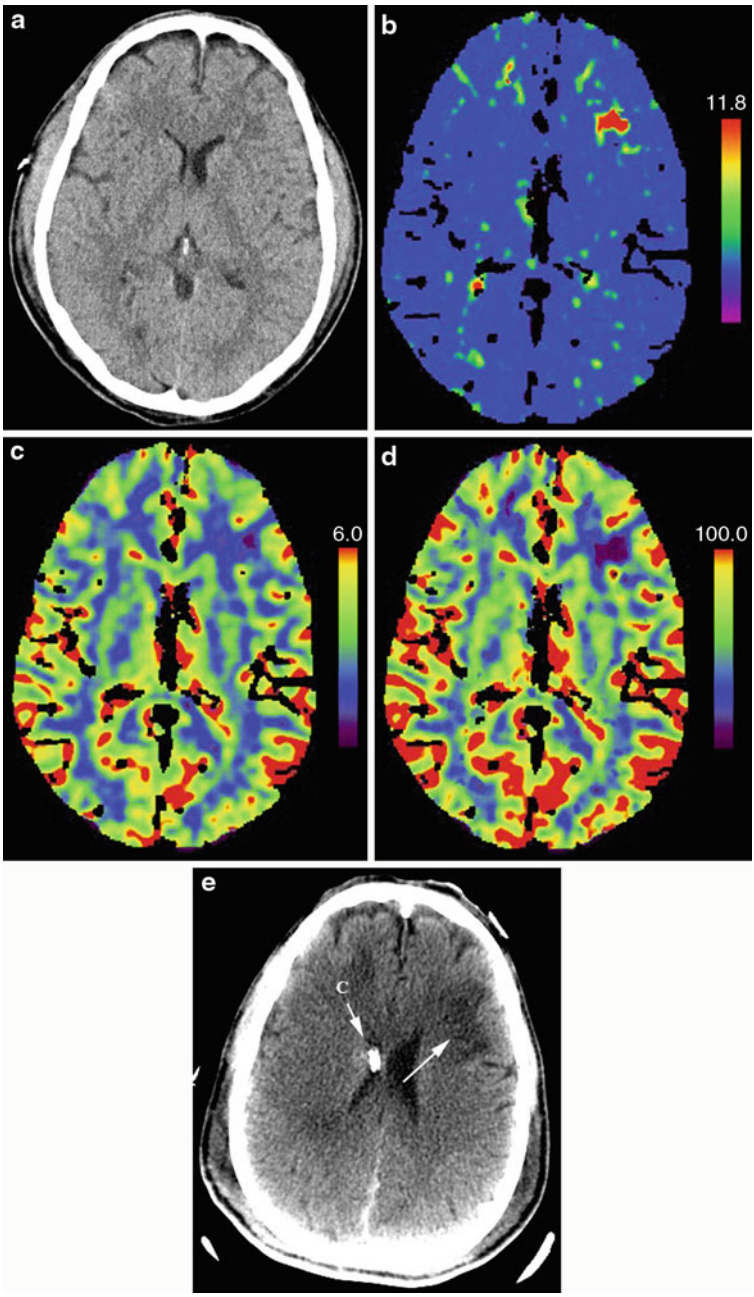

Fig. 20.4 (continued)

The strength of the magnetic field is measured using the unit Tesla (T). One Tesla (equivalent to 10,000 G) is much larger than the Earth's magnetic field of 0.5 G. Clinical scanners generally produce magnetic fields that range from 0.1 T to 3 T; however, 8 T scanners are now available for human imaging. The magnetic field is always turned on, and therefore safety precautions have to be followed when approaching the MRI scanner. No paramagnetic objects must be brought into the scanner room as these objects can be rapidly propelled by the magnetic field and cause great damage and possibly injury to the patient and hospital personnel. All patients should be thoroughly screened for metal, and all hospital personnel should undergo MRI safety training before working in the scanner environment.

When a patient is placed on the MRI table in the supine position and moved inside the bore of the scanner, the patient experiences a uniform magnetic field oriented along the axis of the body (designated the z-axis). An MRI scan, like a CT scan, consists of multiple two-dimensional images through the area of interest such as the brain or spine. To create these images, each point in the brain or spine has to be identified uniquely along the x-, y-, and z-axes. This is done by the use of gradient coils which create slight variations in the magnetic field across the patient that can be used to determine the location in space of each volume of tissue. During imaging, an excitation pulse or RF (radio frequency) pulse is applied to a selected volume of tissue. Following the pulse, the tissue begins to return to its normal state by a process called relaxation. After a set period of time following the RF pulse, an image is acquired using receiver coils. Computer processing of the data results in a series of grayscale images made up of multiple voxels. The signal intensity of each voxel is a reflection of the time required for tissue relaxation which is based primarily on the molecular characteristics of the tissue and specific MR timing parameters that can be set by the scanner operator. Tissue relaxation is accomplished by two main mechanisms known as T1 and T2 relaxation. By manipulation of pulse timing parameters, specific sequences can be created (Fig. 20.6). A sequence that emphasizes T1 relaxation is called T1-weighted, and a sequence that emphasizes T2 relaxation is called T2-weighted. T1-weighted sequences are useful in discriminating between various tissues, such as gray matter–white matter differentiation. T1-weighted images are also sensitive to the presence of intravenous gadolinium-based contrast material and therefore are used in assessing blood–brain barrier breakdown. T2-weighted images are sensitive to the presence of water and therefore are useful in detecting edema. See Yousem, Zimmerman, and Grossman (2010) for further review.

Fig. 20.4 CT perfusion in trauma patient. A 17-year-old status post motor vehicle accident. An axial image (**a**) from the initial noncontrast CT scan demonstrates no evidence of injury. Perfusion CT images obtained at the same time of the initial noncontrast CT exam shows a focal area of abnormally prolonged mean transit time (**b**) and decreased cerebral blood volume (**c**) and cerebral blood flow (**d**) in the left periventricular white matter. A follow-up noncontrast CT scan (**e**) performed 11 days later shows interval development of parenchymal injury in the left periventricular white matter (*white arrow*). Notice the presence of a ventricular catheter (*C*) within the right lateral ventricle and scalp swelling

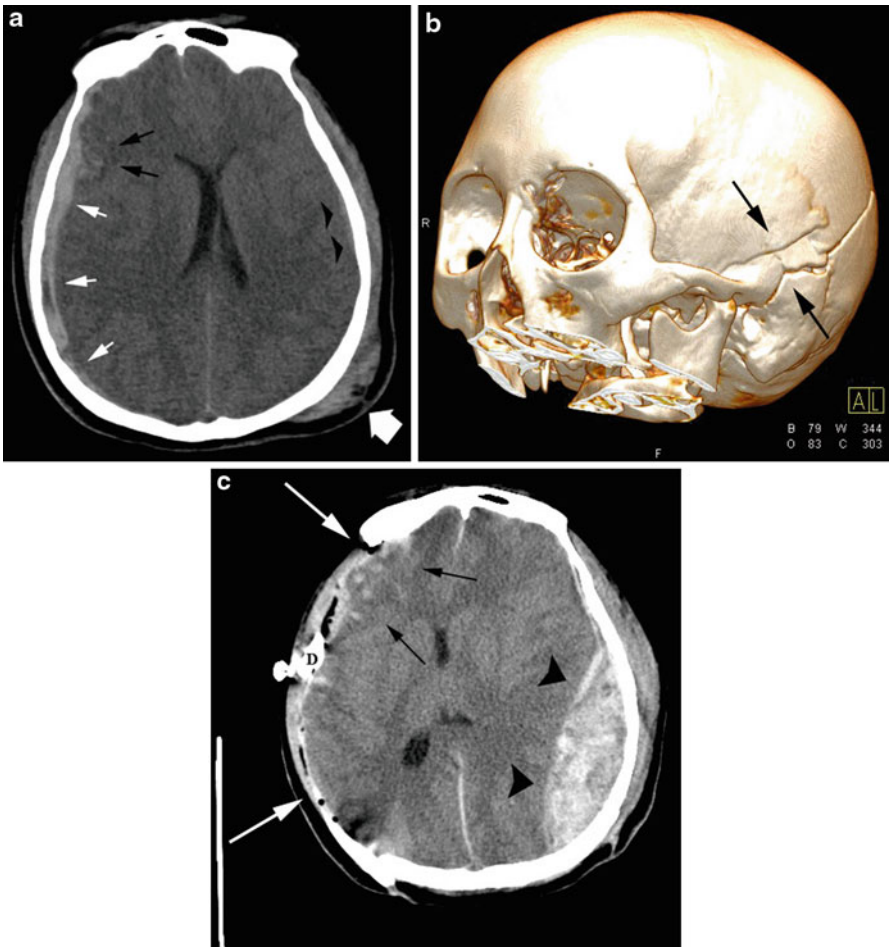

Fig. 20.5 Intracranial injury requiring emergent decompression. 14-year-old female riding on the hood of a car ("car surfing") who fell off at high speed. The adult driver was subsequently charged with child endangerment. The initial noncontrast CT demonstrates an acute right-sided subdural hematoma (*white arrows*), right frontal intraparenchymal hemorrhagic contusions (*black arrows*), and midline shift to the left (**a**). Notice a subtle left-sided extra-axial collection which is lentiform in shape consistent with an epidural hematoma (*black arrowheads*). There is a left parietal scalp hematoma indicating the site of impact (*large white arrow*). A 3D reconstruction of the skull (**b**) demonstrates a comminuted fracture of the left temporal bone (*black arrows*). The patient was taken to the operating room for a right decompressive craniotomy; however, in the recovery room the patient's condition deteriorated, and an emergent follow-up CT (**c**) was obtained which showed rapid interval enlargement of the left-sided epidural hematoma (*black arrowheads*) with partial effacement of the ventricular system and midline shift to the right. Notice the right frontal parietal craniectomy (*white arrows*). Also the hemorrhagic contusions (*black arrows*) are more prominent. A surgical drain and overlying skin staples are partially seen (*D*). The patient returned to the OR for emergent decompression of the left-sided epidural hematoma

To bring out T1- or T2-weighted effects in images, the main magnetic field must be homogeneous, and intrinsic tissue inhomogeneities must be compensated for by the pulse sequence. Intrinsic tissue characteristics, such as the presence of blood products or other paramagnetic substances, can cause the local magnetic field to be inhomogeneous and result in loss of signal. In order to compensate for these effects, a special pulse is given called an inversion pulse. This pulse can also be used to nullify unwanted signal from specific tissues. For example, in a T2-weighted image, cerebrospinal fluid (CSF) is bright and can mask the presence of underlying brain edema. In order to enhance the detection of edema, a specific sequence called FLAIR (fluid-attenuated inversion recovery) is used in which the signal from the bright surrounding CSF is suppressed.

There are times, however, when it is important to detect small-field inhomogeneities, such as when looking for microscopic blood products that could indicate prior trauma. In these cases, a sequence that does not compensate for field inhomogeneities is used, called T2*-weighted sequence, which is very sensitive for the detection of blood, iron, or calcification. T2*-weighted images have typically been acquired with gradient echo imaging (GRE) technique. More recently a technique called susceptibility-weighted imaging (SWI) has been developed which further enhances our ability to detect microscopic blood products.

Diffusion imaging is another MRI sequence that is based on detecting the microscopic movement of water molecules in tissue. Diffusion imaging detects both the magnitude and the direction of water movement. The magnitude of water diffusion gives information concerning the local microenvironment of the tissue. For example, if the tissue is highly cellular, such as in a highly cellular neoplasm, diffusion of water will be decreased relative to the adjacent normal brain tissue. This will appear as a dark signal on the diffusion sequence called apparent diffusion coefficient (ADC) map. Another example of relatively reduced diffusion is an acute infarction of the brain. During hypoxia–ischemia the Na+/K + -ATPase pump fails and the cells begin to swell, accumulating water from the surrounding extracellular space. Shifting of water from the loose extracellular space into highly compartmentalized cells leads to a relative reduction of net water diffusion, which is considered responsible for the resultant low signal on ADC maps. Information about the direction of water movement is also obtained with diffusion imaging. In gray matter, water diffuses in all directions. In white matter, the white matter fiber tracts restrict the movement of water perpendicular to the tracts, with water moving preferentially in a parallel direction along the white-matter tracts. Because water movement occurs preferentially in the direction of the white-matter fiber tracts, models of the fiber tracts can be created based on the direction of water diffusion. This is known as diffusion tensor imaging (DTI). Diffusion imaging may prove useful in detecting more subtle areas of white-matter injury earlier than conventional imaging (Neil et al. 2002; Wilde et al. 2008).

MR can also be used to image vascular anatomy. MR angiography is based on detecting the magnetization of flowing blood while suppressing signal from stationary tissue. The result is selective imaging of vascular structures, both arterial and venous depending on the timing and location of the magnetization pulse. 3D reformats can also be performed and rotated in any direction to enhance detection of vascular injury, stenoses, and vascular malformations.

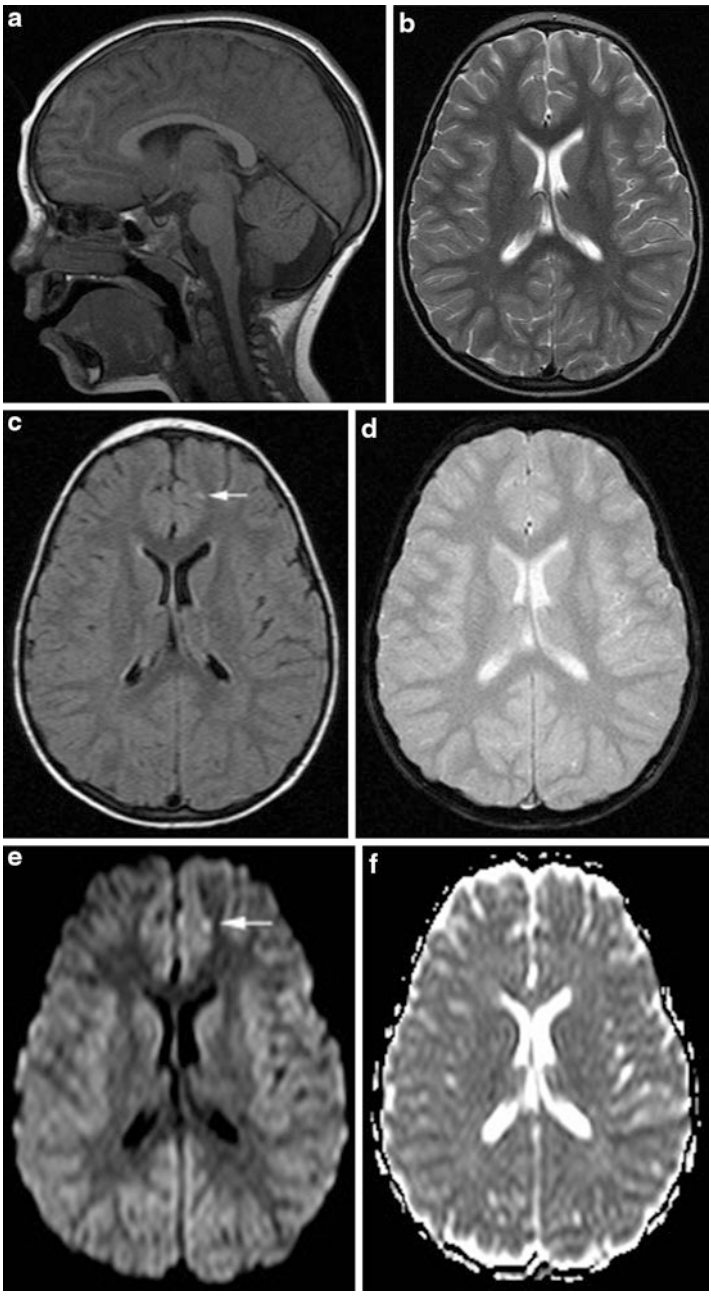

Fig. 20.6 (continued)

MR spectroscopy (MRS) shows metabolite maps of the local tissue environment. The main metabolites identified are *N*-acetylaspartate (a neuronal marker), creatinine (marker of cell energy), choline (membrane marker), myoinositol (glial cell marker), and lactate (product of anaerobic metabolism). MRS may be useful in improving the ability to predict long-term neurological outcome (Cohen et al. 2007; Hunter et al. 2005).

A complete MRI of the brain includes T1- and T2-weighted imaging, a FLAIR sequence, T2*-weighted imaging to improve detection of intracranial hemorrhage, and diffusion imaging. In specific cases contrast may be administered. Optional sequences depend on the clinical situation and include MR angiography and MR spectroscopy. A typical MRI brain study requires approximately 30 min. Although obtaining an MRI study requires more time than a CT scan, there are several advantages to MRI in imaging cases of nonaccidental trauma. MRI avoids the radiation exposure associated with CT scanning. This is particularly important in pediatric patients who are expected to undergo repeated examinations, for example, a child with hydrocephalus requiring multiple imaging studies over a period of time to follow ventricular size. Additionally, MRI has far greater sensitivity for detecting and dating intracranial injury than CT which can be important for clinical as well as medical/legal reasons. For example, small contusions or extra-axial collections that are not visible on CT can often be seen on MRI. Furthermore, signal abnormality from remote hemorrhages persists much longer on MRI than CT, improving the detection of remote trauma and trauma of various ages. MRI offers superior anatomic detail and gray matter–white matter distinction. A variety of MRI sequences are available to characterize different physiological attributes of the brain such as water diffusion, the presence of metal, disruption of the blood–brain barrier, and metabolic makeup of the tissue. MRI is superior to CT at imaging the posterior fossa which can be obscured on CT due to artifact from the bones of the skull base. In spine trauma, when there are neurological deficits present, MRI provides detailed information about soft tissue structures including the intervertebral disc, the ligaments, the thecal sac, the blood vessels, and the spinal cord.

The Imaging Appearance and Dating of Intracranial Hemorrhage

The appearance of hemorrhage on CT and MR is complex and depends on many variables which therefore make exact dating of blood products inaccurate. Variables that influence the appearance of blood on imaging are both physiological and

Fig. 20.6 T1-weighted, T2-weighted, FLAIR, T2*-weighted, and diffusion MR images. 3.5-year-old with a reported history of only minor trauma but with suspected nonaccidental trauma. Images from a noncontrast MRI scan of the brain include a sagittal T1-weighted image (**a**), axial T2-weighted image (**b**), axial FLAIR image (**c**), axial T2*-weighted image (**d**), axial diffusion-weighted image (**e**), and the corresponding ADC map (**f**). Notice the small focus of abnormal T2 signal involving the left frontal lobe at the gray matter-white matter junction which is seen best on the FLAIR and the diffusion images (*white arrow*). This corresponds to a focus of diffuse axonal injury consistent with intracranial traumatic injury

Table 20.1 MR imaging characteristics of blood

	T1 weighted	T2 weighted
Hyperacute (< 12 h) oxyhemoglobin	Isointense to dark	Bright
Acute (1–3 days) deoxyhemoglobin	Isointense to dark	Dark
Early subacute (3–7 days) intracellular methemoglobin	Bright	Dark
Late subacute (7–14 days) extracellular methemoglobin	Bright	Bright
Chronic (>1–3 months) hemosiderin	Isointense to dark	Dark

based on parameters set by the CT or MRI operator during scanning (Atlas and Thulborn 2008). Physiological factors related to the patient include the presence or absence of a coagulopathy, oxygenation status, and hemoglobin level. Local factors affecting the appearance of hemorrhage include the site and size of the hemorrhage, the partial pressure of O_2 and local pH, blood–brain barrier integrity, thrombus formation and clot retraction, and hemoglobin resorption/degradation rate. Machine variables controlled by the operator include tube voltage and current for CT and for MRI, the pulse sequences used, pulse parameters, and the field strength of the magnet.

On CT, acute blood that is more than 1 h and less than 1 week old is typically hyperdense. Subacute blood becomes isodense from 1 to 3 weeks of age. Finally, chronic hematomas, greater than 3 weeks, are typically hypodense.

On MRI, the appearance of blood products is more complex but is primarily influenced by two factors: the oxygenation state of the blood and whether or not the red blood cell (RBC) membrane is intact (Atlas and Thulborn 2008) (Table 20.1). In freshly extravasated blood, hemoglobin is in the oxygenated state and RBC membranes are intact. The imaging characteristics are similar to normal brain being slightly hypointense or isointense to the brain on T1-weighted images and extremely hyperintense on T2-weighted images. A characteristic feature of hyperacute hematomas is a ring of hypointense signal on T2-weighted images due to the rapid deoxygenation of blood products at the periphery of the hematoma. As the surrounding tissue experiences a state of hypoxia due to disruption of the local blood supply, local factors, such as pO_2, pH, and pCO_2, drive dissociation of oxygen from the hemoglobin molecule within the red blood cells in the blood clot. The paramagnetic deoxyhemoglobin in the acute hemorrhage sets up variations in susceptibility throughout the hematoma which result in marked loss of signal on T2-weighted imaging. Thus an acute hematoma contains intact red blood cells with deoxyhemoglobin and appears isointense to slightly dark on T1-weighted imaging and very dark on T2-weighted imaging. Surrounding edema appears as hyperintense on T2-weighted imaging. During the early subacute phase, while the RBC membranes are still intact, hemoglobin is oxidized to methemoglobin which produces a hyperintense signal on T1-weighted imaging. Because the RBC membranes are intact, the hematoma remains hypointense on T2-weighted imaging. Conversion to methemoglobin can initially appear at the periphery of the hematoma and is seen throughout the hematoma during the late subacute phase. At this time, RBC membranes have been lysed, and so the hematoma loses its hypointense signal

and becomes again bright on T2-weighted imaging. In the chronic state, iron storage forms from the breakdown of hemoglobin include ferritin and hemosiderin. This results in a hypointense rim on T1- and T2-weighted imaging that first forms at the periphery and progresses centrally. There is particularly marked hypointensity on T2*-weighted images. The presence of hemosiderin in association with an acute hemorrhage implies that there were multiple episodes of bleeding of different ages, a finding that is particularly useful in evaluating a suspected nonaccidental trauma case. Hypointensity from hemosiderin can remain for years following the hemorrhagic event.

Findings in Inflicted Head Trauma

Since Caffey's original description in 1946 of the association of subdural hematomas and long bone fractures in children (Caffey 1946), imaging of the CNS has played an important role in detecting and documenting child abuse. While there may be little external evidence of injury, significant intracranial injury can exist. In general any evidence of CNS injury that is out of proportion to the provided history should raise suspicion for child abuse. Findings include subdural hematomas (SDH), subarachnoid hemorrhage (SAH), cerebral contusions, diffuse cerebral swelling, ischemic injury, and diffuse axonal injury (DAI). Less common findings include epidural hematomas (EDH) which are more commonly seen following accidental injury. Children are more prone to CNS injury due to their larger head-to-body ratios, weaker cervical musculature, more compliant skull, and softer brain prior to myelination. Multiple sites of injury and hemorrhages at different stages of evolution strongly suggest nonaccidental injury.

Brain Swelling and Hypoxic–Ischemic Injury

There are several underlying abnormalities that can result in brain swelling in the acute-trauma patient (Gean 1994). Particularly in young patients, brain swelling can be due to hyperemia associated with increased cerebral perfusion resulting from trauma-induced alteration of cerebral autoregulation. The most severe form of cerebral edema is cytotoxic edema with failure of the Na+/K + -ATPase pump. On CT images, cytotoxic edema is seen as diffuse loss of gray matter–white matter differentiation, brain swelling with effacement of sulci, and mass effect on adjacent structures such as the ventricles and perimesencephalic cisterns (Fig. 20.7). The brain can appear featureless with loss of distinction of the deep gray nuclei from the overlying cortex. There can be relative sparing of the cerebellum due to preserved blood flow to the cerebellum. The supratentorial brain can then appear hypodense compared with the normal-appearing cerebellum known as the "white cerebellum" sign (Fig. 20.8). The most sensitive method for detecting cytotoxic edema is diffusion MR imaging. Areas of acute ischemia appear "light bulb" bright on diffusion-weighted images and can be detected as early as 30 min following injury. The area involved can be a focal

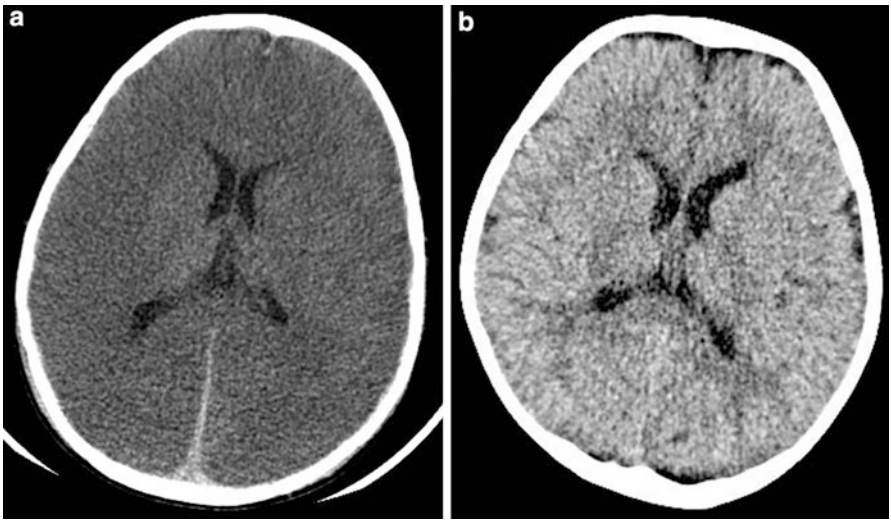

Fig. 20.7 Cytotoxic edema. 18-month-old following nonaccidental trauma. An axial image from a noncontrast CT scan demonstrates diffuse loss of gray matter-white matter differentiation and loss of the normal cortical sulci (**a**). Compare this study to an axial CT image from a normal infant of the same age (**b**)

area of injury, such as may be seen in ischemic lesions of DAI, can involve the deep gray nuclei (Fig. 20.9), or can involve large vascular territories, for example, following traumatic carotid-artery dissection or occlusion.

Vasogenic edema is the most common form of edema in traumatic brain injury (Gean 1994). Vasogenic edema results from disruption of the blood–brain barrier allowing extravasation of fluid into the extracellular space. On imaging, vasogenic edema predominantly involves the white matter as an ill-defined area of signal abnormality with fingerlike projections into the subcortical white matter which appear hypodense on CT, hyperintense on T2-weighted MR images (Fig. 20.10), and hypointense on T1-weighted MR images. Vasogenic edema can be focal with only local mass effect on adjacent structures or can be diffuse, for example, involving an entire cerebral hemisphere resulting in midline shift. Vasogenic edema does not follow vascular territories and usually does not extend across the compact fibers of the corpus callosum. The adjacent dural sinuses can appear as hyperdense due to the increased contrast with the swollen brain and due to vascular stasis from increased intracranial pressure.

Other types of edema include hydrostatic edema, hypoosmotic edema, and interstitial edema (Gean 1994). Hydrostatic edema results from elevated intravascular pressure resulting in efflux of fluid across an intact blood–brain barrier. This can be seen in the setting of an acute hypertensive event or following decompressive craniotomy for increased intracranial pressure. Hypoosmotic edema can be seen in patients with low serum osmolarity such as those with the post-traumatic syndrome of inappropriate secretion of antidiuretic hormone

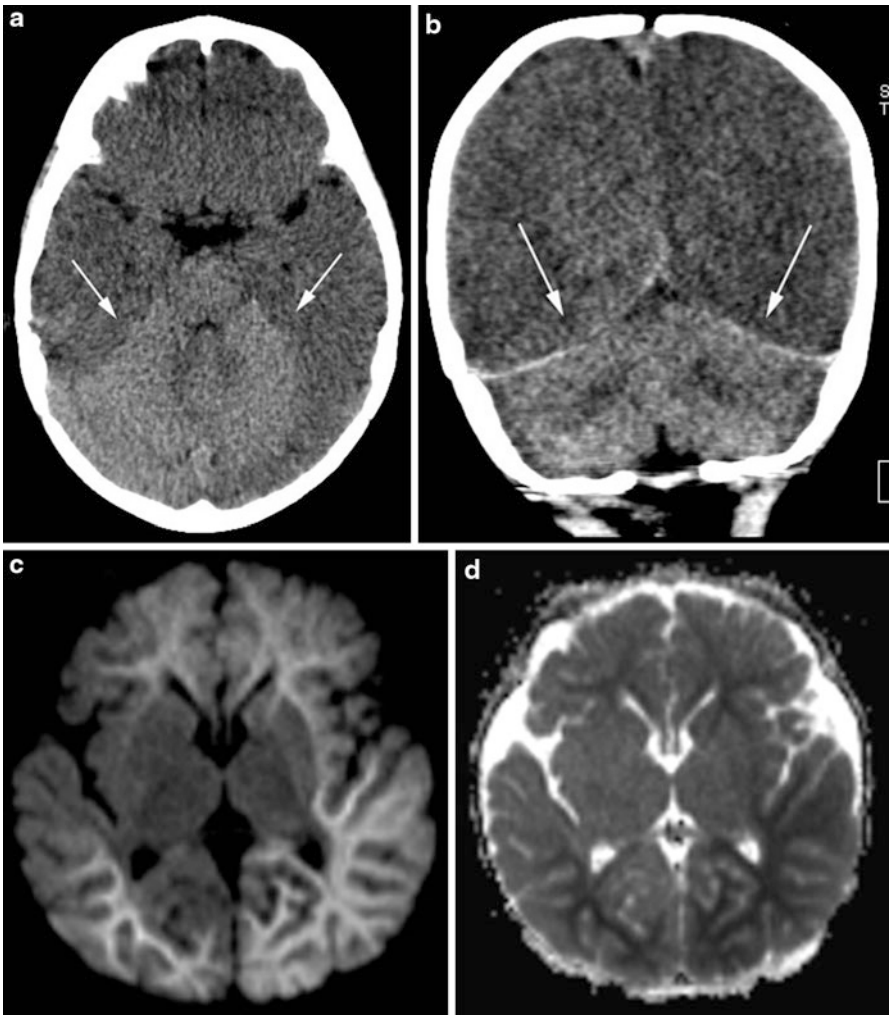

Fig. 20.8 White cerebellum sign. 5-month-old brought in by caregiver for lethargy. Noncontrast axial (**a**) and coronal (**b**) CT images demonstrate relative diffuse hypodensity of the supratentorial brain. Compared with the supratentorial brain, the normal cerebellum appears hyperdense (*arrows*). A follow-up MRI demonstrates widespread areas of decreased diffusion which is bright on the diffusion-weighted image (**c**) and dark on the corresponding ADC map (**d**). These findings are compatible with diffuse hypoxic injury. Notice also the relative sparing of the deep gray nuclei

(SIADH) or in patients who have undergone aggressive IV fluid resuscitation. Interstitial edema involves the movement of fluid into the periventricular white matter such as seen with transependymal flow of CSF due to obstructive hydrocephalus. On CT, transependymal flow of CSF appears as a rim of low density along enlarged ventricles or as a hyperintense signal along the ventricular margins on T2-weighted imaging.

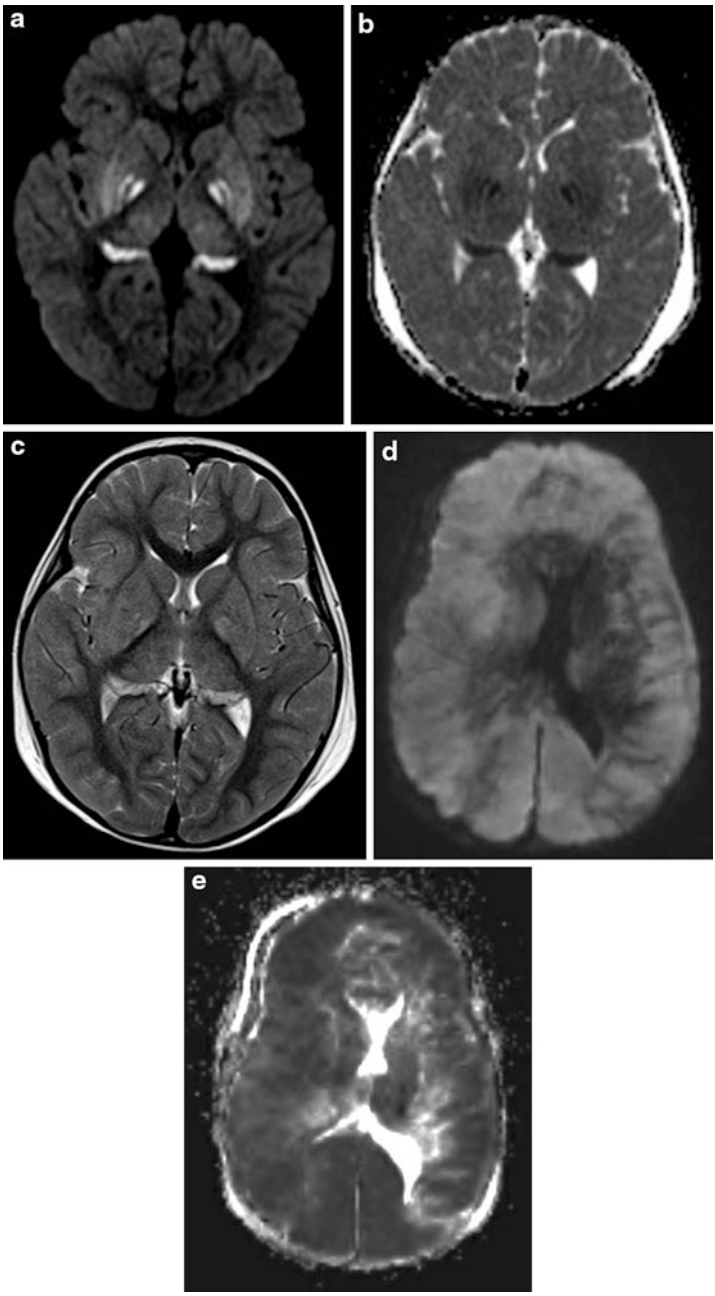

Fig. 20.9 (continued)

As swelling progresses, due to the fixed intracranial volume inside the rigid skull, herniation occurs. An exception to this is seen in young infants prior to suture closure. Due to open sutures, a more malleable skull, and open fontanelles, these young infants can better accommodate brain swelling than an older child. Once sutures are closed, however, children are more susceptible to brain injury from swelling than adults due to the relative lack of extra-axial space. The compartments of the brain are defined in relation to the infoldings of the dura (the falx cerebri and tentorium cerebelli) and the openings of the skull. Types of brain herniation include subfalcine herniation underneath the free edge of the falx cerebri, uncal herniation of the medial temporal lobes, transtentorial herniation, cerebellar tonsillar herniation through the foramen magnum, and external herniation through a fracture or a craniotomy defect (Fig. 20.11).

Subdural Hematoma

On CT, an acute SDH is usually homogeneously hyperdense, although a hyperacute SDH can have mixed density due to unclotted blood, extruded serum during clot formation, or the admixture of CSF from a traumatic tear in the adjacent arachnoid membrane (Fig. 20.12) (Gean 1994; Gean and Fischbein 2010; Provenzale 2007). This finding should not be mistaken for rebleeding into a chronic SDH. The imaging appearance of an SDH can also be influenced by various clinical factors including the patient's hemoglobin level and the potential presence of any underlying coagulopathy (Atlas and Thulborn 2008). An SDH may cross suture lines but is limited by the falx cerebri along the midline and the tentorium cerebelli. SDHs are usually crescent-shaped and spread along the entire hemisphere. This is especially true in infants and young children who, unlike adults, typically lack dural–arachnoid adhesions that would otherwise limit the extent of the SDH. Because of this, a large volume of blood can accumulate in the subdural space relatively unimpeded and result in the child becoming acutely hypovolemic. On cross-sectional imaging because of the extensive spread of the collection, the appearance may be misleading with the SDH being only a few millimeters in thickness despite the presence of a large volume of subdural blood. Acute SDHs can have mass effect on the underlying brain parenchyma (Reed et al. 1986). There can be resultant midline shift toward the contralateral side, and if the SDH continues to grow, there

Fig. 20.9 Patterns of cytotoxic edema. 21-month-old left unattended and found in a pond 1 h later. An axial diffusion-weighted image (**a**) and the corresponding ADC map (**b**) demonstrate decreased diffusion (which is bright on the diffusion-weighted image and dark on the ADC map) involving the globus pallidus, putamen, fornices, and hippocampi bilaterally. Abnormally bright signal can also be seen in these structures on the T2-weighted image (**c**). Axial diffusion-weighted images (**d**) and the ADC map (**e**) in a different patient show restricted diffusion involving the brain diffusely with relative sparing of deep white matter. Notice also the midline shift to the left which is due in part to a right holohemispheric subdural hematoma. This 6-month-old child had a history of suspected nonaccidental trauma

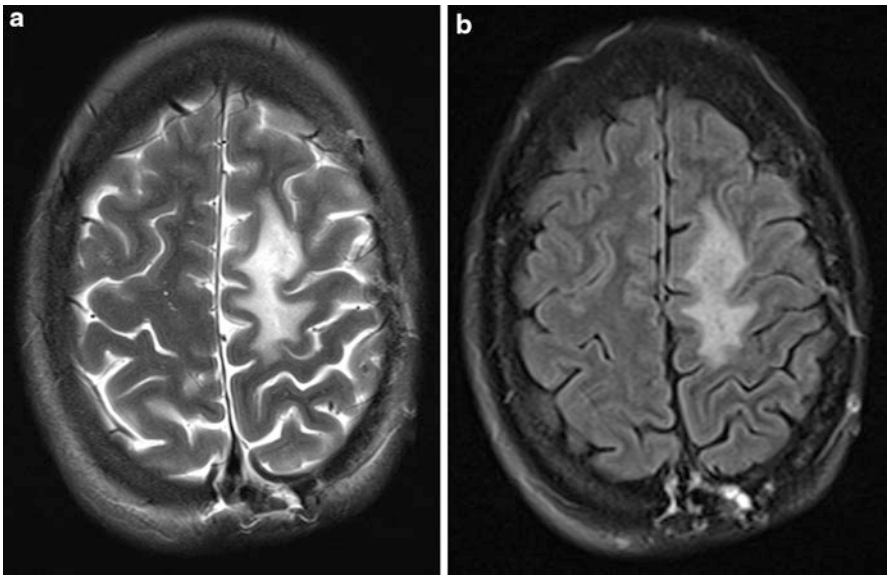

Fig. 20.10 Vasogenic edema. An axial T2-weighted image (**a**) and an axial FLAIR image (**b**) demonstrate abnormal increased signal in the subcortical white matter of the left superior frontal gyrus. Notice the "fingerlike" extension of the signal abnormality along the white matter

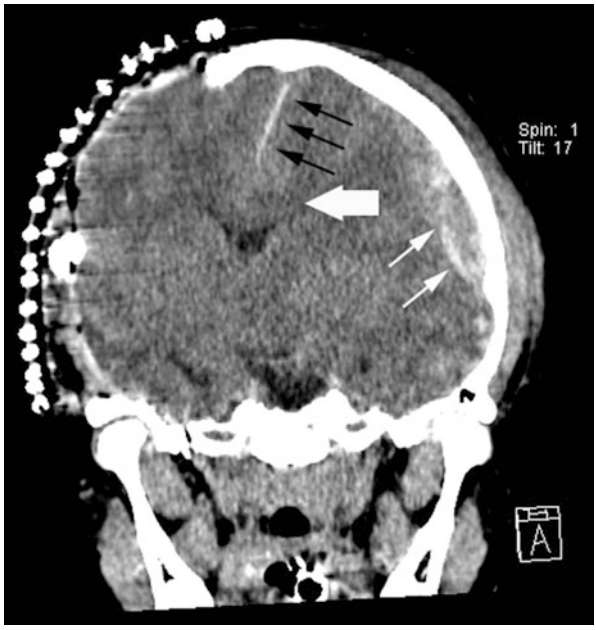

Fig. 20.11 Subfalcine herniation. A coronal noncontrast CT from the same patient as in Fig. 20.5 demonstrates shifting of the brain (*large white arrow*) to the right underneath the free edge of the falx cerebri (*black arrows*) as a result of a large left-sided epidural hematoma (*small white arrows*). The patient had undergone right frontal parietal craniectomy with overlying skin staples

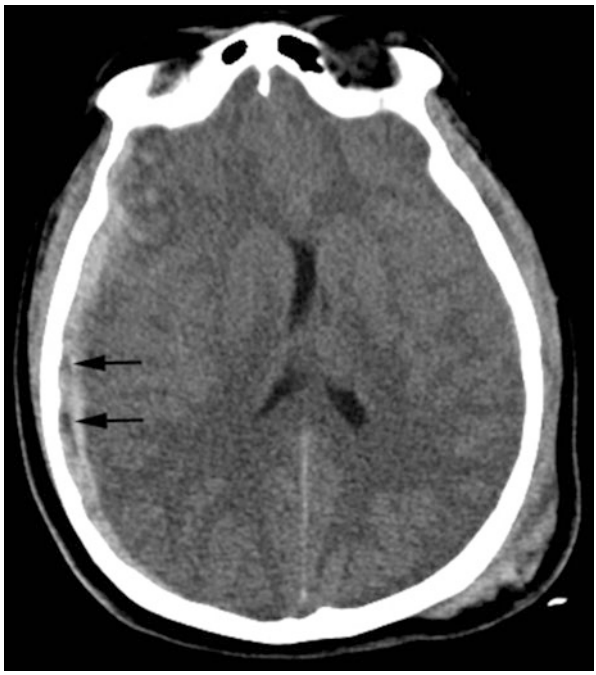

Fig. 20.12 Hyperacute SDH. Notice the low-density components in this hyperacute SDH (*arrows*)

can eventually be brain herniation. Typically, mass effect results in effacement of adjacent sulci and the ipsilateral ventricle. However, if the SDH accumulates rapidly enough, midline shift can result in obstruction of the foramen of Monroe preventing egress of CSF from the ipsilateral ventricle (Fig. 20.13). The appearance would then be dilated lateral ventricles bilaterally with shift of the midline away from the acute SDH. In any case, where there is midline shift without an obvious explanation, the underlying cause should always be sought. The same is true for asymmetric effacement of cortical sulci. Atypically, an acute SDH may appear isodense, with the only indication of its presence being unilateral asymmetric effacement of cortical sulci and the displacement of the cortical margin away from the inner table of the calvarium. Adjusting the windowing on a CT image, which is particularly easy to do on today's digital imaging display monitors, is very useful in helping to detect an acute hyperdense SDH located adjacent to the hyperdense calvarium. SDH can also be seen within the interhemispheric fissure layering along the falx cerebri (Fig. 20.14). Interhemispheric SDHs have previously been regarded as specific for nonaccidental trauma, but more recently this has been called into question with authors describing no statistically significant difference in the proportion of interhemispheric SDHs found in children with nonaccidental versus those suffering from accidental trauma (Tung et al. 2006). SDHs commonly present with other intracranial injuries including subarachnoid hemorrhage,

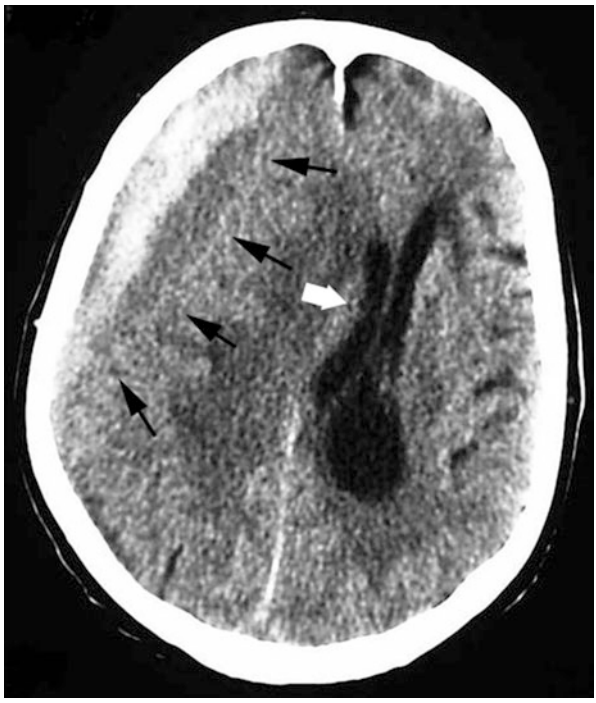

Fig. 20.13 Mass effect from an acute SDH. There is a large right-sided SDH (*black arrows*) with a recent bleed into a hyperdense acute component laterally and a lower density more chronic component medially. There is mass effect resulting in midline shift to the left. Instead of being effaced, the right lateral ventricle is shifted across the midline to the left (*white arrow*). This is the result of the acute component of the SDH accumulating too rapidly to allow egress of CSF from the lateral ventricles

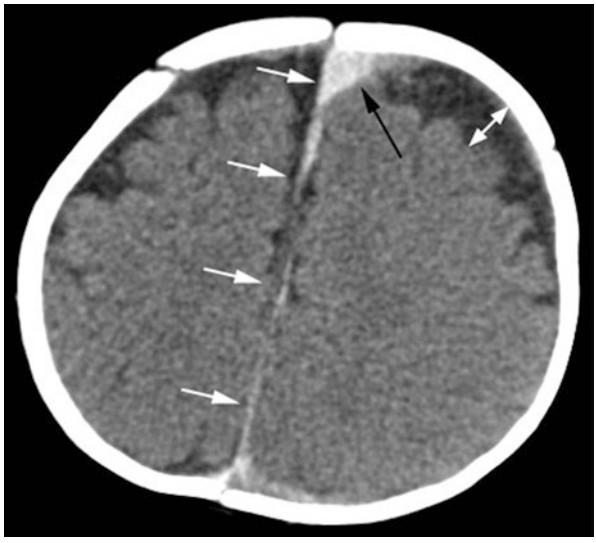

Fig. 20.14 Interhemispheric SDH. 9-month-old with a history of head trauma. There is a hyperdense acute SDH (*black arrow*) extending along the falx cerebri (*white arrows*) on the left. Notice the SDH characteristically does not cross the falx cerebri to the right side. Also notice there is prominence of the subarachnoid spaces bifrontally (*double arrow*) which may indicate benign enlargement of the subarachnoid spaces of infancy

contusions, and epidural hematomas. The presence or absence of additional intracranial injury in a patient with an SDH is most predictive of clinical outcome. Surgical management of an acute SDH is based on the patient's clinical status, the size of the collection, and the associated mass effect (Bullock et al. 2006).

During evolution, SDHs typically go through a subacute phase which occurs 1–3 weeks after injury. On CT scanning, a subacute SDH can appear as isodense to gray matter and be easily missed if subtle changes of mass effect are not sought (Fig. 20.1). The SDH is more obvious on MRI being hyperintense on T1-weighted imaging due to the presence of methemoglobin. T2-weighted imaging can be homogeneously hyperintense or demonstrate multiple loculations which represent ingrowing fibrovascular tissue and a hematocrit effect with fluid/fluid levels. The fluid/fluid levels may be due to settling of the blood products from a recent hemorrhage, disruption of the delicate neovascularity associated with organization of the SDH, or an acute rebleed into an existing SDH (Fig. 20.15). Rebleeding can occur within an existing SDH following only minor injury, often not even noticed by the patient. On T2-weighted images the supernatant is seen superiorly and is hyperintense while the more cellular elements layer dependently along the bottom of the collection and are hypointense.

Although most SDHs resolve, chronic SDHs can sometimes develop (Gean 1994). A chronic SDH that has not rebled has an attenuation value similar to CSF on CT and can be mistaken for prominence of the subarachnoid space due to brain atrophy (Fig. 20.16). Identification of the superficial cortical veins, which course through the subarachnoid space, is useful as these vessels are displaced away from the inner table of the skull in the presence of an SDH but not in the case of cortical atrophy alone. This distinction is particularly important in children who have suffered severe abusive head trauma and can present with atrophy as well as chronic SDHs. MRI better depicts the SDH which is hyperintense to CSF on all sequences even in the chronic phase. A chronic SDH that has rebled demonstrates multiple loculated compartments with blood products of various ages which are best appreciated on FLAIR images, fluid/fluid levels, and neomembranes due to the ingrowing fibrovascular tissue (Fig. 20.17). Administration of contrast can also be useful at times to help identify SDHs. Contrast-enhanced CT may help to identify the displacement of the cortical veins by an SDH, and contrast-enhanced MRI can demonstrate an organizing membrane which first forms along the inner dural margin along the lateral surface of the SDH during organization of the collection (Fig. 20.18).

A normal condition, benign enlargement of the subarachnoid spaces of infancy, can sometimes be misinterpreted as representing chronic SDHs (Barkovich and Raybaud 2011). Benign enlargement of the subarachnoid spaces of infancy is common and can be seen in neurologically normal infants between the ages of 2–7 months and 2 years old, resolving spontaneously. Benign enlargement of the subarachnoid spaces of infancy is hypothesized to be the result of immaturity of the arachnoid villi with resultant decreased absorption of CSF. On imaging, the frontal subarachnoid spaces are prominent, and the supratentorial ventricles, interhemispheric fissure, and sylvian fissures may also be enlarged (Fig. 20.19). The prominence of the CSF spaces can be identified as subarachnoid in location in that cortical vessels cross through the collection. Instead, in the setting of a subdural collection, these vessels would be displaced away from the inner table of the skull. The signal intensity follows CSF on all MRI sequences and on CT, whereas

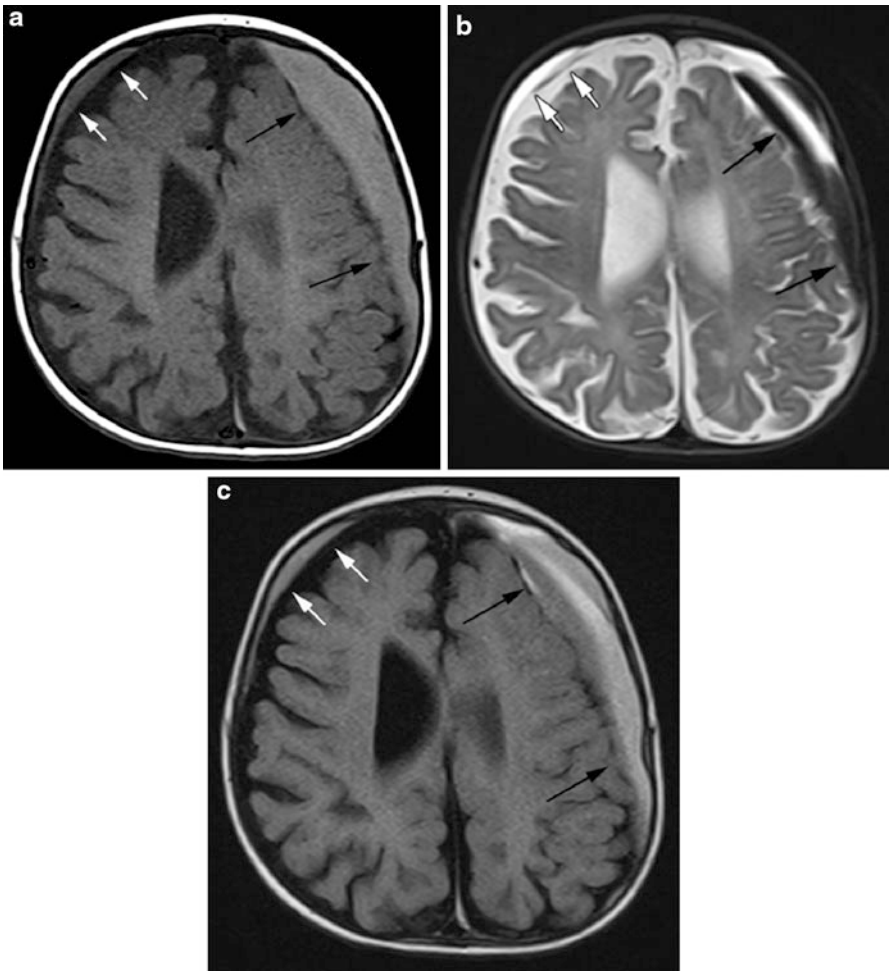

Fig. 20.15 Subacute SDH. 12-month-old with unexplained intracranial hemorrhage, healing posterior rib fractures, and metaphyseal fractures of the distal femurs. Axial T1-weighted (**a**), T2-weighted (**b**), and FLAIR (**c**) images demonstrate a thin SDH along the right frontal lobe (*white arrows*). The collection is homogenously hyperintense to CSF on all of the sequences consistent with late subacute blood products. A larger SDH along the left cerebral hemisphere (*black arrows*) is homogenously hyperintense on the T1-weighted image consistent with the presence of methemoglobin. The collection is more heterogeneous on the T2-weighted and FLAIR images with blood products of various ages from a more recent hemorrhage

a chronic SDH would be slightly hyperdense on CT or hyperintense on MRI to CSF. It has been suggested that the preexistence of benign enlargement of the subarachnoid spaces of infancy may predispose a child to developing SDHs following only mild trauma and therefore should be considered in the differential diagnosis of a child with an unexplained SDH (McNeely et al. 2006).

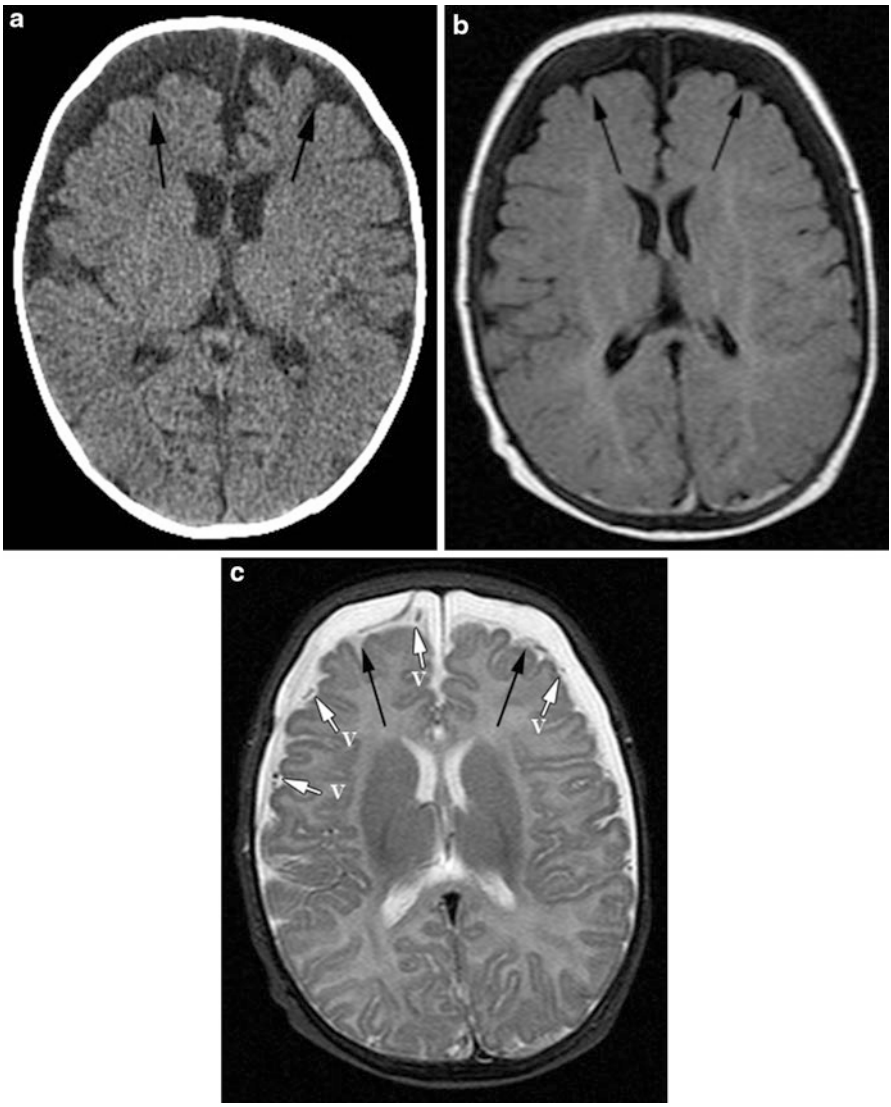

Fig. 20.16 Chronic SDH without rebleed. An axial image from a noncontrast CT scan (**a**) and axial T1-weighted (**b**) and T2-weighted (**c**) images from an MRI show bilateral extra-axial collections (*black arrows*) which are slightly hyperdense to CSF on CT and are slightly hyperintense to CSF on MRI. Notice the displacement of the cortical vessels (*V*) away from the inner table of the skull

SDHs can occur in normal-term neonates as a result of birth trauma in a substantial number of asymptomatic patients (Holden et al. 1999; Looney et al. 2007; Rooks et al. 2008; Whitby et al. 2004). These are clinically silent and typically resolve within a month following birth. Proposed mechanisms for

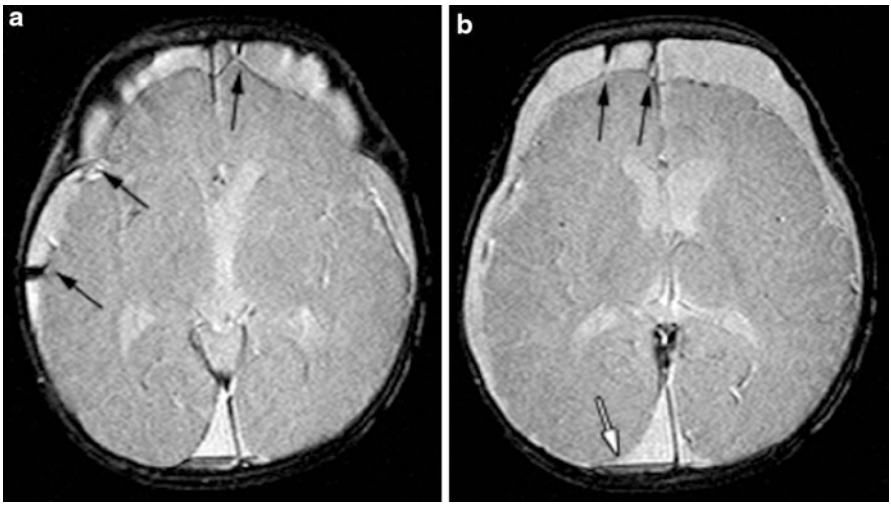

Fig. 20.17 Chronic SDH with neomembranes. T2*-weighted images (**a** and **b**) demonstrate bilateral hyperintense SDHs. There are linear septations coursing through the collections bilaterally which represent neomembranes (*black arrows*). The presence of hemosiderin and ferritin lining the neomembranes makes them appear very dark on T2*-weighted imaging. Notice blood products layering posteriorly (*white arrow*)

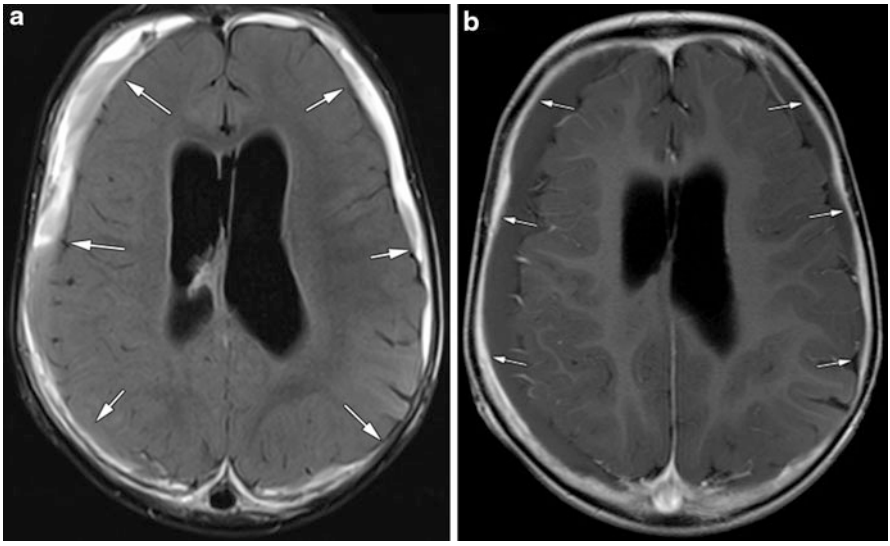

Fig. 20.18 Chronic SDH with enhancing fibrovascular granulation tissue. An MRI FLAIR image (**a**) demonstrates bilateral SDH with blood products of various ages (*white arrows*). On postcontrast imaging (**b**) there is a thick rim of enhancing tissue along the outer margins of the SDHs bilaterally consistent with fibrovascular granulation tissue (*white arrows*)

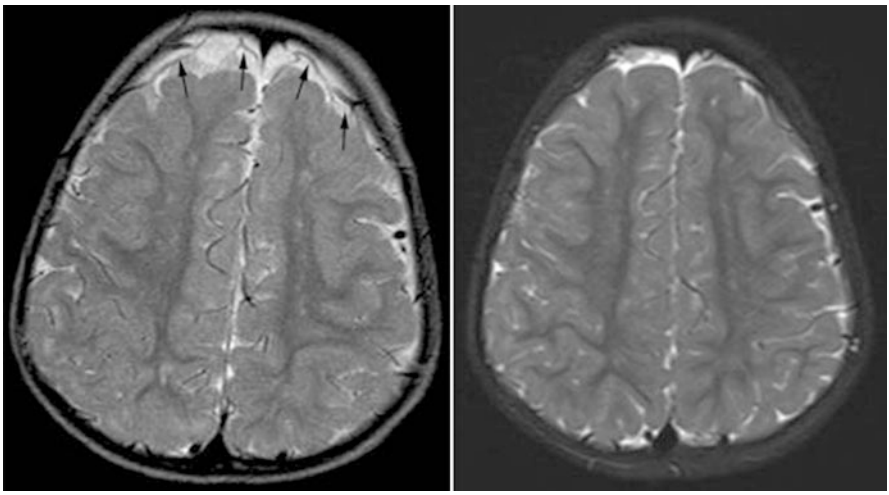

Fig. 20.19 Benign enlargement of the subarachnoid spaces of infancy. A child with normal development who underwent imaging for increasing head circumference. An axial T2-weighted image obtained at 18 months of age shows prominence of the subarachnoid spaces bifrontally. Notice the cortical vessels crossing through the subarachnoid spaces (*black arrows*). A follow-up image of the child at 4 years of age no longer shows prominence of the bifrontal subarachnoid spaces

birth-related SDHs include mechanical compression of the head during vaginal birth or from instrumentation resulting in shifting and overlap of unfused bones of the calvarium with subsequent laceration of the tentorium, falx, and superficial venous structures. SDHs arising from birth trauma have a posterior distribution and occur along the occipital lobes, within the interhemispheric fissure posteriorly, layering along the tentorium cerebelli and along the cerebellar hemispheres (Fig. 20.20). This is in contrast to SDHs seen in the setting of abusive head trauma which usually occur along the convexities and throughout the interhemispheric fissure. An SDH found in an infant after 1 month of age is unlikely to be birth related. Other types of intracranial hemorrhages can be seen in the neonate as well, for example, intraparenchymal birth-related hemorrhages or intraventricular hemorrhage in a preterm infant as the result of a germinal matrix hemorrhage. Subarachnoid hemorrhage can also be seen in these preterm infants. In term infants, subarachnoid hemorrhage is almost always found in association with SDHs.

Problems with Dating of Trauma Based on the Appearance of SDH

Few studies of the temporal evolution of SDHs in infants are available. Much of the work concerning the evolution of intracranial blood products involved intraparenchymal hemorrhage in adults (Fobben et al. 1989; Gomori et al. 1988). The imaging appearance of an SDH, as with other types of intracranial hemorrhage, can be influenced by various clinical and technical factors as discussed above. While signal characteristics of SDHs are generally similar to those of intraparenchymal hematomas, the evolution of SDH blood products is faster than intraparenchymal hematomas and

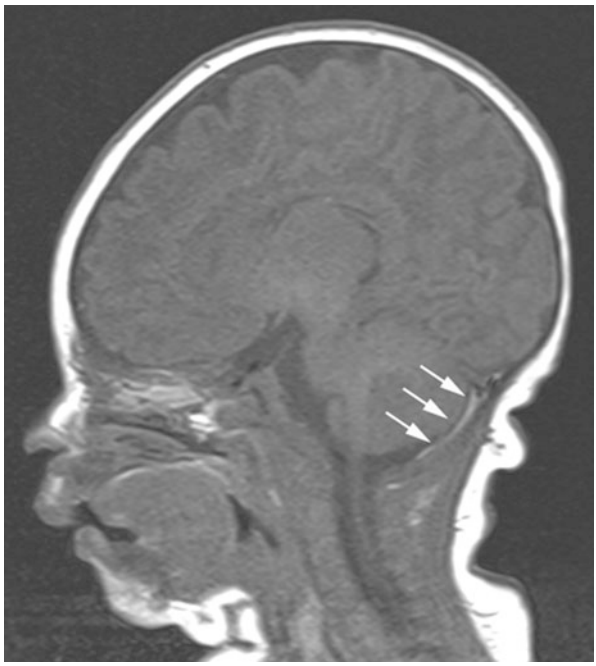

Fig. 20.20 Birth-related SDH. A sagittal T1-weighted MRI image of a 5-day-old newborn shows a small SDH (*white arrows*) along the posterior fossa posterior to the cerebellar hemispheres

differs due to factors such as CSF flow dynamics, high oxygen content of CSF, the absence of a blood–brain barrier which permits phagocytic clearance of debris within the collection, and the potential for rebleeding into an existing collection.

Subarachnoid Hemorrhage

Subarachnoid hemorrhage (SAH) is very common following significant head trauma due to the relative movement between the brain and the arachnoid resulting in injury to small cortical vessels (Gean 1994; Gean and Fischbein 2010; Provenzale 2007). Acute SAH is detected on noncontrast CT and appears as an area of curvilinear high density along the brain surface extending into the sulci (Fig. 20.21). SAH can also appear as clumped foci of high-density material within the subarachnoid space. Admixture with CSF can result in redistribution through the subarachnoid spaces, particularly in infants who have not developed adhesions or other restrictions to CSF flow. Over time, as the SAH evolves, it loses attenuation and becomes less apparent on CT. MRI with FLAIR imaging is the most sensitive imaging technique for detecting SAH and is particularly useful for detecting subacute and chronic SAH that may not be visible on CT. For example, the FLAIR MRI sequence depicts hyperintense proteinaceous material such as blood within the subarachnoid space against a background of hypointense CSF.

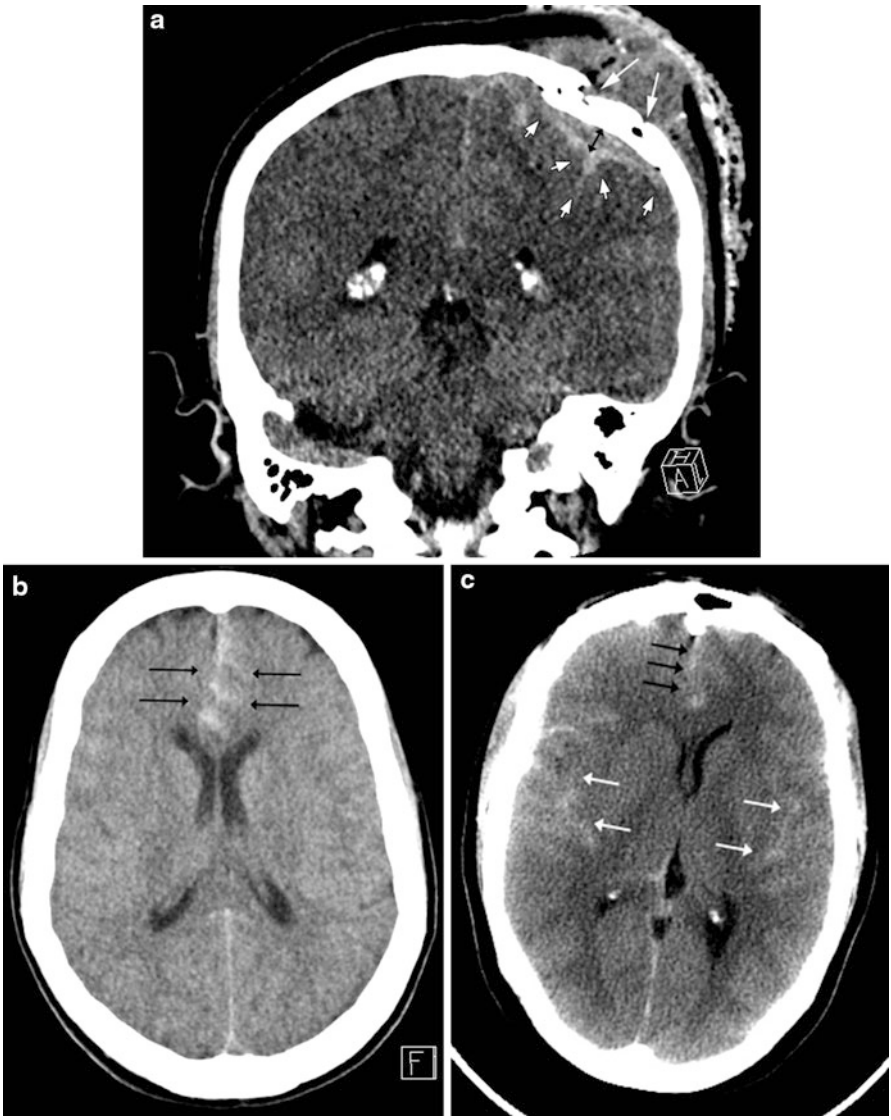

Fig. 20.21 Subarachnoid hemorrhage (SAH). 16-year-old status post assault with a baseball bat. A coronal noncontrast CT image (**a**) demonstrates a large scalp hematoma with a depressed left parietal skull fracture (*long white arrows*). There is an epidural hematoma underlying the skull fracture (*double-headed arrow*). There is also hyperdense blood along the left parietal lobe which follows the sulci consistent with SAH (*short white arrows*). An axial noncontrast CT scan in another patient demonstrates SAH (*black arrows*) along the frontal lobes bilaterally (**b**) and in another patient within the sylvian fissures bilaterally (*white arrows*) as well as along the frontal lobes (*black arrows*) (**c**)

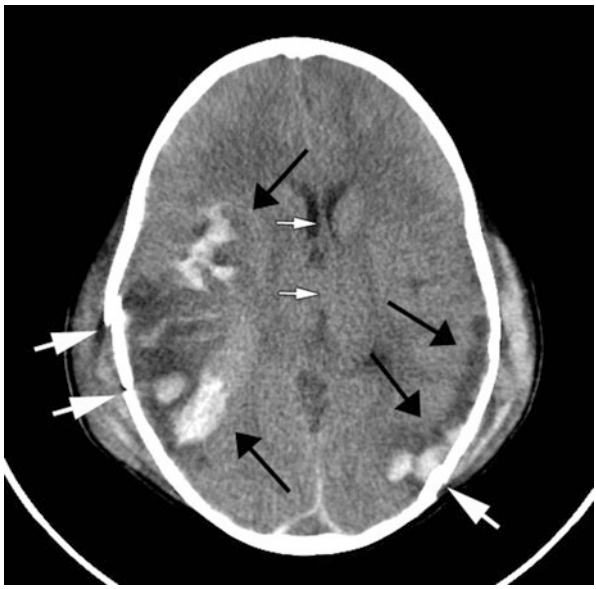

Fig. 20.22 Hemorrhagic contusions. A 4-year-old thrown out a second-story window by her mother. A noncontrast axial CT image demonstrates bilateral intraparenchymal hemorrhagic contusions with associated edema (*black arrows*). There is midline shift to the right (*small white arrows*). Bilateral scalp hematomas and skull fractures (*large white arrows*) are also seen

A T2*-weighted sequence is useful for detecting small hemorrhages and chronic hemorrhages with hemosiderin. Superficial siderosis can be seen on MRI as a dark linear signal lining the surfaces of the brain.

Contusions and Parenchymal Injury

Coup contusions involve the brain underlying the site of impact and are due to direct injury to the brain from the traumatic force. Coup contusions typically occur when the stationary head is struck by a moving object. Contrecoup contusions occur directly opposite from the impact site involving the contralateral side of the brain (in Fig. 20.5, there is a left posterior scalp injury indicating the site of impact, and directly opposite from the impact site, there are right frontal hemorrhagic contusions and a right cerebral hemisphere SDH). The classic mechanism for contrecoup contusions is a moving head hitting a stationary object. For contrecoup contusion to occur, the head must be unsupported (Gean 1994).

Cerebral contusion can be hyperdense and hemorrhagic or, less frequently, predominantly low in density consistent with edema. Surrounding edema appears within a few hours and progresses over the next several days following trauma; therefore, lesions will become more prominent on follow-up scans. The appearance on CT is that of a well-defined area of low density surrounding a focal hematoma (Fig. 20.22). Common locations are along the inferior frontal lobes and the anterior and lateral temporal lobes. Small focal lesions can also be seen along the convexities. Commonly, multiple lesions are present. The lesions are typically superficial with relative sparing of the underlying white matter. There can be associated subarachnoid

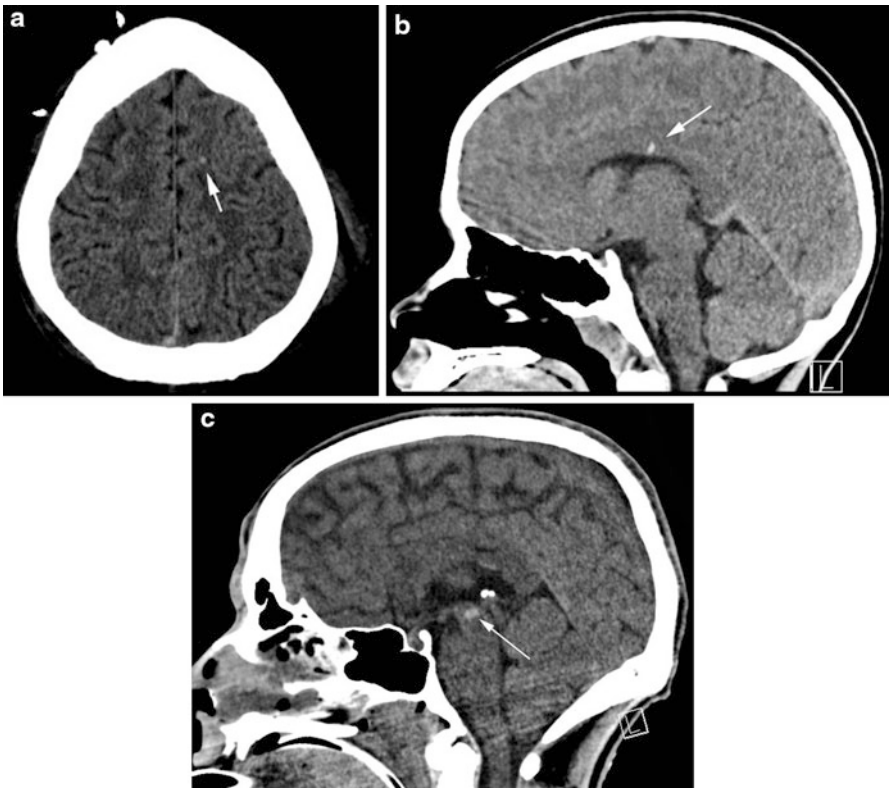

Fig. 20.23 Diffuse axonal injury (DAI). Foci of hemorrhagic DAI in various patients imaged with CT. An axial noncontrast CT image (**a**) shows a focus of hyperdensity (*white arrow*) at the gray matter-white matter junction of the left frontal lobe. A sagittal noncontrast CT image (**b**) through the midline shows a focal hyperdensity (*white arrow*) within the body of the corpus callosum. A sagittal noncontrast CT image (**c**) shows a focal hyperdensity (*white arrow*) within the midbrain

hemorrhage, and at times it can be difficult to distinguish between superficial hemorrhagic contusions and subarachnoid hemorrhage. Large contusions can result in associated mass effect on adjacent structures. Severe cases may require surgical evacuation. As the hematoma resolves, it progressively decreases in density on CT and can become isodense with normal brain between 1 and 3 weeks of age. At this stage, the subacute hematoma is better visualized on MRI. The evolving hematoma follows the signal characteristics of blood on MRI as described earlier.

Diffuse Axonal Injury

Diffuse axonal injury (DAI) is thought to be a type of shear–strain injury induced by rapid rotational acceleration of the brain (Adams et al. 1989; Gean and Fischbein 2010;

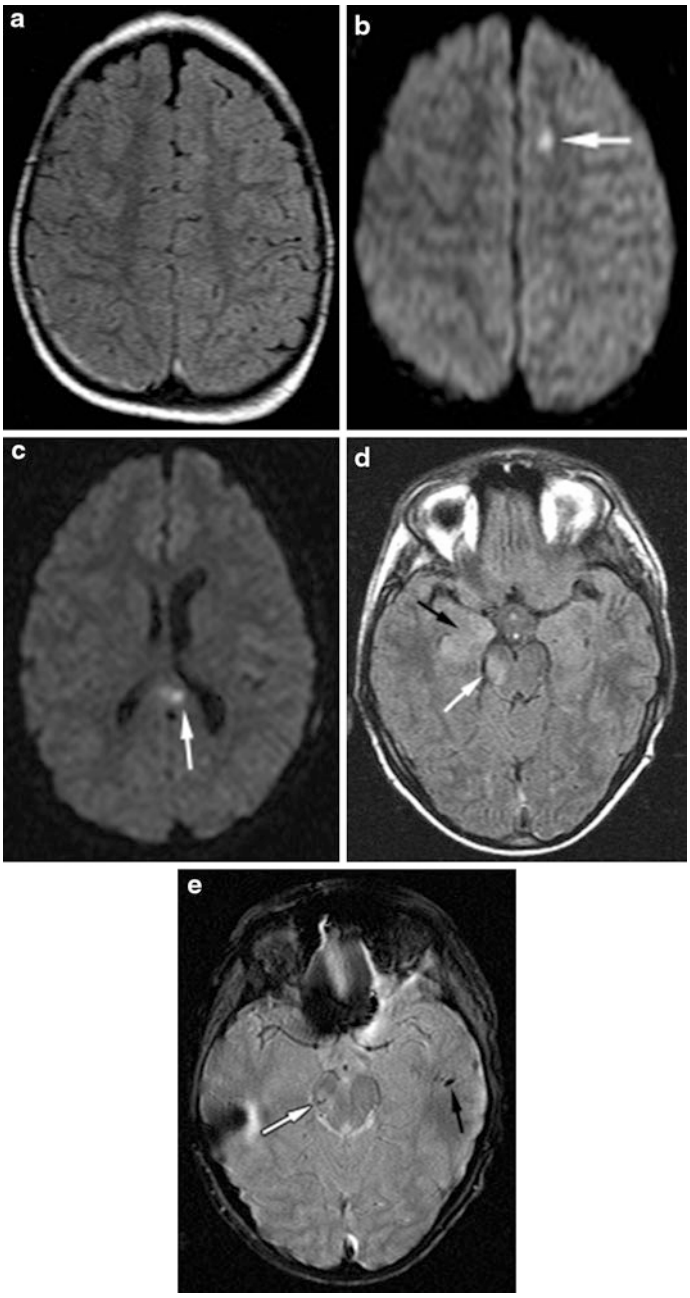

Fig. 20.24 (continued)

Provenzale 2007). The brain undergoes dynamic tissue deformation resulting in rapid inertial loading at the interface between tissues of different densities and tensile and elastic characteristics. There are three main locations where DAI tends to occur, in order of severity: the lobar white matter, the posterior body and splenium of the corpus callosum, and the dorsolateral aspect of the midbrain and upper pons. DAI can be classified according to Adam's classification as mild, moderate, or severe. Severity of the injury increases with depth; therefore, lobar white-matter lesions are a mild form of injury, whereas brainstem lesions represent a severe form of injury. As a general rule, hemorrhagic brainstem lesions are not seen in the absence of supratentorial lesions.

CT scanning can be relatively insensitive for the detection of DAI; however, larger lesions that are hemorrhagic can be seen with CT as focal areas of hyperdensity involving the white matter at the gray matter–white matter junction and sparing the cortex (Fig. 20.23). This is useful for differentiating DAI from focal hemorrhagic contusions which tend to occur along the gyral surface. Parasagittal frontal lobe and temporal lesions are common. In the white matter of the corona radiata, lesions are oval-shaped and aligned along the white-matter tracts. In the corpus callosum, lesions can involve both dorsal and ventral fibers of the splenium and posterior body. At times the adjacent septum pellucidum may be involved. In the brainstem, lesions involve the dorsal and lateral aspect of the mesencephalon and upper pons. This is in distinction to Duret hemorrhages which tend to involve the ventral paramedian brainstem. Nonhemorrhagic lesions can occasionally be seen as focal areas of hypodensity.

Many more lesions can usually be detected with MRI than are visible on CT (Scheid et al. 2003) (Fig. 20.24). On MRI, DAI is hyperintense on the FLAIR sequence. Hemorrhagic lesions are hypointense on T2-weighted imaging and can be especially well seen on the T2*-weighted sequences. Newer imaging techniques, such as susceptibility-weighted imaging, have been shown to demonstrate even more hemorrhagic lesions than the conventional gradient echo sequence (Tong et al. 2008). Diffusion imaging is the most sensitive imaging technique for detecting lesions of DAI as some nonhemorrhagic lesions are only seen on diffusion imaging. Diffusion tensor imaging has also been investigated as a potential sequence for evaluating DAI. Although neuroimaging techniques can depict DAI lesions, definitive diagnosis and the full extent of injury can currently only be made at autopsy using techniques such as immunostaining for β–amyloid precursor protein (β–APP). Axonal pathology has been shown to evolve over hours to days after

Fig. 20.24 Diffuse axonal injury (DAI). Foci of DAI in various patients imaged with MRI. An axial FLAIR image (**a**) is negative, but the corresponding diffusion-weighted image (**b**) demonstrates a focus of low diffusion (*white arrow*) at the gray matter-white matter junction of the left frontal lobe. Another diffusion-weighted image (**c**) demonstrates a focus of low diffusion (*white arrow*) involving the splenium of the corpus callosum. An axial FLAIR image (**d**) demonstrates abnormal signal within the posterior lateral aspect of the midbrain on the right (*white arrow*). Also note the right mesial temporal contusion (*black arrow*). The corresponding T2*-weighted image (**e**) shows the lesion to be hemorrhagic DAI (*white arrow*). Also seen is an additional focus of DAI within the left temporal lobe (*black arrow*)

initial insult with mechanical injury resulting in alterations in ion-channel permeability, disruption of axonal transport, and eventually the formation of axon "retraction balls" leading to axonal disconnection. This delay in progression of injury provides a potential window of opportunity for treatment, and several novel treatment regimes are currently under investigation. Evolution of hemorrhagic DAI follows the signal intensity characteristics similar to other intraparenchymal hemorrhagic lesions. A subacute lesion would be hyperintense on T1-weighted imaging due to the presence of methemoglobin.

Epidural Hematoma

Epidural hematomas (EDHs) occur much less frequently in nonaccidental head injury than SDHs. This can be due to the fact that the child's skull is more pliable and the groove for the middle meningeal artery is shallower in children than in adults. Therefore, the middle meningeal artery is more commonly displaced, rather than lacerated, by traumatic forces. EDHs can be of two types, arterial and venous. Arterial EDHs are by far the most common and occur in the supratentorial compartment. Due to the protective skull base and the rich venous network and dural sinuses of the posterior fossa, infratentorial EDHs are less common and, when they occur, are usually of venous origin. A classic EDH is a homogeneously hyperdense extra-axial collection, biconvex in shape, and limited by the cranial sutures (Fig. 20.25). The margins of an EDH are sharp and well defined due to the strong adherence of the dura to periosteum along the margins of the EDH. EDHs occur almost always at the site of impact and are associated with an overlying fracture which strips the dura away from the bone. A portentous sign is the presence of areas of low density within the collection which indicates active bleeding. An EDH can rapidly expand over time and result in significant mass effect requiring neurosurgical decompression. A common location for an EDH is in the temporal parietal region where a fracture of the temporal squamosa can result in laceration of the middle meningeal artery. Venous EDHs usually occur in the posterior fossa and, due to its epidural location, can cross superficial to the transverse sinus extending into the supratentorial compartment. Less common locations for venous EDHs are along the anterior temporal lobes associated with disruption of the sphenoparietal sinus and along the midline associated with disruption of the superior sagittal sinus. An EDH in this location crosses the midline superior to the superior sagittal sinus indicating its location within the epidural space.

Vascular Injury

Extra- and intracranial vascular injuries can occur as a result of trauma. Manipulation of the neck, skull base or cervical fractures, blunt trauma, or penetrating

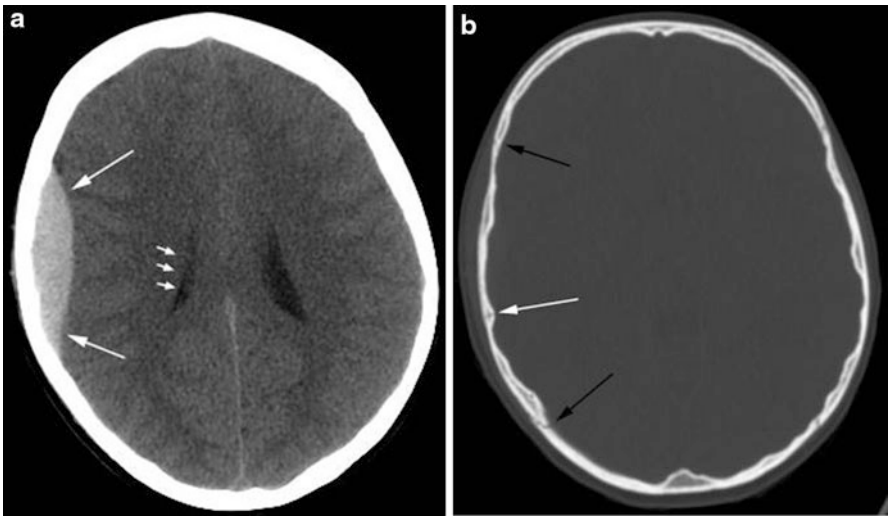

Fig. 20.25 EDH. 11-year-old fall from the top bunk of a bunk bed. An axial noncontrast CT image (**a**) shows an acute epidural hematoma (*large white arrows*) which has mass effect on the adjacent right frontal and parietal lobes with partial effacement of the right lateral ventricle (*small white arrows*). The corresponding CT image in bone windows (**b**) shows a fracture of the right parietal bone (*white arrow*). Notice how the epidural hematoma is limited by the coronal and lambdoid sutures indicated by the *black arrows*

injury can result in dissection or laceration of the cervical vessels. CT angiography, MRI angiography, and conventional catheter angiography can be useful in diagnosing vascular injury (Fig. 20.26). At angiography, there is an eccentric tapered appearance with narrowing of the vessel which can result in complete or incomplete occlusion. MRI can be useful in assessing vascular dissection. On MRI, the dissection appears as an eccentric area of increased signal best seen on T1-weighted imaging which represents the subacute hematoma in the wall of the injured vessel. An adjacent normal-flow void can be seen corresponding to the true lumen of the vessel or may be absent if the dissection results in complete occlusion. Vascular dissection of the vertebral arteries is relatively frequent in patients with cervical-spine fractures, and these patients can commonly be asymptomatic at presentation. Carotid artery dissection typically involves the internal carotid artery just distal to the bifurcation. Intimal disruption at the site of the dissection can be a stimulus for thrombus formation, and emboli from fragmentation of the thrombus can result in multiple infarcts within a vascular territory. Complete vascular transection can present as an enlarging hematoma within the neck. On postcontrast imaging, active extravasation of contrast can indicate active bleeding.

Pseudoaneurysms can develop weeks to months following trauma. The patient can present with a pulsatile neck mass, neck pain, or episodes of acute infarction due to

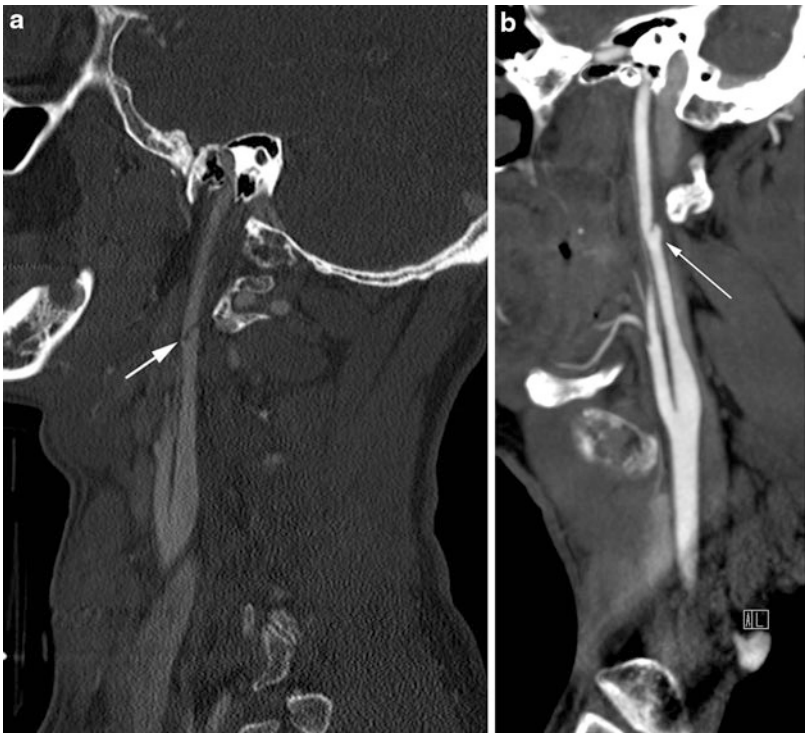

Fig. 20.26 Carotid dissection and pseudoaneurysm formation. A CT angiogram (**a**) in a patient following a motor vehicle accident demonstrates a dissection flap in the internal carotid artery (*white arrow*). A repeat CT angiogram (**b**) obtained 2 months later shows formation of a pseudoaneurysm at the site of previous vascular injury (*white arrow*)

distal embolization of mural thrombus. The wall of the pseudoaneurysm, composed of an encapsulated hematoma, appears irregular at angiography. CT and MRI can demonstrate both the thrombosed and non thrombosed portion of the aneurysm.

Vascular injury and traumatic subarachnoid hemorrhage can lead to vasospasm with diffuse narrowing of the vessels which can result in diffuse ischemic injury. Skull-base fractures can lead to traumatic disruption of the cavernous carotid artery with resultant communication with the cavernous sinus known as a carotid cavernous fistula. Traumatic disruption of a dural venous sinus can lead to occlusion or venous thrombosis.

Spinal Injury

Several factors contribute to the unique injury patterns seen in the pediatric spine compared with the adolescent and adult (Barkovich and

Raybaud 2011; Lustrin et al. 2003). These include small occipital condyles, horizontally oriented facet joints, laxity of the ligamentous structures, incomplete ossification, weak neck muscles, and a relatively large head. Because of these factors, young children are particularly predisposed to injury of the craniocervical junction and upper cervical spine. By the time a child is approximately 12–15 years old, the spine achieves more of an adult configuration, and therefore the sequelae of pediatric trauma in older children are similar to adults.

Interpreting plain radiographs of the pediatric spine can be challenging because of unfused epiphyses and normal physiological variants. In adults, the distance from the posterior aspect of the anterior arch of the C1 vertebrae and the anterior aspect of the dens is normally up to 3 mm. This is termed the atlanto-dental interval (ADI), and widening can indicate instability with ligamentous disruption. In pediatric patients this interval can normally be up to 5 mm (Lustrin et al. 2003). In children, the C2 vertebral body can be displaced up to 4 mm anteriorly compared with C3, and also C3 can be displaced anteriorly with respect to C4. This finding is known as pseudosubluxation and should not be mistaken for ligamentous injury. Following spinal trauma, edema or hematoma formation within the prevertebral soft tissues can result in swelling of the soft tissues visible on plain film. However, in children, prominence of the prevertebral soft tissues can be normal particularly during expiration. Also in infants, the cervical vertebral bodies have more of an oval shape instead of the adult rectangular shape, which can be mistaken for anterior wedging injury.

Radiological evaluation of traumatic spine injury includes plain films; however, if initial radiographs are negative and spinal injury remains suspected clinically, further imaging is indicated. CT with multiplanar reformats provides detailed evaluation of bony structures and is the most sensitive technique for detection of fractures (Fig. 20.27). Additionally, CT can be obtained rapidly at the same time imaging of other areas of injury is performed. MRI is less sensitive for detecting subtle fractures but is very useful for assessing the spinal cord for injury and for evaluating soft tissues and ligaments. In fact, there can be severe cord injury even in the presence of negative radiographs (the concept of SCIWORA = spinal cord injury without radiological abnormality). MRI can demonstrate injury to the interspinous soft tissues, ligamentous structures, epidural hematomas, acute disc herniations, and cord injury. There may be signal abnormality within the spinal cord, including intramedullary hemorrhage, compression of the cord, or cord transaction (Fig. 20.28). Types of injuries include atlantooccipital dislocation which is usually fatal and less severe atlantoaxial dislocation.

Few studies are available evaluating spinal injury in children suffering abuse. Fractures of the cervical spine, thoracolumbar fractures, dislocations, cord injury, and spinal subdural hematomas associated with intracranial injury have all been reported.

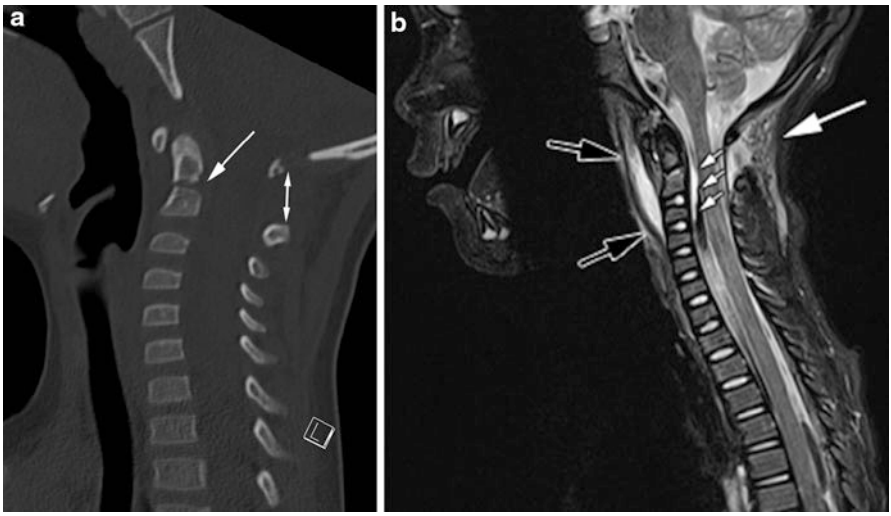

Fig. 20.27 Odontoid fracture. 3-year-old following a motor vehicle accident. A sagittal noncontrast CT image (**a**) shows a fracture (*white arrow*) at the base of the dens ossification center (type II odontoid fracture). The tip of the dens is tilted anteriorly. There is also splaying of posterior elements of C1 and C2 (*double-headed arrow*) indicating posterior ligamentous injury. A T2-weighted sagittal MR image obtained using a technique that suppresses signal from fat (**b**) shows edema (*white arrow*) within the posterior interspinous ligaments at C1–C2 consistent with ligamentous injury. There is an EDH (*small white arrows*) which narrows the spinal canal; however, the spinal cord itself demonstrates normal signal intensity without evidence of acute injury. There is also a fluid collection within the retropharyngeal soft tissues (*open arrows*)

Mimics of Abusive Head Trauma

When interpreting imaging studies of potential child abuse, the clinician should be aware of other entities that can mimic abusive head trauma. These include rare metabolic disorders, infection, and various coagulopathy disorders (Fig. 20.29).

Glutaric aciduria type I is an autosomal recessive disorder resulting in deficiency of glutaryl-CoA dehydrogenase, an enzyme required for metabolism of L-lysine, L-hydroxylysine, and L-tryptophan (Barkovich and Raybaud 2011). Children present with an acute episode of encephalopathy, progressive loss of motor function, and macrocephaly. On neuroimaging, there is enlargement of the CSF spaces along the anterior temporal lobes and sylvian fissures, abnormal signal within the basal ganglia and periventricular white matter, and delayed myelination. Bilateral SDHs and retinal hemorrhages can also be present and lead to a misdiagnosis of child abuse. Later, the children develop atrophy of the basal ganglia as well as diffuse

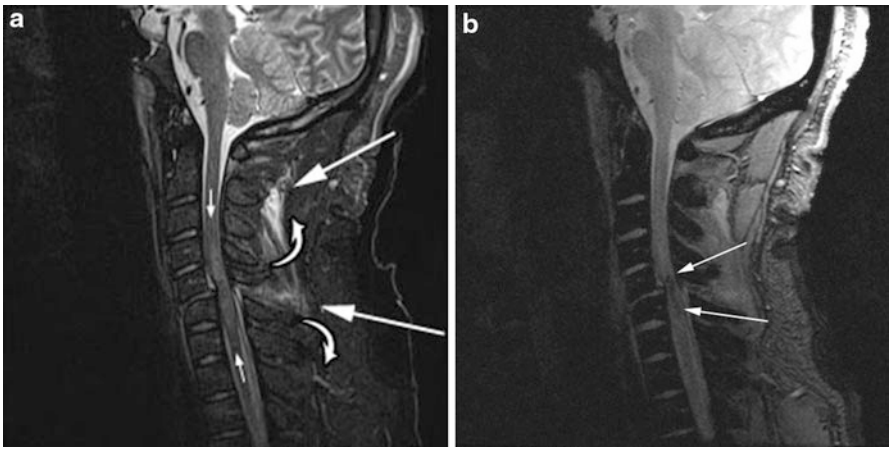

Fig. 20.28 Spinal cord injury. 17-year-old found in a ditch who was thought to have been thrown from a motorcycle. A sagittal T2-weighted MR image through the cervical spine in which signal from fat has been suppressed (**a**) shows grade 1 traumatic anterolisthesis of C5 on C6. There is resultant spinal canal narrowing at the C5–C6 level with compression of the spinal cord. There is a small T2-weighted bright epidural fluid collection posterior to the C5 vertebral body. There is severe acute cord injury, with signal abnormality extending from approximately C3 down to C7 (*small white arrows*). Edema is seen throughout the interspinous ligamentous complex (*large white arrows*), most severe between the widened C5 and C6 spinous processes (*curved arrows*) consistent with ligamentous injury. A sagittal T2*-weighted image (**b**) shows susceptibility artifact within the cord indicating cord hemorrhage at C5–C6 (*white arrows*)

cerebral atrophy. The disease is diagnosed by abnormal amounts of glutaric acid, and it metabolites in the urine and deficiency of glutaric acid dehydrogenase.

Menkes disease is an X-linked recessive disorder resulting from deficiency in copper absorption and resultant impairment in cytochrome oxidase activity (Barkovich and Raybaud 2011). Children can present with failure to thrive, truncal hypotonia, hyperthermia, and seizures and have characteristic sparse, coarse hair with frayed ends. Because of this, the disease is often called Menkes kinky hair disease. On imaging, the brain is atrophic and there can be large subdural hematomas. The intracranial vessels are elongated and tortuous. The bones are osteoporotic, and there can be associated fractures. The diagnosis of copper deficiency is usually made on the basis of low serum levels of copper and low ceruloplasmin levels (Russell and Suter 2012).

Neonatal herpes simplex meningoencephalitis is typically acquired due to exposure to maternal type II lesions within the birth canal (Barkovich and Raybaud 2011). The disease destroys much of the brain with widespread signal abnormality progressing to extensive encephalomalacia. Children 6 months and older are usually affected by type I virus. The infection usually begins in the temporal lobes and spreads to the orbital frontal lobes, cingulate gyri, and insular

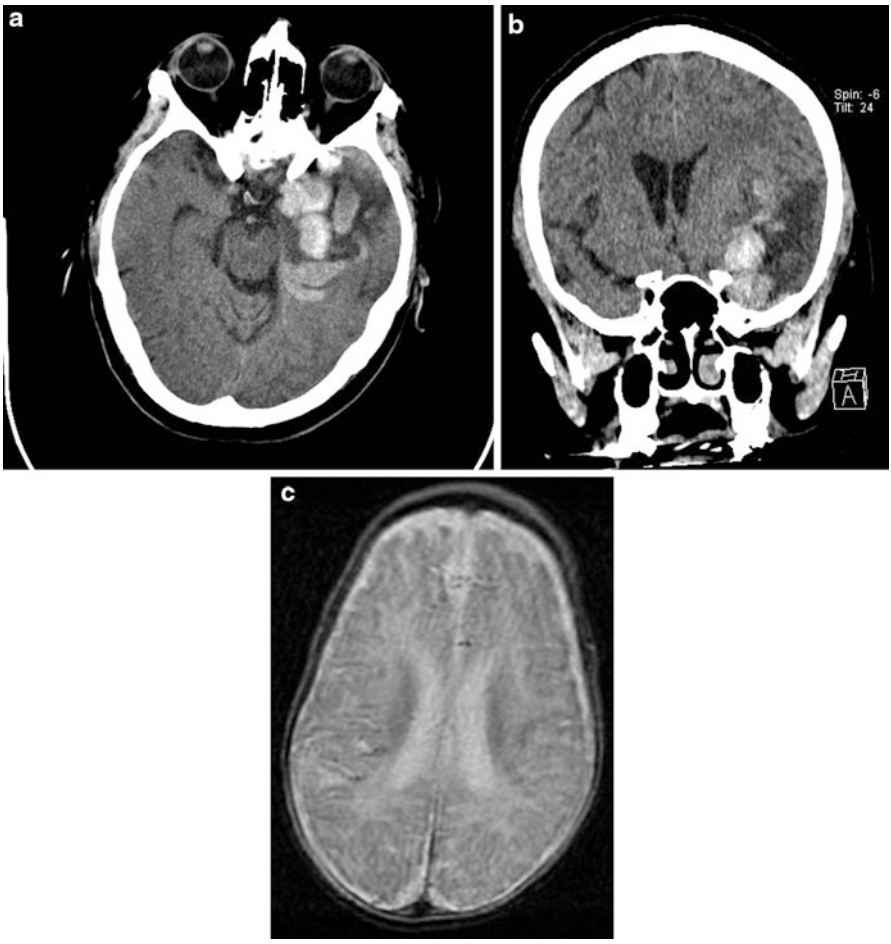

Fig. 20.29 Child abuse mimic. College student with altered mental status. An axial image from a noncontrast CT scan (**a**) shows a large left temporal parenchymal hemorrhage with surrounding edema. There is mass effect on the brainstem. A coronal image (**b**) from the same CT scan again shows the left temporal parenchymal hemorrhage as well as mass effect on the left lateral ventricle. The patient was diagnosed with herpes encephalitis. In another patient with known Menkes kinky hair disease, an axial T2-weighted MR image (**c**) is marred by patient motion artifact but shows thin bilateral subdural collections (Image courtesy of Dr. Ken Holden)

cortex. Diffusion imaging is positive, early showing reduced water diffusion. Later, T2-weighted and FLAIR images show corresponding areas of signal abnormality. Postcontrast enhancement is variable. Occasionally, areas of hemorrhage are seen within the involved areas. Diagnosis is made by detection of viral DNA in CSF.

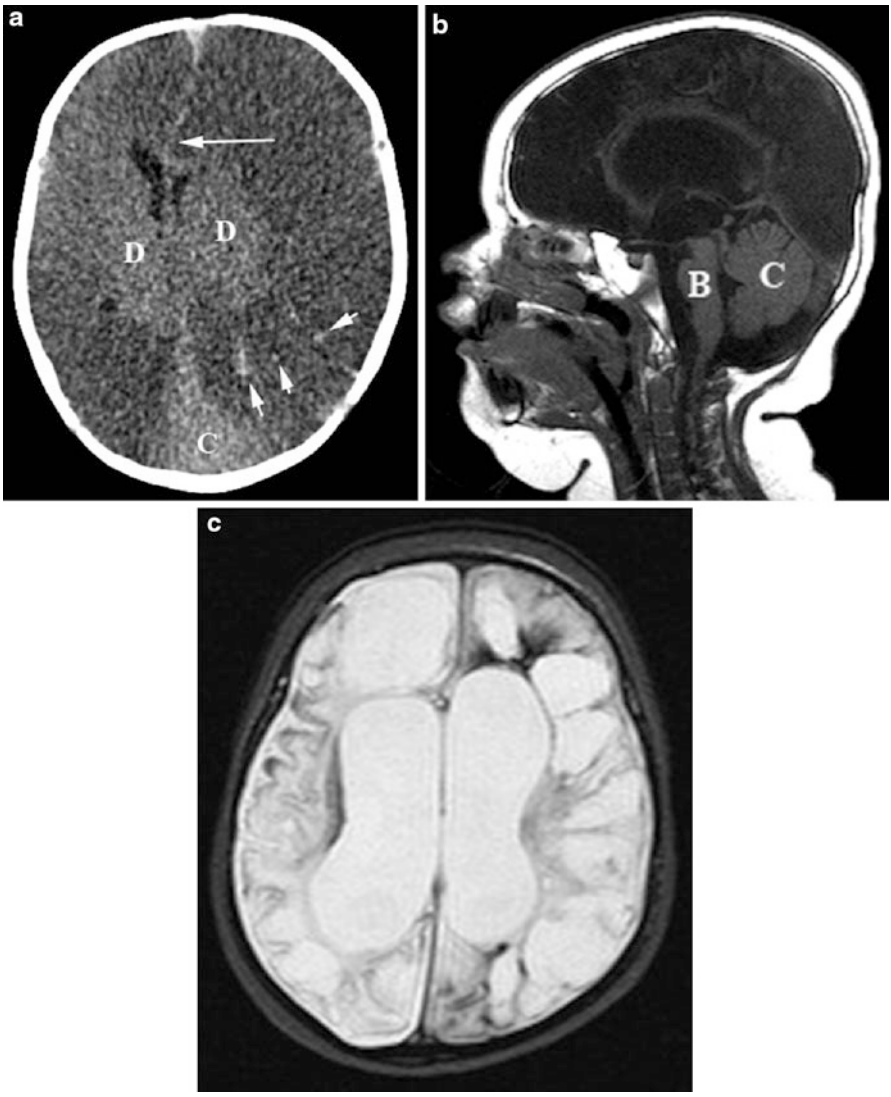

Fig. 20.30 Long-term sequelae. 2-month-old whose mother admitted to shaking the infant. An axial noncontrast CT image (**a**) obtained on admission shows diffuse loss of gray matter-white matter differentiation with relative sparing of the *deep gray* nuclei (*D*) and the cerebellum (*C*), shifting of the brain to the right (*large white arrow*), and scattered areas of intraparenchymal hemorrhage (*small white arrows*). A follow-up MRI was obtained 2 years later. A sagittal T1-weighted MR image (**b**) and an axial T2-weighted image (**c**) show diffuse loss of the cerebral hemispheres with sparing of the cerebellum (*C*) and brainstem (*B*)

Additional considerations include benign enlargement of the subarachnoid spaces of infancy and birth trauma as discussed above, disorders of coagulation, arterial–venous malformation, dural venous sinus thrombosis, and infectious etiologies such as *Haemophilus influenzae* meningitis and osteogenesis imperfecta. Each differential diagnosis should be considered and excluded on the basis of clinical examination, medical and family history, neuroimaging, and screening laboratory studies.

Conclusion

The long-term prognosis in children of abuse can be devastating. Among the survivors, the outcome of a single severe episode or multiple repeated episodes of abusive head injury is diffuse loss of brain tissue. On imaging, there is diffuse prominence of the ventricles and sulci. Areas of old hemorrhage can be seen years later as hypointense on T2-weighted imaging with increased prominence of signal loss on T2*-weighted imaging. Widespread cystic areas representing encephalomalacia and chronic bilateral SDHs are often present (Fig. 20.30).

The goal is for early detection in order to provide appropriate protection of at-risk children from abuse. Neuroimaging plays an important role in detecting and documenting child abuse. Often, findings of severe intracranial injury are first identified on imaging, as the clinical history is commonly misleading. In addition to being important for directing patient treatment plans, CNS imaging also plays an important role in documenting as fully as possible the presence, extent, and timing of injury and providing objective evidence of abuse to prosecutors which has important medicolegal consequences. Access to both CT and MRI has become more available, and new scanning techniques have improved detection of even small areas of injury. Finally, imaging provides essential data concerning the condition of the brain and spine in the living child, often immediately following the injury – data that cannot be acquired in the postmortem state.

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Non-Central Nervous System Imaging of Pediatric Inflicted Injury

21

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Contents

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Abstract

After dermatological findings such as bruises, contusions, and burns, fractures are the most common sequelae of non accidental trauma. This chapter will discuss the non-CNS radiological findings including soft tissue injuries, fractures, and visceral injuries of child abuse as well as the appropriate radiological investigations for their identification and documentation.

Introduction

Child abuse or neglect in some form is unfortunately a fairly common problem. This is compounded by underdiagnosis and underreporting (Van Rijn et al. 2010). Imaging plays a vital role in the elucidation of injuries associated with non accidental trauma as child abuse typically presents with soft tissue or skeletal injury. In fact, it was a pediatric radiologist who first recognized a constellation of injuries to be indicative of inflicted trauma. While there are no fractures pathognomonic of child abuse, some fractures are more specific for abuse than others. These include metaphyseal fractures (classic metaphyseal lesions) seen as corner fractures or bucket-handle fractures on radiographs, posterior rib fractures, vertebral spinous-process fractures, and sternal and scapular fractures. Epiphyseal and diaphyseal fractures can also occur. Diaphyseal fractures in non accidental trauma are typically spiral fractures and are seen commonly in the humerus and femur. In the absence of an appropriate history, multiple fractures in a young child, especially in various stages of healing (Fig. 21.1), are suspicious for child abuse. Although imaging findings may be extremely compelling, the diagnosis of non accidental trauma is usually made by integrating the clinical findings, inconsistent history, and radiological findings.

Soft tissue injuries like bruises or contusions and burns are more common than fractures and are easily assessed by clinical examination of the patient. More severe injuries to the chest and abdomen can result in injury to the underlying organs. Some of these injuries will be illustrated and discussed in this chapter.

Radiological Investigations in Suspected Child Abuse

Conventional Radiographs

Radiographic whole-body skeletal survey has been the mainstay of the initial radiological investigation in children suspected to have been abused. The American

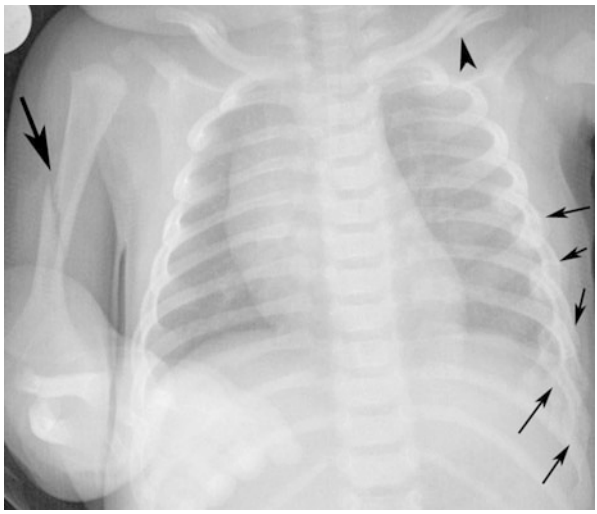

Fig. 21.1 Frontal chest radiograph showing an acute oblique fracture of the right humeral diaphysis (*large arrow*), bilateral clavicle fractures (*arrowhead* showing left clavicle fracture) with varying stages of healing, and multiple healing/healed left lateral lower rib fractures (*small arrows*)

Table 21.1 Recommendation for a complete skeletal survey as per ACR-SPR guidelines

Appendicular skeleton (frontal projection)	Both arms
	Both forearms
	Both hands
	Both thighs
	Both legs
	Both feet
Axial skeleton	Skull – frontal and lateral views
	Cervical spine (lateral)
	Thorax – frontal, lateral, and bilateral oblique views to include ribs, thoracic spine, and upper lumbar spine
	Lumbosacral spine (lateral)
	Pelvis (frontal) to include mid-lumbar spine

College of Radiology-Society of Pediatric Radiology (ACR-SPR) has guidelines published on their website (http://www.acr.org/~/media/9BDCDBEE99B84E87BAAC2B1695BC07B6.pdf). The Royal College of Radiologists (RCR) with input from the British Society of Pediatric Radiology (BSPR) in collaboration with the Royal College of Pediatrics and Child health has a document titled "Standards for radiological investigations of suspected nonaccidental injury" (http://www.rcr.ac.uk/docs/radiology/pdf/RCPCH_RCR_final.pdf) with guidelines for performing the skeletal survey. The recommendations of these organizations are shown in Tables 21.1 and 21.2.

Radiographs should be performed on good-quality equipment with individual segments of the extremities on separate radiographs. The radiographs must be

Table 21.2 Skeletal survey recommendation by the Royal College of Radiologists

Skull	Frontal and lateral views
	Towne's view (if clinically indicated)
Chest	Frontal (including both clavicles)
	Bilateral oblique views
Abdomen	Frontal (including the pelvis and hips)
Spine	Lateral view (separate exposures may be needed for the cervical, thoracic, and thoracolumbar regions)
	Additional views (if the spine is not seen on the frontal chest and abdomen radiographs)
	Frontal view of cervical spine only at the discretion of the radiologist
Extremities (frontal views)	Both arms
	Both forearms
	Both hands
	Both thighs
	Both legs
	Both feet

reviewed by a radiologist before the patient is released from the radiographic suite. Additional radiographs, such as dedicated views of the individual joints including the metaphyseal region or lateral views of extremity bone fractures, can be obtained as deemed necessary by the radiologist.

Bone Scintigraphy

Radionuclide bone scan may be complementary to radiographic skeletal survey in detecting acute rib fractures or fractures involving the feet and pelvis. However, there is no uniform consensus regarding its routine usage.

Computed Tomography (CT), Ultrasonography (US), and Magnetic Resonance Imaging (MRI)

Other than plain radiography, CT is the next most commonly utilized imaging modality in cases of suspected abuse. As is the case with accidental trauma, CT is the imaging modality of choice in suspected visceral injuries in non accidental trauma and may better delineate acute nondisplaced rib fractures than plain radiographs. Physeal injuries and long bone fractures can be seen with US, but this modality is not routinely employed. Although not mainstays of imaging of the abused child, US and MRI may be performed at the discretion of the radiologist to answer specific clinical questions on a case-by-case basis.

Follow-Up Radiographic Skeletal Survey

Kleinman et al. (1996b) concluded that follow-up skeletal survey is warranted for a thorough and accurate assessment of skeletal injuries since additional fractures may be seen on this follow-up imaging. Healing rib fractures especially become more conspicuous due to callus formation.

Based on published evidence (Kleinman et al. 1996a; Zimmerman et al. 2005), the American College of Radiology (ACR) appropriateness criteria (2009) also recommends a follow-up skeletal survey 2 weeks after the initial survey to include all areas of the body except the skull, since changes of healing will not be evident there (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Diagnostic/SuspectedPhysicalAbuseChild.pdf).

Similarly, the Royal College of Radiologists, in their document "Standards for radiological investigations of suspected nonaccidental injury," recommends a full skeletal survey 2 weeks after the initial survey with additional views as necessitated by the initial radiographic survey.

Reporting of Findings and Communication

Needless to say, the reports of all radiological investigations should be conveyed urgently to the referring physician to facilitate rapid diagnosis and to help in additional clinical and legal investigations.

Occasionally, fractures that are suspicious for abuse may be seen on chest or other radiographs as an incidental finding in the absence of an appropriate history or predisposing condition. It is the duty of the radiologist to detect these and to alert the referring team to the possibility of inflicted injury or abuse. Speedy diagnosis and notification of the appropriate legal authorities would help to remove the child from the abusive environment sooner and prevent further abuse and potentially life-threatening injuries.

Skeletal-Survey Screening of Siblings of Abused Children

Based on the evidence in the literature, van Rijn and colleagues (2010) recommend that the siblings of an abused child who are less than 2 years of age should undergo a complete skeletal survey.

Postmortem Imaging

Skeletal surveys are performed on all young children and infants with an unexplained cause of death to exclude abuse. The postmortem skeletal survey should be of similar high quality as a survey done to evaluate abuse in a living child. The ACR-SPR or RCR guidelines for skeletal survey should be followed.

Individual bones can be dissected at the time of autopsy, evaluated by the pathologist, and radiographed. Virtual autopsy with CT or MRI has been reported and may become more prevalent in the future.

Radiation Doses in Imaging Children for Abuse

ACR appropriateness criteria (2009) estimate the pediatric effective radiation dose for a radiographic skeletal survey to range between 0.3 and 3 mSv. Non contrast head CT and Tc-99 m radionuclide bone scan also have a similar range of effective radiation dose. Although small, there is a risk of radiation exposure within these dose ranges, and the risks and benefits of the imaging modality must be considered prior to imaging.

Soft Tissue Injury

As previously stated, injuries to the soft tissues, including bruises and contusions, are the most common manifestation of physical abuse. These injuries are better assessed with clinical examination than with imaging. Radiographs may show soft tissue swelling (Fig. 21.2) at the site of injuries but these findings can be often overlooked if they are subtle. Heterotopic ossification, that is, ossification of the soft tissues adjacent to bones and joints, has also been reported due to non accidental trauma by Sawyer and colleagues (2009) and is readily seen on plain radiography. CT and MRI can show stranding or edema in the subcutaneous adipose tissue at the site of contusions but these imaging techniques are never utilized primarily to evaluate these injuries. Similar changes may be seen with other more significant injuries to the underlying deeper structures. Muscle contusions are better seen with MRI as areas of feathery-appearing edema that show increased signal on T2-weighted images with intact underlying muscle fibers. Muscle lacerations or tears can be seen as focal areas of increased T2 signal on MRI with disruption of the muscle fibers. Intramuscular and soft tissue hematomas can be seen on CT or MRI as areas of focal fluid collections. The appearance of the hematoma on CT can vary from being hyperdense to hypodense (Fig. 21.3) depending on the delay between the time of injury and the time of imaging. On MRI, hematomas have mixed-signal characteristics on T1- and T2-weighted images depending on the stage of hemoglobin breakdown products such as deoxyhemoglobin, intra- or extracellular methemoglobin, and hemosiderin. Muscle lacerations and hematomas may also be seen with ultrasonography. Extensive muscle injury from abuse can lead to rhabdomyolysis, myoglobinuria, and also acute renal failure.

Skeletal Injury

Skeletal trauma is the second most common form of injury in child abuse after soft tissue injuries such as bruises and burns. Before a child is ambulatory, that is,

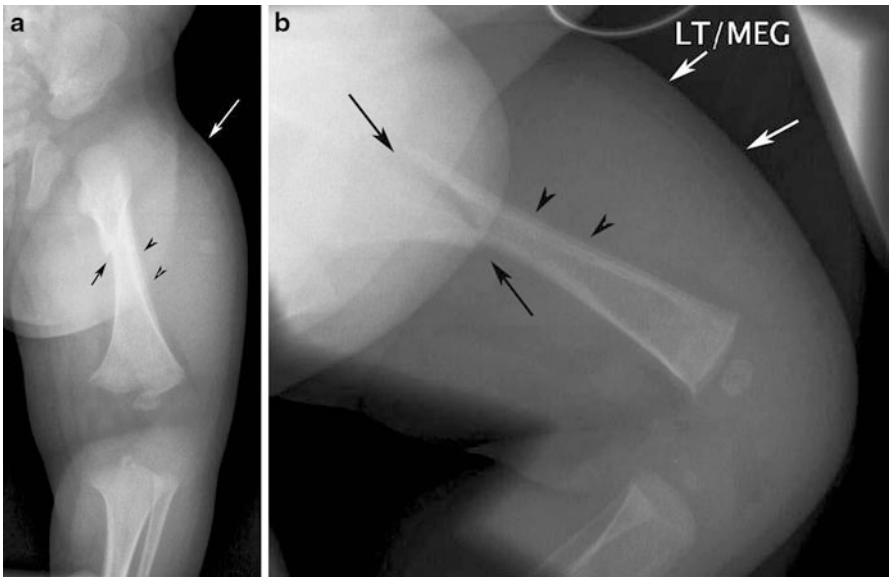

Fig. 21.2 (**a**) and (**b**) Frontal and lateral radiographs of the left femur showing an oblique fracture in the proximal diaphysis (*black arrows*) with subperiosteal new bone formation (*arrowheads*) and extensive soft tissue swelling (*white arrows*) indicative of soft tissue hematoma

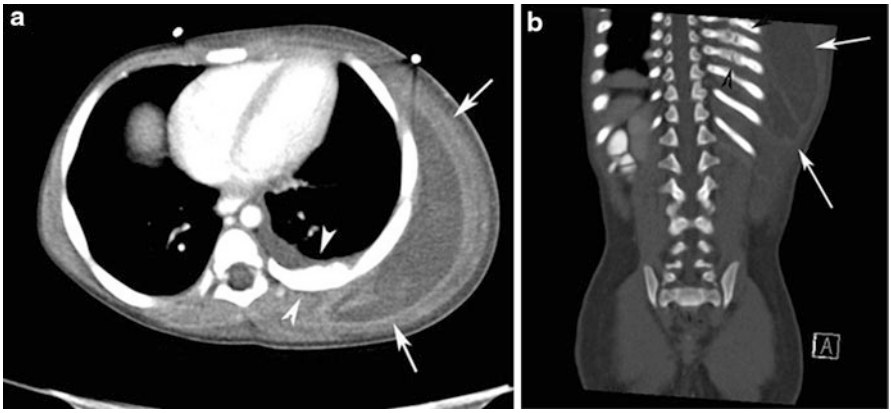

Fig. 21.3 Axial (**a**) and coronal reconstructed CT image (**b**) in a 2-year-old male with multiple bruises from non accidental trauma showing lateral chest wall fluid collection (*arrows*) indicative of a hematoma or seroma from blunt direct trauma. Healing posterolateral rib fractures with associated small left pleural effusion are also noted (*arrowheads*)

in the first year of life, long bone fractures are unusual. Therefore, any long bone fracture in infancy should be evaluated with the possibility of abuse in mind. Extremity long bone fractures in abused infants typically involve the femur, tibia, and humerus.

Table 21.3 Specificity of fractures in non accidental trauma (Adapted with permission from Kleinman 1998a)

High specificity	Moderate specificity	Low specificity
Classic metaphyseal lesions	Multiple fractures, especially bilateral	Subperiosteal new bone formation
Rib fractures, especially posterior	Fractures in different stages of healing	Clavicle fractures
Scapular fractures	Epiphyseal separations	Long bone shaft fractures
Vertebral spinous process fractures	Vertebral body fractures and subluxations	Linear skull fractures
Sternal fractures	Fractures of the digits	
	Complex skull fractures	

Kleinman (1998a) has categorized fractures as being highly specific, moderately specific, or having low specificity for non accidental trauma (Table 21.3). These findings become more specific in infants.

Extremity Long Bone Injuries

Diaphyseal Fractures

A variety of fractures have been reported in the diaphysis of the long bones in abused children. Spiral fractures in the shafts of the femur (Fig. 21.4), tibia, and humerus (Fig. 21.5) in infants less than 1 year of age are highly suggestive of abuse. Spiral fractures are fractures that extend in a spiral fashion with respect to the long axis/shaft of the bone. They occur due to torsion or forceful twisting of the affected extremity, mechanisms which rarely occur with accidental injury. Once the child is ambulatory, however, spiral fractures are more common especially in the tibia (toddler stress fracture) and are less specific for abuse (Lonergan et al. 2003). In the ambulatory child, falls that happen while walking, running, climbing, or falling down the stairs can be associated with twisting of the extremity and can result in spiral fractures.

Metaphyseal Fractures

Metaphyseal fractures were first described by Caffey (1957), a pediatric radiologist, and are considered highly specific for child abuse in non ambulatory infants. Kleinman, Marks, Richmond, and Blackbourne in 1995 and later Kleinman and Marks (1996a, b, c and 1998) termed this a "classic metaphyseal lesion" (CML). These are most commonly seen in the distal femur, proximal tibia, distal tibia, and proximal humerus. Classic metaphyseal lesions represent a series of microfractures in the subphyseal metaphysis (Kleinman et al. 1986) in the region of the primary spongiosa, which is the weakest portion of the metaphysis (Alexander 1976; Merten et al. 1983). CMLs result from shearing or distracting forces that may occur with shaking of an infant. These forces are unique to shaking and are therefore not seen

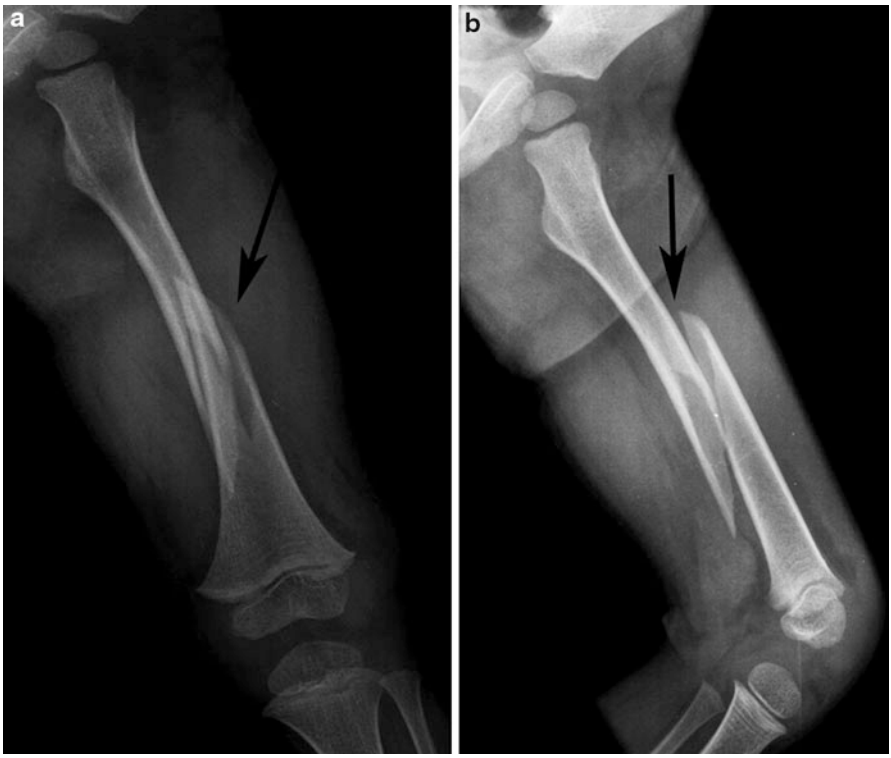

Fig. 21.4 Frontal (**a**) and lateral radiographs (**b**) of the femur demonstrate an acute spiral fracture (*arrow*) in the midshaft in this abused infant

with routine falls or blunt-trauma injuries. CMLs can be complete or incomplete across the metaphysis. The complete fracture would have a disc or wafer of the subphyseal portion of the metaphysis separated from the rest of the bone. At the corners of the metaphysis, the fracture line is angled obliquely toward the diaphysis and therefore the periphery is thicker than the central portion of the fracture where the fracture line is closer and parallel to the physeal cartilage. Since the central portion can be very thin, it may be difficult to detect radiographically. The wider metaphyseal fracture is more conspicuous as triangular fragments. These are described as corner fractures (Figs. 21.6 and 21.7). These are seen as discrete metaphyseal corner-bone fragments when the X-ray beam and the view are tangential to the physis. If the fracture is viewed at an oblique angle or if there is a thicker central portion, the fracture can be seen in its entirety as a linear fragment paralleling the lucent physis, reminiscent of a "bucket handle" (Fig. 21.8). Corner fractures and bucket-handle fractures are, therefore, manifestations of the same injury (Kleinman et al. 1986). CML-type injuries, however, are not pathognomonic of non accidental trauma, as they have been reported secondary to obstetric trauma during the difficult delivery of an infant with shoulder dystocia or footling breech

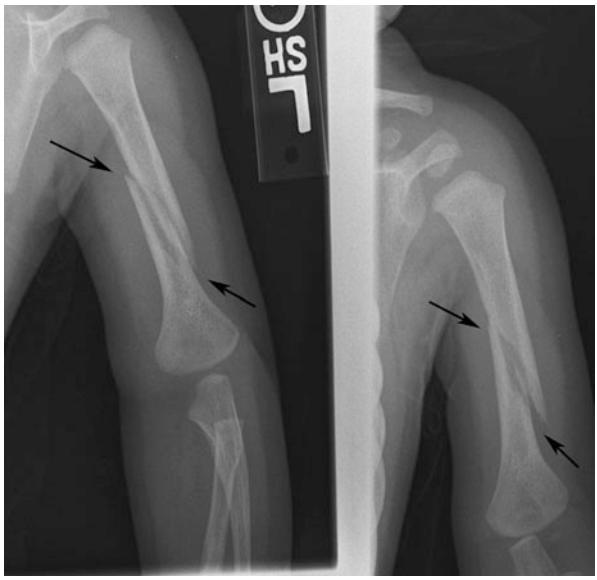

Fig. 21.5 Frontal and lateral radiographs of the left humerus demonstrate an acute spiral fracture in the midshaft (*arrows*)

(Dwek 2011; Snedecor and Wilson 1949). After the first year of life, the CML loses some of its specificity for abuse since it may occur in accidental trauma (Dwek 2011). Metaphyseal irregularity or fractures can also occur due to other conditions such as rickets, congenital insensitivity to pain, osteomyelitis, congenital syphilis, metaphyseal dysplasias, methotrexate therapy, copper deficiency, and Menkes syndrome.

Because CMLs occur in the area of enchondral bone formation, there is often little periosteal reaction and callus formation when CMLs heal. This makes the radiographic dating of these fractures difficult (Fig. 21.9).

Epiphyseal Fractures

Overall epiphyseal separation injuries/fractures are much less common than CML or diaphyseal fractures in non accidental trauma and can be seen in various locations as described below. Epiphyseal separations are considered to be moderately specific injuries for abuse. The mechanism of epiphyseal separations is thought to be similar to that of the classic metaphyseal lesions but the magnitude of the force needed for epiphyseal separation is much more than that of CML. There is no fracture line visible radiographically since the injury happens in the non ossified cartilaginous physis. In young infants, the epiphysis itself may not be ossified, making radiographic diagnosis all the more challenging. US or MRI can show the relationship of the non ossified epiphysis to the rest of the bone and help in diagnosis. Unlike CML injuries, the epiphyseal separation injuries have significant potential to cause growth arrest and deformities.

Epiphyseal separation injuries in the proximal humerus usually result from pulling, twisting, and swinging of the arm. Prior to ossification of the humeral

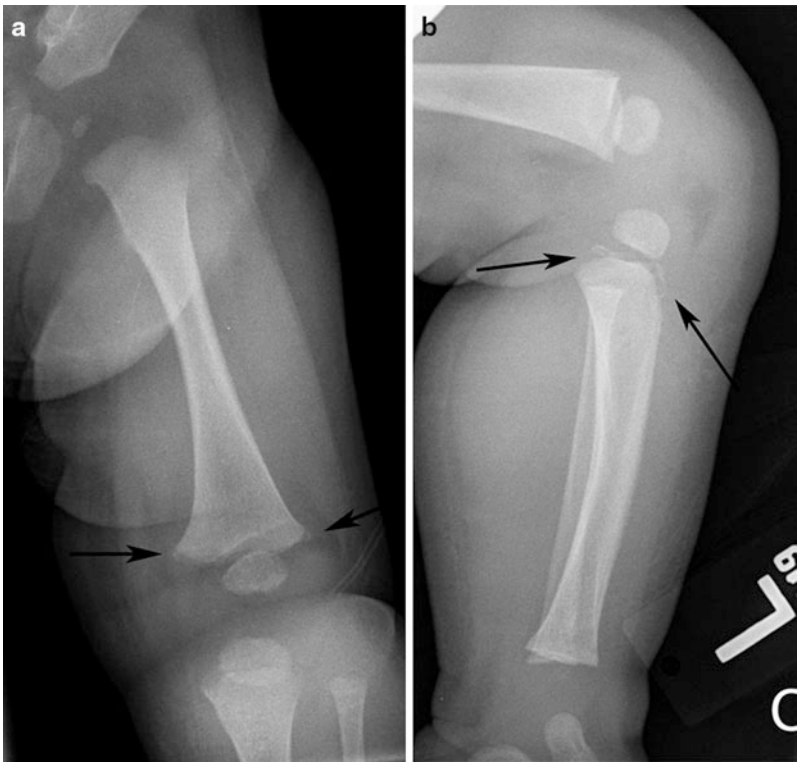

Fig. 21.6 A 3-month-old female showing acute metaphyseal medial and lateral corner fractures (*arrows*) in the distal femur (**a**) and an acute bucket-handle fracture (*arrows*) in the proximal tibial metaphysis (**b**)

epiphysis at the shoulder, there may be subtle misalignment of the humeral metaphysis with the glenoid. Following ossification of the humeral head epiphysis, an epiphyseal separation injury results in the medial displacement of the humeral shaft with respect to the ossification center. In the absence of epiphyseal displacement, evidence of healing such as subperiosteal new bone formation or subtle irregularity of the metaphyseal end of the physis may be the only indication of a prior epiphyseal separation fracture on delayed radiographs (Merten et al. 1981).

At the elbow, the epiphyseal separation injury may be misinterpreted as an elbow-joint dislocation. However, dislocations do not occur in the infant elbow. Since the physeal cartilage is weaker than the capsule and other structures reinforcing the joint, the physis will fracture first. In elbow-joint epiphyseal separation, the capitellum is displaced medially and posteriorly with respect to the humeral metaphysis, with normal proximal radioulnar-joint alignment (Nimkin et al. 1995).

Injury to the proximal femoral physis causing separation of the femoral head epiphysis can cause significant hip-joint deformity. Prior to ossification of the

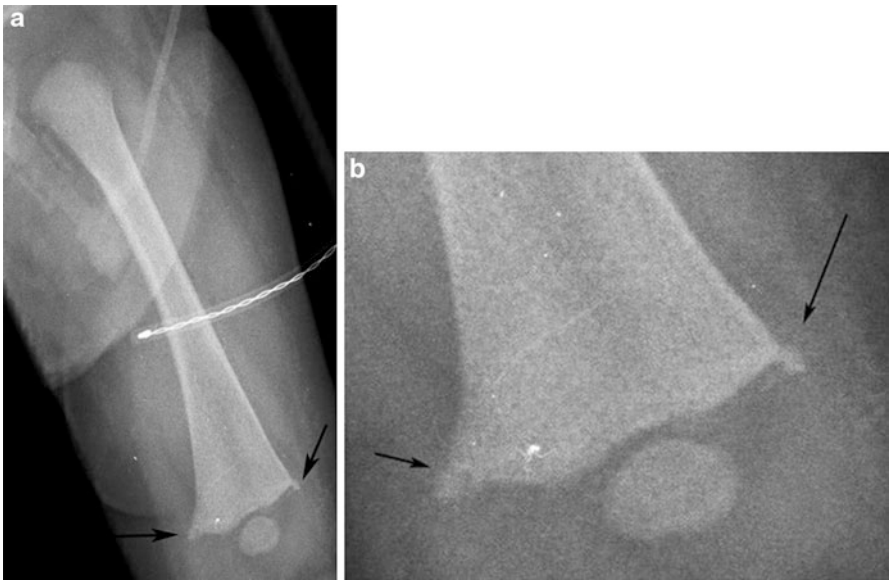

Fig. 21.7 (**a**) Distal femoral metaphyseal acute corner fractures (*arrows*) in an infant that are better seen on magnification (**b**)

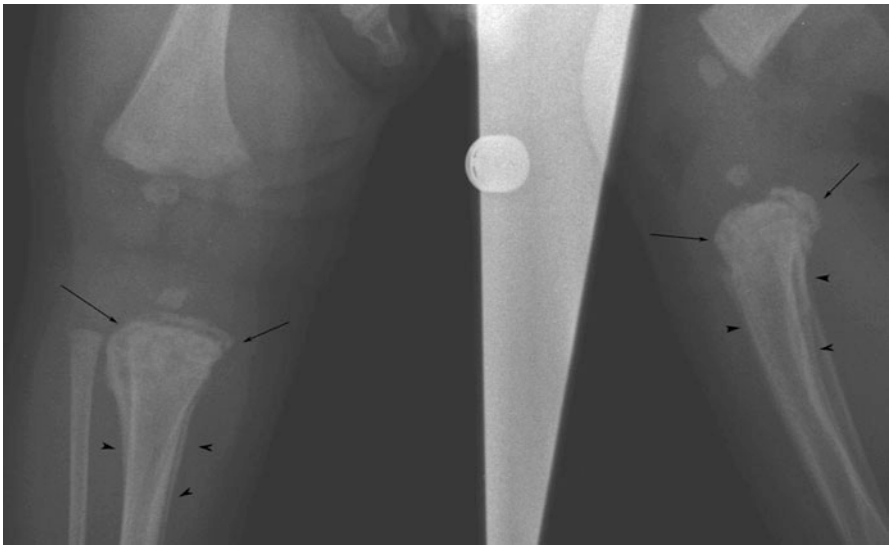

Fig. 21.8 Frontal and lateral radiographs of the knee in an infant showing proximal tibial bucket-handle-type metaphyseal fracture (*arrows*) in the proximal tibia with subperiosteal new bone formation (*arrowheads*)

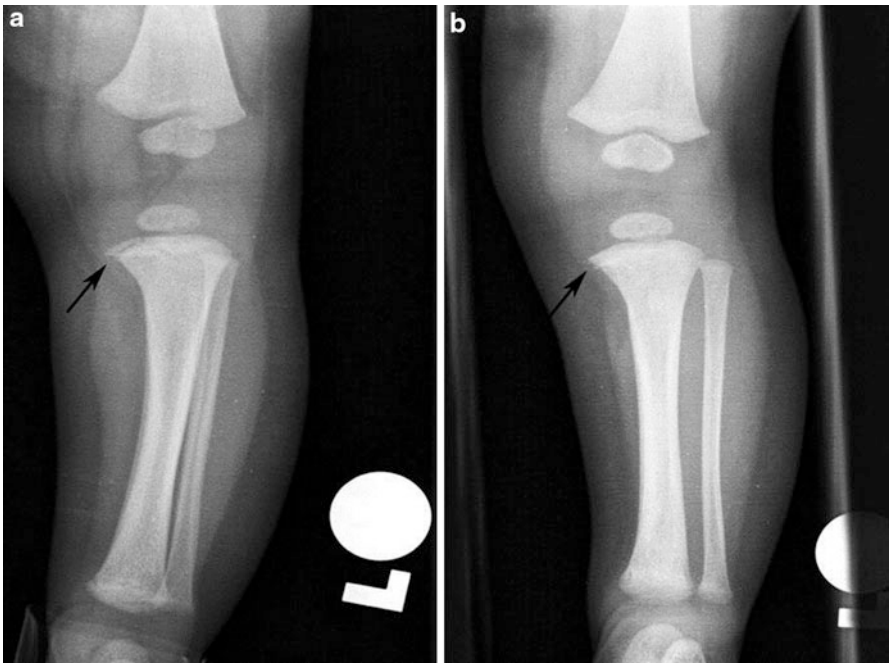

Fig. 21.9 Proximal tibial medial CML at initial presentation (**a**) that has healed on the follow-up image obtained 3 weeks later (**b**)

proximal femoral epiphysis, diagnosis of a physeal injury on conventional radiographs is difficult unless there is displacement of the femoral shaft with respect to the acetabulum. The radiographic findings could be misinterpreted as developmental dysplasia of the hip (DDH), but unlike DDH, the acetabulum is normally developed in an epiphyseal separation. Superolateral displacement of the femoral shaft can result in a coxa vara deformity. Comparison with the contralateral hip may be helpful in identifying this. US and MRI may be utilized to delineate the alignment of the non ossified femoral head with the neck and shaft. When there is some ossification of the femoral head epiphysis, the superior and lateral displacement of the femoral neck with respect to the femoral head ossification center is more obvious on a conventional radiograph (Fig. 21.10). The presence or absence of birth trauma is an important piece of clinical history in the evaluation of potential non accidental trauma, as obstetric injuries have been reported to result in epiphyseal separation injury in the proximal femur (Kleinman 1998c).

Epiphyseal separation injuries can also occur in the distal femur and proximal tibia. In the acute stage these are usually associated with soft tissue swelling. Lateral radiographs are helpful since the epiphysis is displaced in the anteroposterior plane. In the proximal tibia, the unossified apophysis of the tibial tuberosity may also be involved and the separated epiphysis is displaced anteriorly. MRI and US can better demonstrate the presence and extent of these injuries.

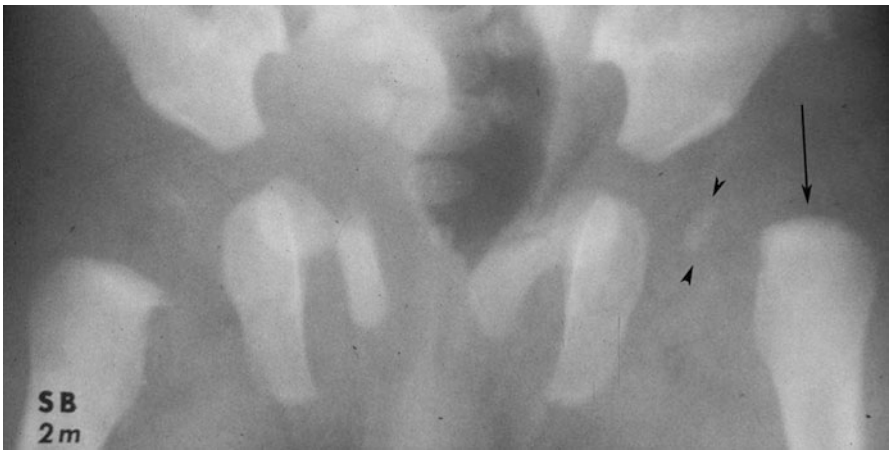

Fig. 21.10 Frontal radiograph of the pelvis in an infant showing nonalignment with superior and lateral subluxation of the left femur shaft (*arrow*) with respect to the ossification center of the left femoral head epiphysis (*arrowheads*). In contrast normal alignment of the right femur shaft with the femoral head ossification center is noted

Fractures in the Hands and Feet

Soft tissue injuries in the hands are much more common than fractures in non accidental trauma. When fractures occur with abuse, there is a predilection for fractures of the second and third metacarpals in young children. Subperiosteal new bone formation along the shafts of the metacarpals, described as metacarpal cloaking, can be seen with healing fractures but has also been reported to be caused by vigorous passive exercise in infants (Helfer et al. 1984). Subperiosteal new bone formation may be seen as early as 4–7 days after injury in infants.

Phalangeal fractures are rare and can be the subtle buckle or torus fractures. Buckle or torus fractures are incomplete fractures that result from compressive forces where the cortex is bent either inward or outward. Follow-up radiographs, oblique radiographic projections, and radionuclide bone scan improve their detection. Hand fractures typically result from twisting or bending injuries rather than direct-impact injuries. Phalangeal fractures are probably due to hyperextension of the fingers. An exception to this pattern of phalangeal injury is secondary to repeated beating on the knuckles resulting in irregularity and sclerosis at the articular surface of these bones (Kleinman 1998b).

Fractures in the hand from accidental trauma are common in the older pediatric and adolescent age groups and typically involve the peripheral fingers (thumb and little finger) (Yeh and Dodds 2009; and Vadivelu et al. 2006). Accidental crush injuries from hands getting trapped in closing doors result in tuft and distal phalangeal fractures and are more common in the infant and toddler age group (between 0 and 4 years) (Rajesh et al. 2001).

Fractures in the foot are uncommon in abuse but their presence in infants is strongly suggestive of abuse. Metatarsal fractures are more common and include buckle- and avulsion-type fractures. Acute fractures may be difficult to identify, and subperiosteal new bone formation may be seen later on follow-up radiographs. Additional oblique radiographic projections, follow-up radiographs, and radionuclide bone scans are helpful in detecting these injuries. In infants, the metatarsal fractures are typically the result of excessive manipulation of the feet rather than blunt direct injury. After infancy, blunt impact probably causes most inflicted fractures (Kleinman 1998c).

Metatarsal fractures are the most common fractures in the foot from accidental trauma and result from direct or indirect forces. These are most likely to be nondisplaced or minimally displaced fractures. Avulsion fracture of the base of the fifth metacarpal is the most common isolated traumatic fracture in the foot resulting from inversion or adduction forces (Owen et al. 1995) and is most common in children over 5 years of age. The second most common fracture is of the first metatarsal which tends to occur in children less than 5 years of age. According to Singer et al. (2008), falls from a height were the typical cause of metatarsal fractures in children less than 5 years of age. Phalangeal fractures usually result from falling objects or stubbing a toe (Ribbans et al. 2005).

Metacarpal and metatarsal fractures from abuse are rarely isolated and are usually associated with additional fractures in the same (ipsilateral) extremity that are more typical of abuse.

Rib Fractures

Rib fractures secondary to abuse, usually identified in children less than 2 years of age, are most often due to forceful squeezing of an infant's chest and can therefore be seen anteriorly, laterally, or posteriorly. Since these fractures result from chest compression by an adult, they are seen in the younger age group where the chest diameter is not too large for the adult to encircle the chest with his/her hands. Given the mechanism of manual compression, it is not surprising that non accidental rib fractures often involve multiple contiguous ribs. Fractures of the first rib, although very specific for abuse, are uncommon. Posterior rib fractures at the costovertebral and costotransverse junctions are highly specific for child abuse in infants due to the unique compressive forces required to cause this injury. As expected, compressive forces over the lateral chest wall cause distraction of the outer cortex of the rib with buckling and impaction of the inner cortex. Costochondral-junction fractures can be seen anteriorly due to sternal compression and inward bending of the rib (Kleinman et al. 1996a).

Acute rib fractures are seen radiographically and on CT as lucent linear breaks across the rib (Figs. 21.11 and 21.12). Acute rib fractures are very difficult to recognize on radiographs if they are incomplete, nondisplaced, overlapped by other structures, or oblique to the X-ray beam. As a result, they are easily overlooked or missed on the initial skeletal survey. Healing rib fractures are more

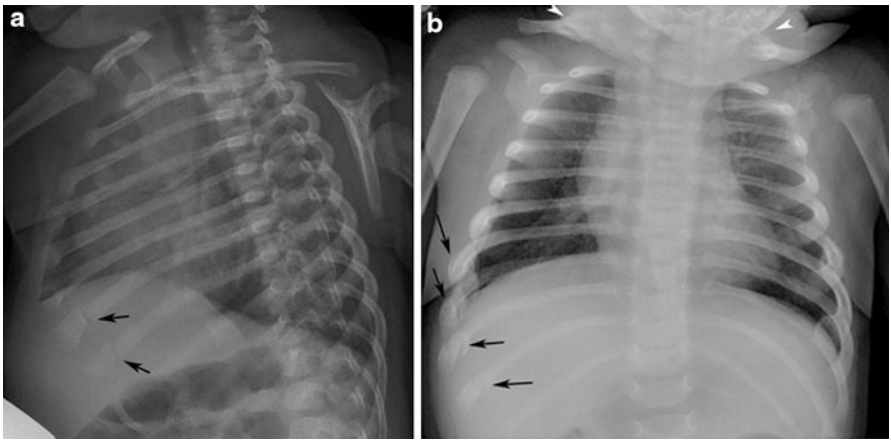

Fig. 21.11 (**a**): Oblique chest radiograph in a 1-month-old female showing slightly displaced acute rib fractures (*arrows*) in the lateral parts of the lower right ribs. (**b**): Follow-up chest radiograph obtained 2 weeks from figure (**a**) shows callus formation at the right lower rib fracture sites (*arrows*) and in both clavicles (*arrowheads*)

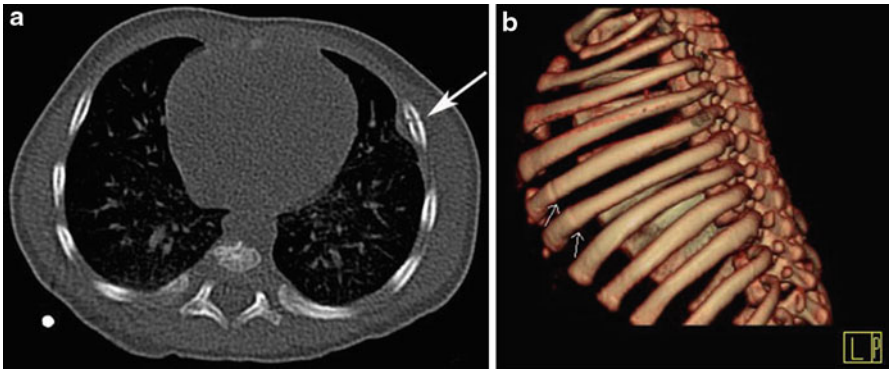

Fig. 21.12 Axial CT chest image in a 2-month-old male in bone window (**a**) and 3D reconstructed CT image (**b**) show nondisplaced acute fractures in left anterolateral portion (*arrows*)

conspicuous due to subperiosteal new bone and callus formation manifesting as bulbous areas at the injured sites (Fig. 21.13). Follow-up radiographs in 2 weeks (Fig. 21.11b) are therefore helpful in detecting healing rib fractures. In addition to the frontal projection, right and left oblique views are obtained on the follow-up skeletal survey to improve fracture detection. Radionuclide bone scans are very sensitive in detecting rib fractures and can be complementary to radiographs. CT also demonstrates rib fractures very well (Fig. 21.12) but it is not routinely obtained as part of child abuse evaluation in part due to the radiation dose involved. CT is typically reserved for the evaluation of suspected internal visceral injuries.

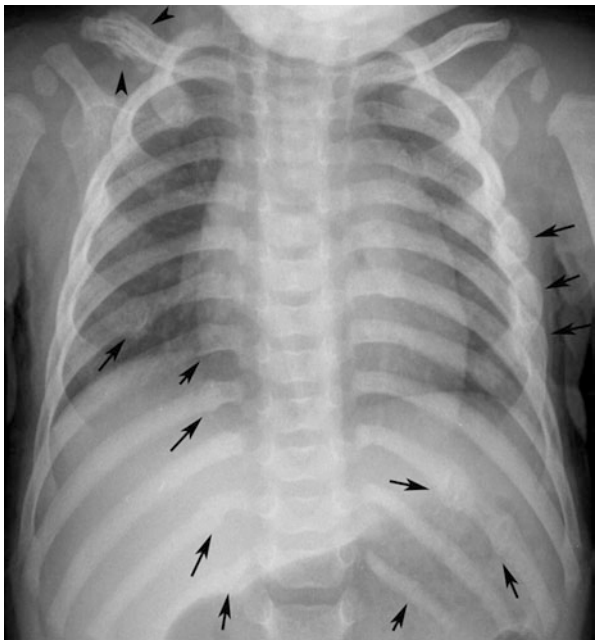

Fig. 21.13 Frontal chest radiograph showing multiple posterior and lateral healing and healed rib fractures seen with callus formation (*arrows*). Healing right clavicle fracture (*arrowheads*) is also seen

Very rarely, rib fractures may be secondary to birth trauma or cardiopulmonary resuscitation (CPR). The rib fractures in these scenarios, however, are typically anterior, not posterior, in location.

Skull Fractures

Skull fractures can be seen in up to one third of abused children who are less than 2 years of age and usually result from contact injury. Parietal and occipital bones (Figs. 21.14 and 21.15) are the most commonly involved. Fractures are called simple or linear if there is no branching or significant separation at the fracture site. These fractures typically do not cross the suture lines or synchondroses. Fractures can also be complex with branching or radiating patterns (Fig. 21.14). If there is separation at the fracture site, it is known as a diastatic fracture. When fractures involve the sutures, there could also be associated sutural widening. Significant focal impact can also cause depression or ping-pong-type skull fracture (Fig. 21.16) at the site of blunt injury. "Ping-pong skull fracture" is a focal depressed fracture seen in newborns and infants who have a thin calvarium that is also very plastic and bends rather than developing a break. The calvarium at the site of injury is depressed inward without a break or a fracture line seen. In the newborn, ping-pong fractures have been reported with difficult forceps extraction and also due to compression by the sacral promontory of the mother during vaginal delivery.

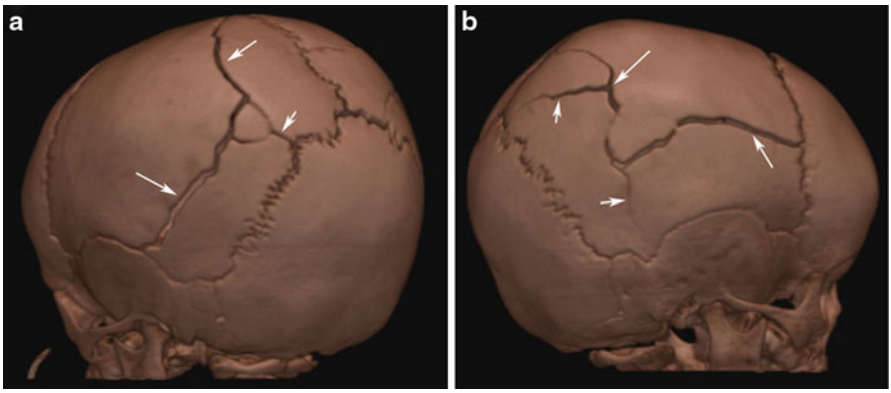

Fig. 21.14 3D reconstructed CT images showing complex bilateral parietal bone fractures (*arrows*) in this infant (right parietal bone in figure (**a**) and left parietal bone in figure (**b**)) who also had subdural hematoma

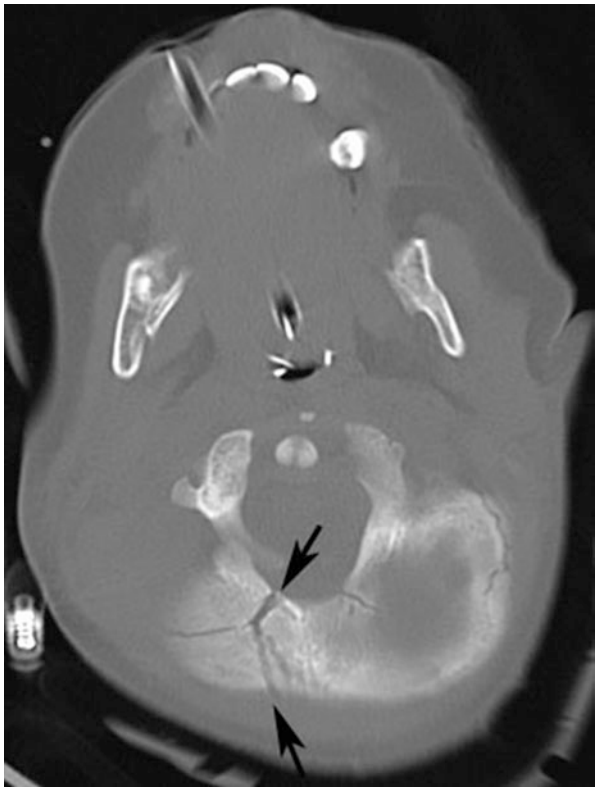

Fig. 21.15 Axial CT image through the skull base in an 18-month-old male showing a fracture in the right occipital bone extending to the foramen magnum (*arrows*)

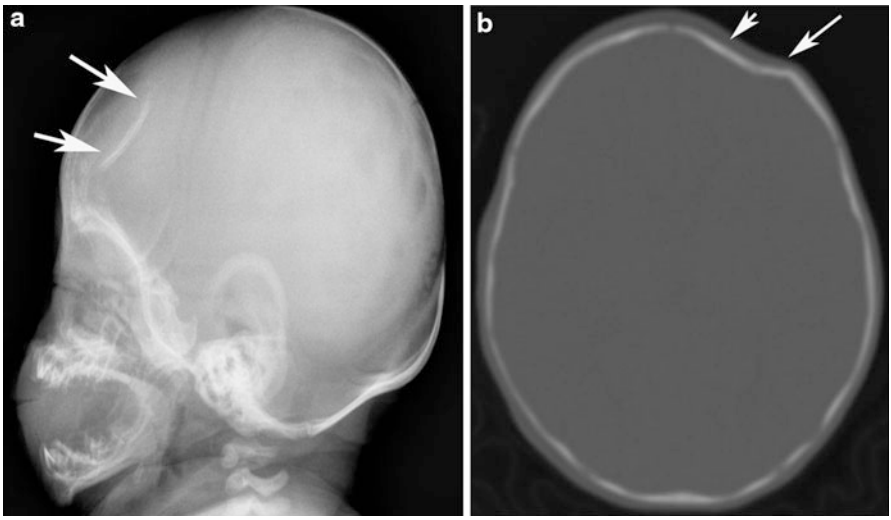

Fig. 21.16 Lateral skull radiograph (**a**) and axial CT image in bone window (**b**) showing a depressed or ping-pong-type fracture in the left frontal bone (*arrows*)

Since accidental trauma can cause calvarial fractures, correlation with mechanism of injury is essential to identify abuse. Traumatic skull fractures most often result from motor vehicle accidents and falls from heights of at least 1 m. Occipital and basilar skull fractures from accidental trauma can occur and are typically seen with high-force blunt-impact injuries such as from motor vehicle accidents.

Studies have shown that multiple fractures, fractures that cross sutures, and bilateral skull fractures are more likely to be associated with abuse (Lonergan et al. 2003). There is no direct correlation between skull fractures and intracranial injury. Also, it is to be remembered that a single impact can cause a fracture to extend across suture lines into the adjacent bones (Kleinman and Barnes 1998).

Spinal Fractures

Overall, injuries to the vertebral column are uncommon both in accidental and non accidental injuries in children. Motor vehicle accidents are the most common cause of such injuries and are usually associated with other injuries. Injuries due to falls from heights and sport-related activities can also cause vertebral fractures in older children.

Shaking causes hyperextension and hyperflexion injuries of the spine manifested as vertebral body compression fractures in the thoracolumbar region and avulsion of the interspinous ligament (Fig. 21.17) (Kleinman and Marks 1992). Due to the mechanism, these are more specific for abuse. The ligamentous

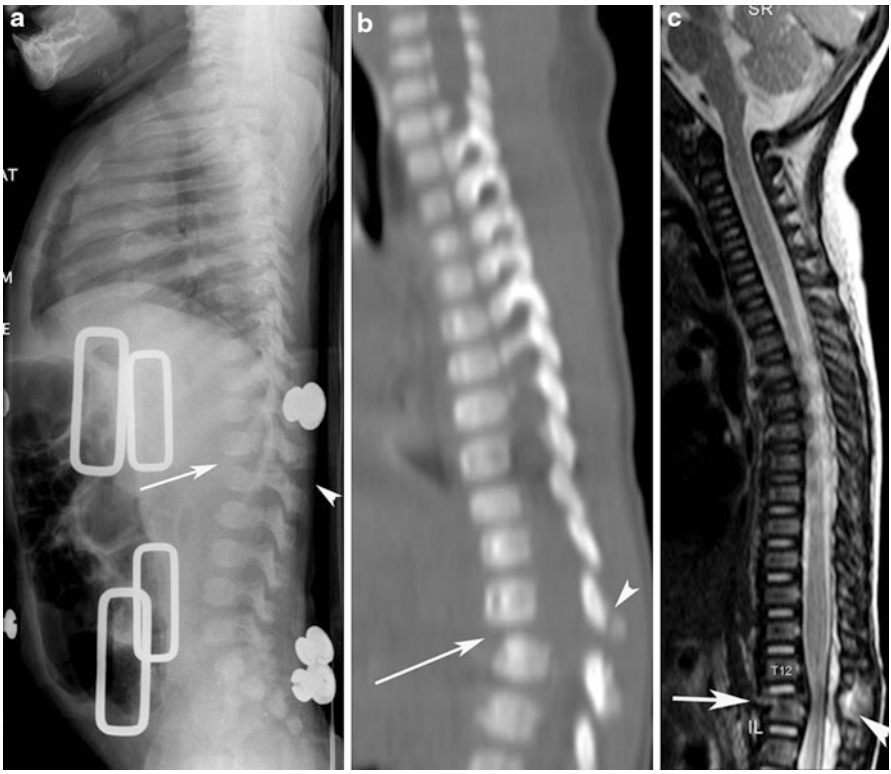

Fig. 21.17 (**a**): A 4-month-old female showing compression fracture of L1 vertebral body with grade 1 spondylolisthesis of T12 on L1 (*arrow*) and increased interspinous distance between T12 and L1 vertebrae (*arrowhead*) indicating ligamentous injury. (**b**): Sagittal CT image better shows the alignment abnormality (*arrow*) and spinous process avulsion fracture (*arrowhead*). (**c**): Sagittal T2-weighted image with fat suppression showing the vertebral body compression fracture (*arrow*) and increased signal (*bright area*) in the interspinous region between T12 and L1 vertebra indicating edema from interspinous ligamentous injury/tear (*arrowhead*)

injury may not be evident on initial plain radiographs. MRI will easily show this injury as an area of edema with increased T2 signal in the interspinous region (Fig. 21.17c). When they are seen on radiographs, widened interspinous distance and loss of alignment of the corresponding portions of vertebral bodies and posterior elements may be seen.

Spinal cord injuries can be present in the absence of radiographic findings, and so neurological evaluation will be helpful. Also vertebral compression fractures have been reported from severe seizure activity due to excessive and repetitive muscular contraction. As in other injuries associated with non accidental trauma, correlation with the injury mechanism and clinical history is recommended to diagnose or exclude non accidental trauma as a cause of spinal injury/fractures.

Other Fractures

As described previously, variable types of fractures (Figs. 21.18 and 21.19) are possible, based on the mechanism of injury. Any fracture that would not be expected based on the child's age, developmental ability, and history of trauma should raise suspicions of abuse or non accidental trauma.

A fall down stairs is a common history given to explain non accidental trauma. A recent study (Zielinski et al. 2012) showed that falls down stairs most commonly result in injuries to the head and neck region followed by the extremities, with the truncal region being the least affected. In the head and neck injuries, lacerations and other soft tissue injuries were much more common followed by closed-head injury. In this study, children less than 1 year of age were more likely to be injured in walkers or strollers or while being carried by an adult. Riding down the stairs in a tricycle or similar device was found to be a common cause of injury in 2-year-old children in this study whereas children older than 4 years had injuries from jumping down the stairs resulting in fractures of the upper and lower extremities. Another study of household falls down stairs in children (Huntimer et al. 2000) demonstrated a similar pattern of soft tissue injuries primarily in the head and neck region. Additionally, this study had no instances of intra-abdominal visceral injuries. Joffe and Ludwig (1988) suggested that falls from stairs result in an initial, mildly-to-moderately severe impact followed by a series of low-energy non injurious falls. This explained their finding that most injuries were typically not severe and involved a single region of the body. Therefore injuries that are more severe, those that involve the truncal region of the body, intra-abdominal injuries, or those that involve more than a single region are suspicious for abuse when the history of falling down the stairs is offered. Careful correlation with the mechanism of injury based on the history is always indicated.

Scapular fractures (Fig. 21.20) and sternal fractures, both of which are very uncommon and require significant force, are also highly specific for abuse (Kleinman 1998d).

Dating of Fractures

Multiple fractures in various stages of healing are moderately specific for abuse (Kleinman 1998a) but when these fractures also include the CMLs or posterior rib fractures, they become highly specific.

Fracture healing is influenced by multiple factors including the age of the child, site of injury, physeal involvement, nutritional status, presence of motion, and other systemic and metabolic conditions. Because of the many variables influencing the rate of fracture healing, the radiographic dating of fractures is an inexact science. Fractures in children heal faster than adults. As a general rule, the younger the age the faster is the healing. Upper extremity fractures heal faster than lower extremity fractures.

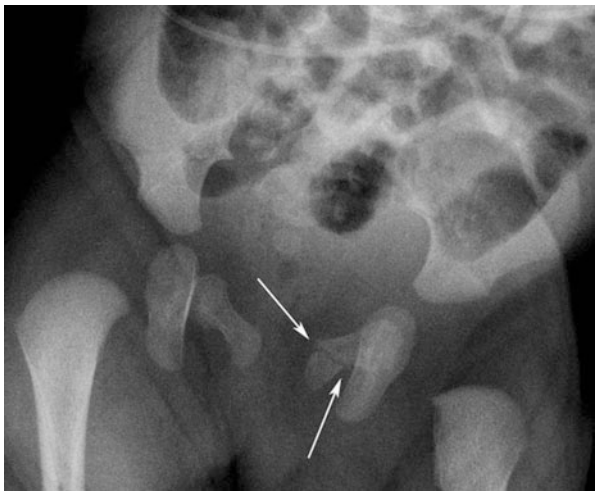

Fig. 21.18 Frontal radiograph of the pelvis in a 1-month-old male showing a non-accidental acute left superior pubic ramus fracture seen as a transverse lucency (*arrow*)

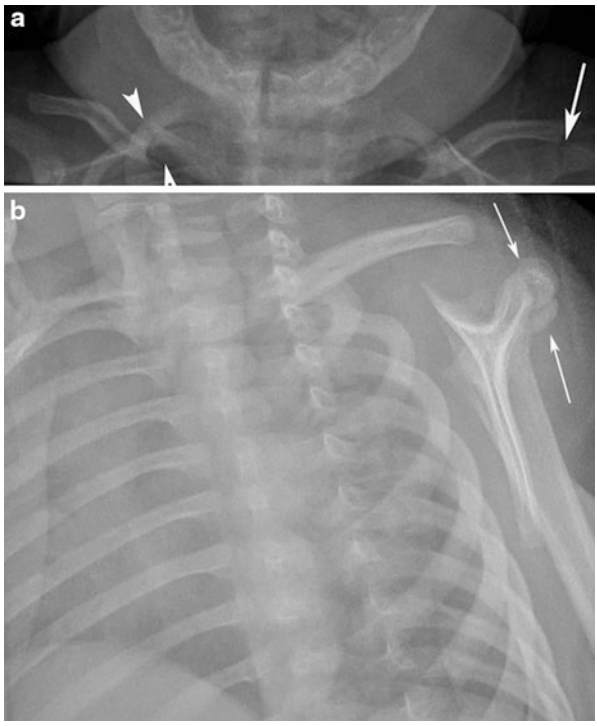

Fig. 21.19 (**a**): Frontal radiograph in a 1-month-old female with non accidental trauma showing an acute transverse nondisplaced fracture in the acromion process of left scapula seen as a vertical lucency (*arrow*). Acute right clavicle fracture can also be seen with displacement (*arrowheads*). (**b**): Follow-up oblique view radiograph done 2 weeks after the initial skeletal survey shows callus formation in the acromion process of left scapula (*arrows*)

The usual time course of fracture healing in children is as follows (O'Connor and Cohen 1998):

1. 4–10 days for resolution of soft tissue swelling
2. 10–14 days for subperiosteal new bone formation

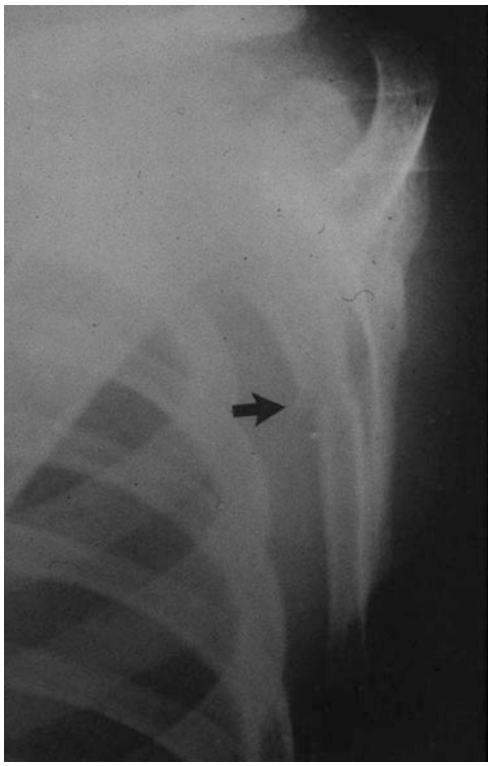

Fig. 21.20 Radiograph in scapular Y-view position showing an acute fracture in the body of the scapula (*arrow*) from non accidental trauma

3. 14–21 days for immature or soft callus formation and loss of fracture-line definition
4. Greater than 21 days for hard or mature callus formation

Nonetheless, these time frames are not exact. In infants the healing process is markedly accelerated. Newborns may show callus formation in 4 days (Chapman 1992) as seen in clavicle fractures from birth trauma. Malone et al. (2011) have reported that the various stages of healing have different durations in different age groups from infancy to 5 years.

Skull fractures are notoriously difficult to date as they do not demonstrate the aforementioned stages of healing. The constant motion of the ribs may alter the timing of callus formation and also hinder the accurate dating of rib fractures.

As previously described, it is also difficult to date classic metaphyseal fractures since there may be little to no periosteal reaction and callus formation (Fig. 21.9). Classic metaphyseal fractures may not be visible on the follow-up radiographs obtained 2 weeks after the initial survey since they may have healed completely. On follow-up radiographs, periosteal reaction may be absent in areas where the fracture is intra-articular (Dwek 2010). Callus formation may also be minimal if the injured extremity was immobilized very early in treatment.

Radiographic Pitfalls and Normal Variants

1. Metaphyseal collar: The metaphysis flares gradually and smoothly toward the physis. At the end however, there is an abrupt vertical interruption of this slope 1–2 mm in length, and this is known as the metaphyseal collar. It is physiological and can be well seen at the distal radial metaphysis. As the collar extends around the unossified physis, a small spur may be seen mimicking a corner fracture (Fig. 21.21) (Kleinman et al. 1991). However there is no break or lucency extending into the physis beneath the zone of provisional calcification (Dwek 2011). There is also no periosteal new bone formation.
2. Distal medial femoral and proximal medial tibial metaphyseal irregularity (Fig. 21.22) with a triangular fragment can sometimes be seen. This is thought to be due to the normal varus angulation (Kleinman et al. 2009) and asymmetric weight bearing or stress.
3. Beak-like appearance in the medial proximal tibial (Fig. 21.22) and humeral metaphysis is also physiological due to rapid bone turnover with bone resorption and formation causing remodeling (Kleinman et al. 1991).
4. Physiological subperiosteal new bone formation is seen in infants 1–5 months of age along the diaphysis of the humerus, tibia, and femur (Figs. 21.23 and 21.24). It is usually bilateral and symmetric in appearance, due to the rapid growth of infants. It is seen in the first 4 months as a thin hazy area of increased density, separated from the bone by a thin lucency. At 4–5 months of age, subperiosteal new bone formation appears similar to normal fracture callus as it progressively ossifies and gets incorporated into the bone. Physiological subperiosteal new bone formation should not be greater than 2 mm in thickness (Kwon et al. 2002).

Skeletal Mimics and Other Differential Diagnoses of Abuse (Table 21.4)

1. Rickets: Rickets is a metabolic disorder resulting from decreased vitamin D levels causing hypocalcemia, hypophosphatemia, and secondary hyperparathyroidism. Rickets results in decreased bone mineralization and deposition of unossified osteoid matrix. The radiographic changes are typically noted in the metaphyses of the rapidly growing bones like the distal radius and ulna, distal femur, proximal and distal tibia, proximal humerus, and anterior ends of the ribs (Shore and Chesney 2013). Osteopenia, loss of provisional zone of calcification which is the dense line at the ends of the metaphyses, metaphyseal splaying or widening, and metaphyseal fraying/irregularity with cupping of the metaphysis can be seen in rickets (Fig. 21.25). Bowing of the weight-bearing bones and insufficiency fractures perpendicular to the shafts of the long bones may also be seen in the diaphysis of the long bones. Palpable, expanded anterior ends of the ribs at the costochondral junction, a metaphyseal equivalent, are evident radiographically and are clinically described as the "rachitic rosary."

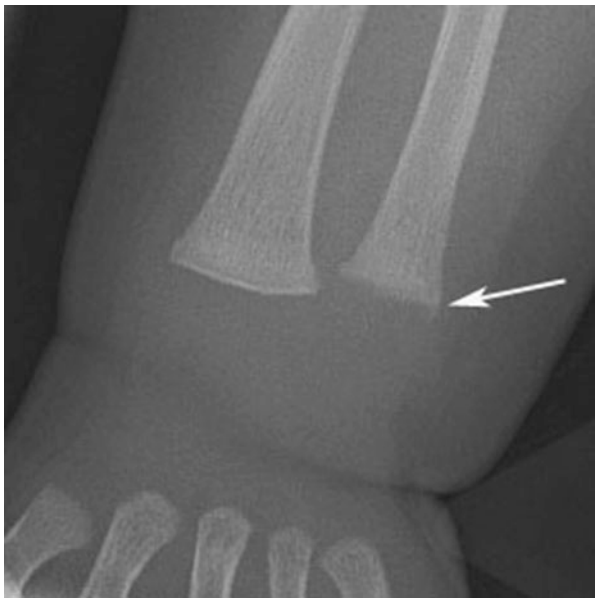

Fig. 21.21 Frontal left wrist radiograph in a 4-month-old male who had subdural hematoma and CML fractures in the right femur, showing a small spur (metaphyseal collar) in the medial distal ulnar metaphysis (*arrow*)

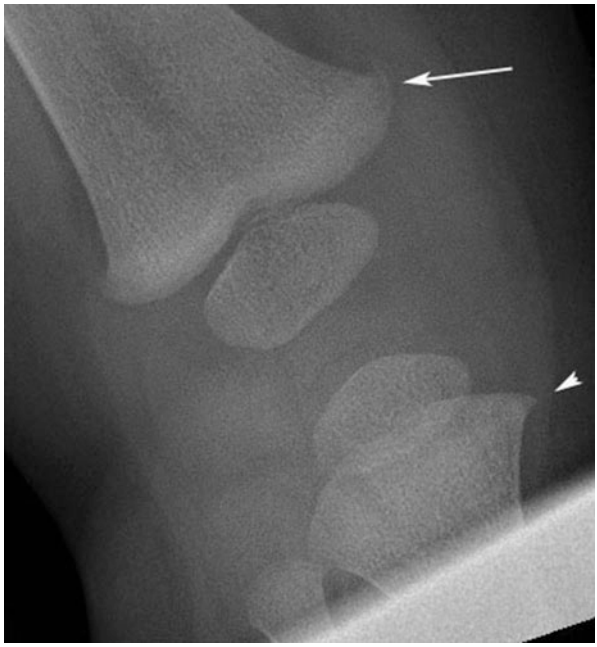

Fig. 21.22 Frontal right knee radiograph in a 9-month-old male who had injuries from burns showing incidental normal metaphyseal irregularity (*arrow*) in the medial aspect of distal femoral metaphysis. Beaking of medial proximal tibial metaphysis is also noted (*arrowhead*)

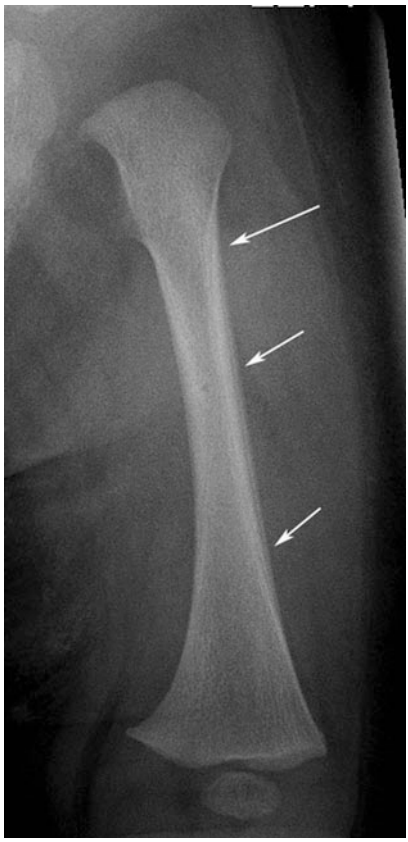

Fig. 21.23 Frontal left femur radiograph in a 2-month-old male with non accidental trauma showing physiological subperiosteal new bone formation in the lateral aspect of the diaphysis (*arrows*)

Vitamin D deficiency causing osteopenia and other changes of rickets can be seen in premature children (Fig. 21.26) and other children with chronic liver (Fig. 21.27) or renal disease. Fractures including those similar to CMLs can be seen in premature children with rickets. Chapman and colleagues (2010) found that most children (over 80 %) with rickets did not have fractures. Those children who had fractures had severe and obvious radiographic changes of rickets. The observed fractures were usually isolated insufficiency fractures in mobile infants and toddlers. In this study, fractures did not resemble the classic metaphyseal lesion of abuse and did not involve the posterior ribs or the skull. The metaphyseal corner fractures seen in their study were associated with other changes of rickets in the metaphysis, and diagnosis was straightforward. Clinical and laboratory information assist in identifying the diagnosis and underlying etiology of rickets in these patients.

Fractures can occur in these premature infants and children during their stay in the hospital or after discharge to their homes. Dating of these fractures and correlation with the patient's clinical background would be helpful to exclude

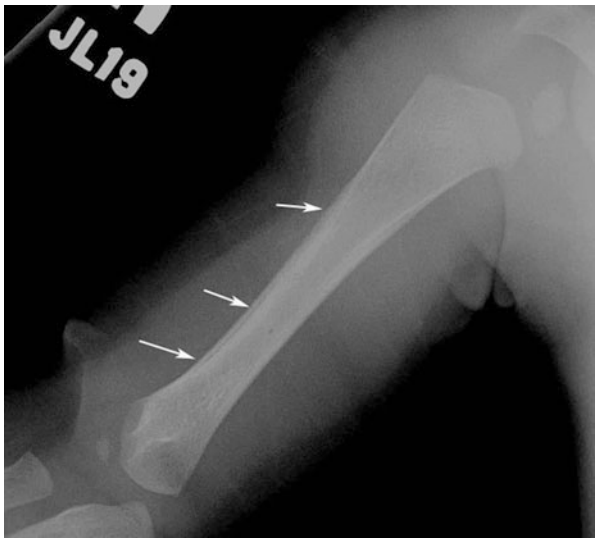

Fig. 21.24 Frontal right humerus radiograph in a 3-month-old female with non accidental trauma showing physiological subperiosteal new bone formation in the lateral aspect of the diaphysis (*arrows*)

non accidental trauma. Evaluation for other higher-specificity fractures such as posteromedial rib fractures should be done if there is a clinical concern for abuse.

The terms osteopenia and osteoporosis refer to increased radiolucency/decreased radiodensity of the bone and ideally are measured by bone densitometry studies. Radiographs are not sensitive to detect osteopenia since 30–50 % of the bone mineralization must be lost before being evident on radiographs. As bone mineralization worsens, the bones appear more lucent and have decreased trabeculation. Cortical thinning can be seen due to resorption of the endosteal cortex. In contrast to the qualitative analysis of plain radiography, bone mineral density (BMD) can be quantitatively evaluated with dual-energy X-ray absorptiometry (DXA) scanning where a z-score is generated and compared with charts obtained from age- and sex-matched healthy controls.

2. Osteogenesis imperfecta (OI): OI is a disorder due to abnormal collagen formation in the bones and other soft tissues. Of the eight types of OI described, types I to IV result from mutations in the COL1A1 and COL1A2 genes that code for the alpha-1 and alpha-2 types of collagen type-1 which is a major component of the collagen tissue in the bones. OI patients have increased bone fragility due to abnormal bone collagen in addition to deficient bone mineralization/osteopenia. These patients have multiple fractures that typically involve the shafts/diaphysis of long bones (Figs. 21.28 and 21.29) in various stages of healing. CMLs are extremely rare, if they ever occur. Rib fractures in OI are usually lateral and are uncommon posteromedially. Wormian bones (accessory intrasutural bones) in the skull may be present (Fig. 21.30). However, wormian bones are not specific for osteogenesis imperfecta. They are associated with a variety of disorders and may be a normal finding. The diagnosis of OI is often made with a combination of genetic analysis, clinical features, and radiographic findings.

Table 21.4 Differential diagnosis for non accidental trauma in children (Adapted from Nimkin and Kleinman 1997)

Disease	Shaft fracture	Subperiosteal new bone formation	Metaphyseal irregularity	Generalized osteopenia	Comments
Non accidental trauma	+	+	+	–	1. History of injury and fractures do not match
					2. Age inappropriate injuries
Rickets	+/–	+/–	+	++	1. Common in premature infants
					2. Metaphyseal changes in rapidly growing bones
					3. Shaft fractures are not common but are mostly insufficiency stress fractures
Osteogenesis imperfecta	++	–	+/–	++	1. 8 types of OI
					2. COL1A1 or COL1A2 genetic mutation could be present
					3. Wormian bones, blue sclera, etc.
					4. Possible family history
Spinal dysraphism	+	+	+	–	Clinical history
Congenital insensitivity to pain	+	+	+	–	Pain and occasionally temperature sensation is altered with otherwise preserved neurological findings
Birth trauma	+	+/–	–/+	–	1. Clavicle and humerus are most commonly fractured
					2. Birth history may be helpful
					3. Fractures are usually evident at birth
Congenital syphilis	-	+	+	–	1. Uncommon
					2. Clinical history and other physical findings may be helpful
					3. Wimberger sign

(*continued*)

Table 21.4 (continued)

Disease	Shaft fracture	Subperiosteal new bone formation	Metaphyseal irregularity	Generalized osteopenia	Comments
Osteomyelitis	+/−	+	+/−	−	1. Clinical features
					2. Often multifocal in infancy
Scurvy	−	+	+	++	1. Vitamin C deficiency
					2. Uncommon
					3. Clinical and various radiographic features
Methotrexate	+	−	+/−	++	Clinical history of treatment for leukemia or CNS tumors
Hypervitaminosis A	-	+	−	+/−	1. Increased intracranial pressure may be present
					2. Periosteal new bone formation is similar to enthesopathy
Caffey disease	−	++	−	−	1. Mandible, clavicle, and ribs usually involved
					2. Possible family history
					3. COL1A genetic mutation could be seen
					4. Fever, soft tissue swelling, leukocytosis, and increased ESR
Prostaglandin E1 therapy	−	+	−	−	1. History of treatment for ductal-dependent congenital heart disease
					2. Periosteal reaction thickness depends on duration of therapy and usually reversible

(*continued*)

Table 21.4 (continued)

Disease	Shaft fracture	Subperiosteal new bone formation	Metaphyseal irregularity	Generalized osteopenia	Comments
Acute leukemia	+/−	+	−	+	1. Transverse metaphyseal lucency
					2. Permeative appearance of the bone
					3. Other clinical and laboratory tests
Menkes syndrome and other copper metabolism disorders	−	+	+	+/−	1. Not common
					2. Sparse depigmented hair
					3. Wormian bones
					4. Low serum copper

ESR erythrocyte sedimentation rate

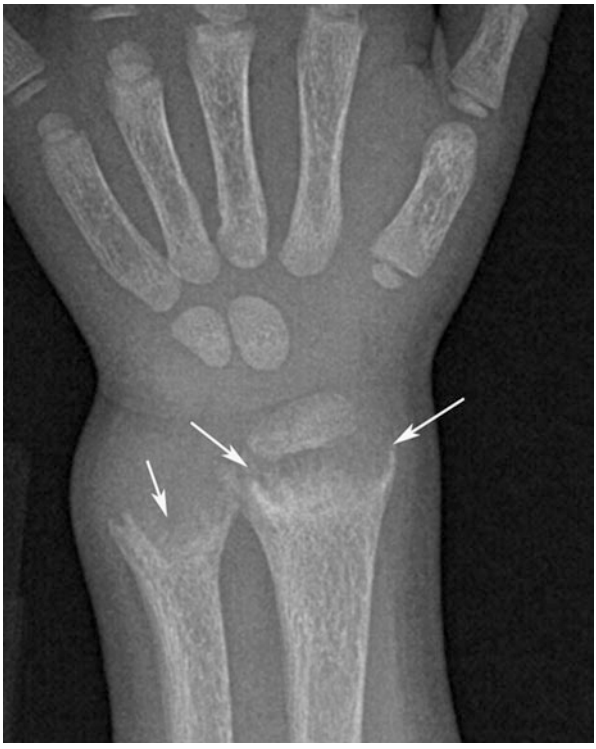

Fig. 21.25 Frontal radiograph of the wrist in an older child showing osteopenia with cortical thinning and radiolucency in all the bones, loss of the zone of provisional calcification, metaphyseal cupping, metaphyseal fraying, and splaying at the distal ends of radius and ulna (*arrows*)

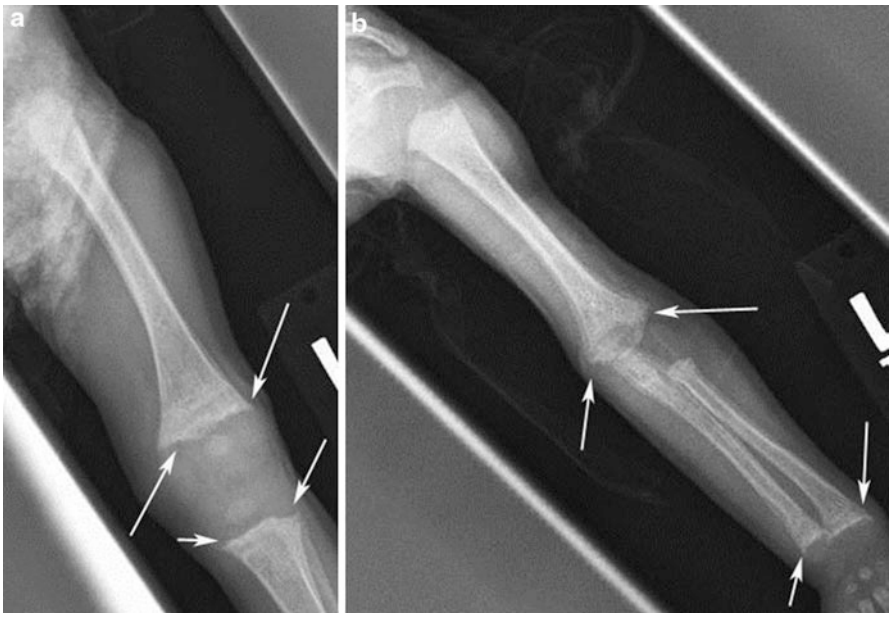

Fig. 21.26 Frontal radiographs of the left femur and left upper extremity in two different preterm infants showing osteopenia, metaphyseal fraying/irregularity, and splaying in the distal femur and proximal tibia (**a**) and distal humerus, distal radius, and ulna (**b**) consistent with rickets

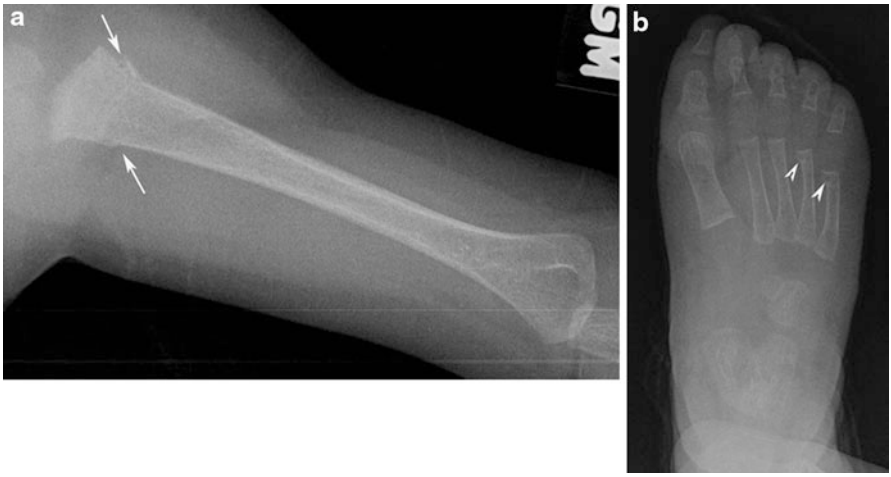

Fig. 21.27 Frontal radiographs of the humerus (**a**) and foot (**b**) in a 21-month-old child with biliary atresia showing diffuse osteopenia and fractures in the proximal humeral meta-diaphyseal region (*arrows*) and buckle fractures in the distal meta-diaphyseal region of the 4th and 5th metatarsals from vitamin D deficiency (*arrowheads*)

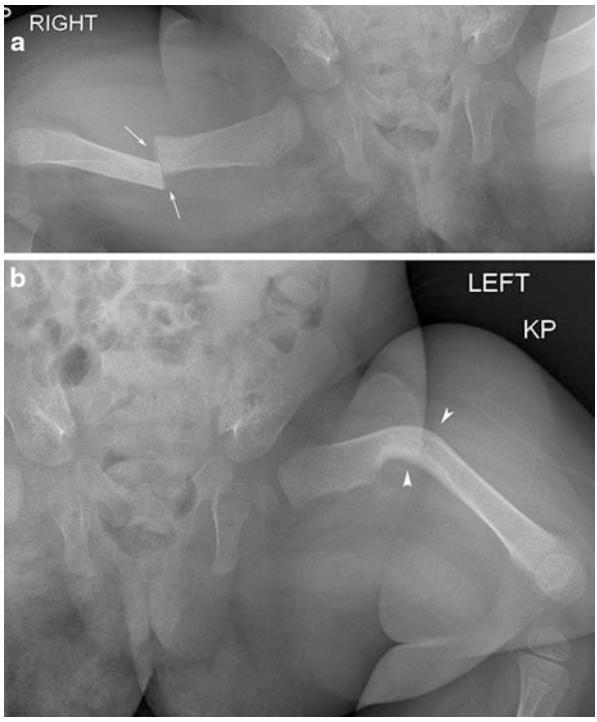

Fig. 21.28 Radiograph of the pelvis and right femur (**a**) and left femur (**b**) in a 5-month-old infant with osteogenesis imperfecta type-1 showing an acute transverse diaphyseal fracture in right femur (*arrows* in **a**) and bowing deformity in the left femur (*arrowheads* in **b**) probably from prior healed fracture

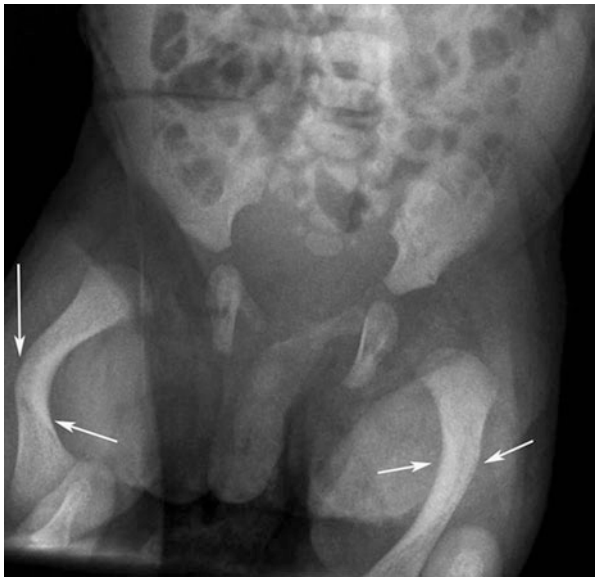

Fig. 21.29 Frontal radiograph of the pelvis in an infant with osteogenesis imperfecta showing bowing deformity in both femoral diaphyses (*arrows*) probably from prior healed fractures

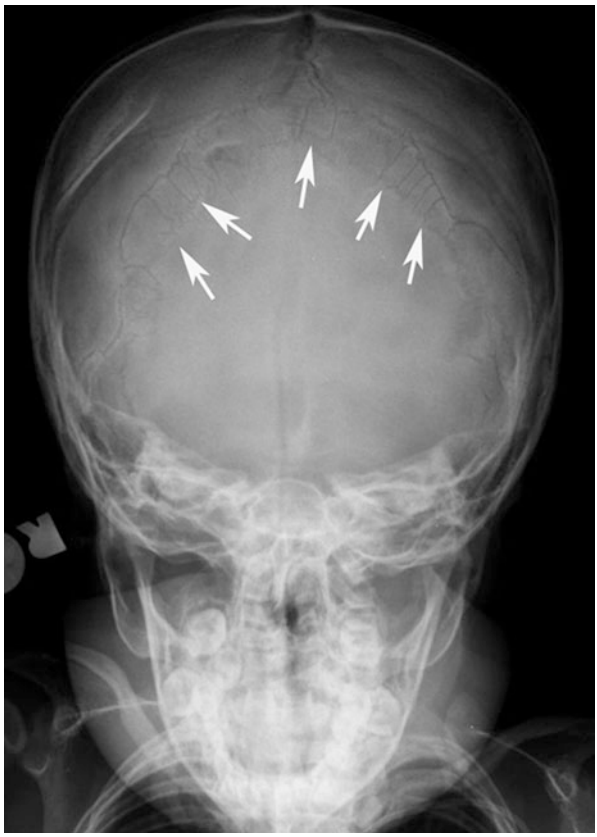

Fig. 21.30 Towne's view radiograph of the skull showing multiple wormian bones (*arrows*) bilateral lamboid sutures in this young child with osteogenesis imperfecta

3. Conditions causing impaired sensation like spinal dysraphism and congenital insensitivity to pain may result in multiple fractures. Clinical history and neurological examination help in the diagnosis.
4. Congenital syphilis causes fragmented metaphysis and subperiosteal new bone formation in the diaphysis in neonates. The presence of Wimberger sign, a lucency in the proximal tibial metaphysis (Fig. 21.31), aids in differentiation from abuse. Clinical findings combined with history and serological tests help in diagnosis of this condition.
5. Osteomyelitis can also cause metaphyseal irregularity, subperiosteal new bone formation, erosions, or destruction of the bone (Fig. 21.32) with a permeative appearance of the bones. Osteomyelitis is typically caused by hematogenous spread of various microorganisms to the bones and can involve multiple bones in neonates. Conventional radiographs are not sensitive in the evaluation of acute osteomyelitis. MRI and radionuclide scans are helpful to diagnose acute osteomyelitis before radiographic changes are evident. MRI is extremely sensitive but not specific in the evaluation of acute osteomyelitis with a near 100 % negative predictive value.

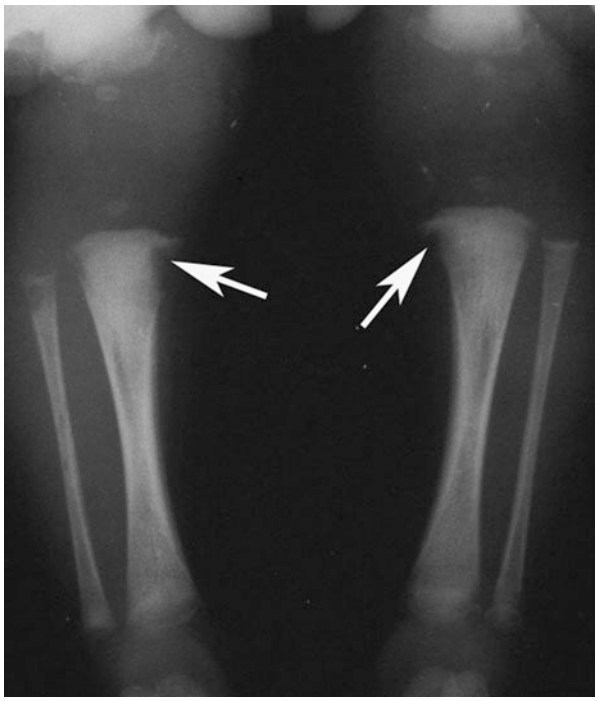

Fig. 21.31 Frontal radiograph of both legs in an infant with congenital syphilis showing ill-defined metaphyseal lucencies in the distal tibia bilaterally, proximal right fibula with medial proximal tibial metaphyseal lucency (Wimberger sign) (*arrows*)

6. Scurvy is due to vitamin C deficiency and uncommon. The bone changes are seen in areas of rapid growth of the skeleton at the knees, wrists, and costochondral junctions. On radiographs, scurvy is characterized by generalized osteopenia with cortical thinning, increased density and thickness of the zone of provisional calcification at the metaphyseal ends known as the white line of Frankel, and sclerotic margins of the epiphyseal centers of ossification, known as the Wimberger ring sign. Overgrowth of the zone of provisional calcification at the metaphyseal corner results in bone spurs known as Pelkan spurs. Subperiosteal hemorrhage from increased bleeding tendency results in subperiosteal new bone formation seen most commonly at the distal ends of the femur, tibia (Fig. 21.33), and proximal humerus. Scorbutic line or zone is the transverse metaphyseal band or lucency seen adjacent to the white line of Frenkel in the metaphysis. Spontaneous epiphyseal separations can also occur in scurvy (Aroojis et al. 1998). Due to the constellation of clinical and radiographic findings, the diagnosis of scurvy is not problematic.
7. Methotrexate is one of the chemotherapeutic agents used in the treatment of acute lymphoblastic leukemia, osteosarcoma, and pediatric central nervous system tumors (Ecklund et al. 1997; Meister et al. 1994). Methotrexate has a strong inhibitor effect on osteoblastic activity resulting in methotrexate osteopathy which has radiographic changes that are similar to those of scurvy, including severe diffuse osteopenia, dense zone of provisional calcification,

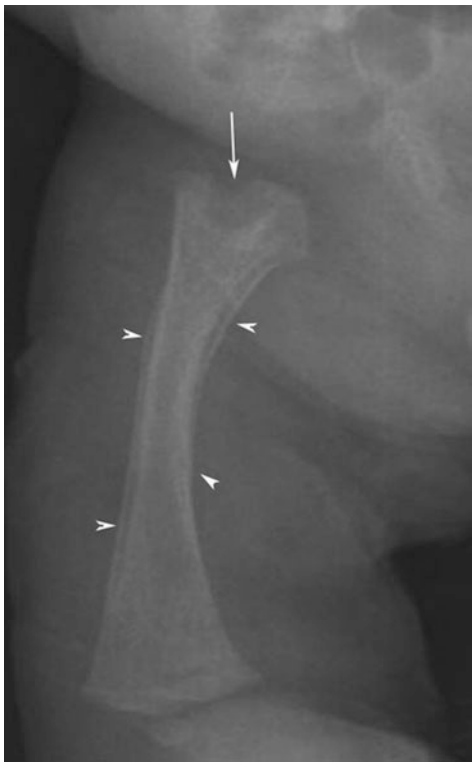

Fig. 21.32 Frontal radiograph of the femur in an infant with osteomyelitis showing focal area of destruction in proximal femoral metaphysis (*arrow*) with subperiosteal new bone formation (*arrowheads*)

and metaphyseal fractures. Methotrexate osteopathy most commonly affects the distal tibia, distal radius, proximal humerus, calcaneus, and pubic ramus. (Ecklund et al. 1997).

8. Vitamin A is typically ingested orally through various food sources and dietary supplements. One of its metabolites, retinoic acid, is also used topically for therapeutic purposes in various skin conditions. Acute or chronic toxicity can result based on the amount and duration of vitamin A administered. Acute vitamin A intoxication can cause increased intracranial tension, vomiting, and lethargy. Chronic excessive vitamin A intake causes pruritus, failure to thrive, and tenderness in the bones and muscles. Chronic toxicity can also result in liver damage and liver failure (Saltzman and King 2007). Radiographs show osteopenia, cortical thickening, wavy dense metaphyseal bands, and asymmetrical closure of the growth-plate cartilage resulting in flared metaphysis, narrowed diaphysis, and abnormal angulation at the physis due to the bone bridging and subperiosteal new bone formation beginning at the sites of musculotendinous attachment (enthesopathy). This bone formation can finally bridge adjacent bones. Cortical thickening and subperiosteal new bone formation are seen in children over 6 months of age, most commonly in the bones of the feet and appendicular skeleton. Extraspinal calcification of ligaments and tendons and fractures may also be seen (Ved and Haller 2002). The associated

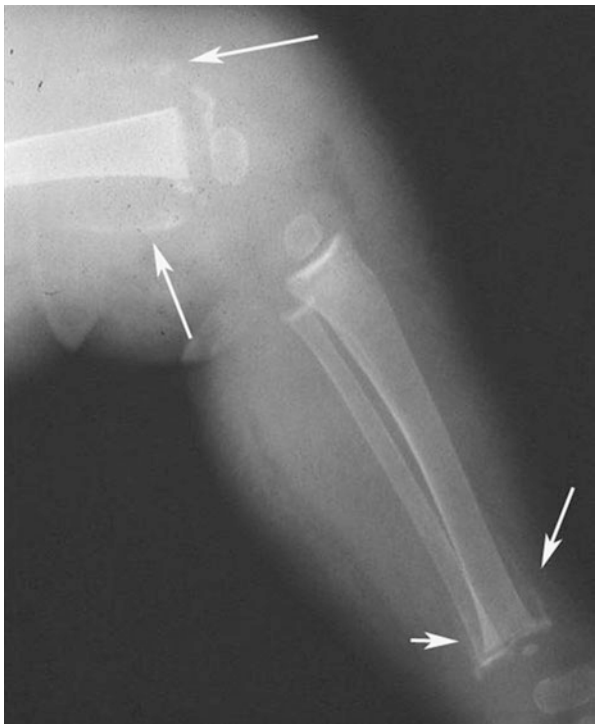

Fig. 21.33 Lateral radiograph of the leg including the distal femur in an infant with scurvy showing osteopenia and subperiosteal new bone formation in the distal femur, distal tibia, and fibula (*arrows*)

clinical and radiological findings help differentiate Vitamin A toxicity from non accidental trauma.

9. Infantile cortical hyperostosis or Caffey disease (Fig. 21.34) is a self-limiting disorder that causes subperiosteal new bone formation in the diaphyseal and metaphyseal regions of multiple long bones, mandible, and clavicle during infancy. This disease can be due to spontaneous mutation or has autosomal recessive or autosomal dominant genetic transmission. An association with a mutation in COL1A1 gene that codes for collagen type-1 has been reported in patients with autosomal dominant transmission. The average onset is around 9 weeks of life persisting for 2 weeks to 3 months duration. The triad of irritability, cortical-bone thickening, and soft tissue swelling are thought to be characteristic (Ved and Haller 2002), and there may be associated fever. Leukocytosis and increased erythrocyte sedimentation rate (ESR) are present as markers of acute inflammation. Radiographs show well-defined cortical thickening or subperiosteal new bone formation with a smooth surface and soft tissue swelling, most commonly involving the mandible, clavicle, ribs, and long bones. Long bone involvement is asymmetric between the right and left sides.
10. A recent study (Nemec et al. 2012) has described prenatal cortical hyperostosis as Caffey dysplasia to differentiate this entity from Caffey disease or infantile type of cortical hyperostosis. This prenatal condition has been reported with COL1A1 genetic mutation and can be lethal. In this prenatal type, onset is

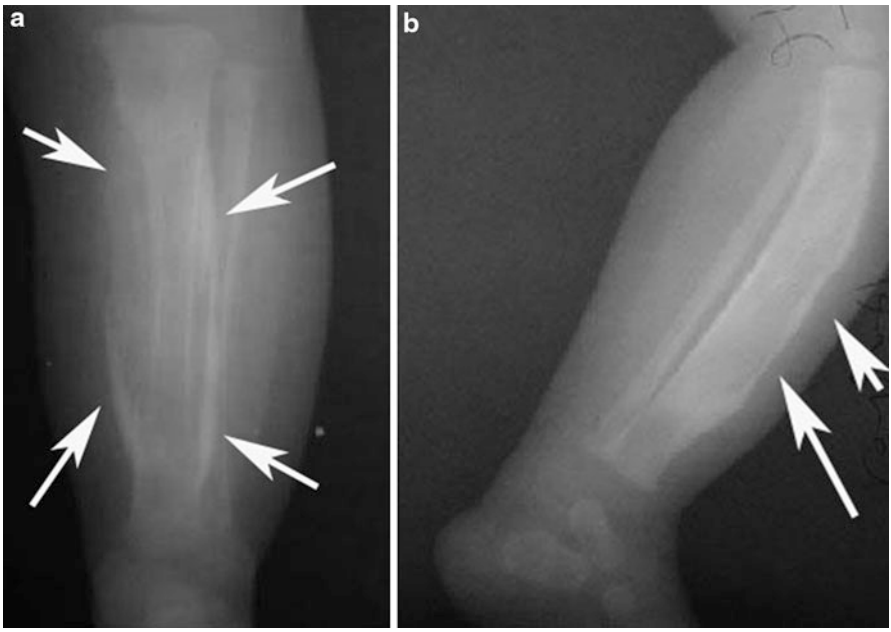

Fig. 21.34 Frontal (**a**) and lateral (**b**) radiographs of the leg showing extensive periosteal reaction in the diaphysis of the tibia (*arrows*) in an infant with Caffey disease/infantile cortical hyperostosis

usually before 35 weeks of gestation and may be recognized on antenatal sonography as hyperechoic and irregular-appearing bones with possible polyhydramnios. Cortical thickening with cotton-wool-like subperiosteal new bone and irregular shape was found to be most common on radiographs. The distribution was similar to that of infantile cortical hyperostosis, involving the mandible, ribs, scapula, and ilia. In contrast to Caffey disease, long bone involvement was symmetric and often associated with shortening and bowing.

11. Prostaglandin E1 (PGE1) is commonly administered to neonates with various types of ductal-dependent cyanotic congenital heart disease to keep the ductus arteriosus patent. The most common side effects of PGE1 infusion in neonates include apnea, hyperthermia, diarrhea, skin flushing, and edema. On radiographs, treatment with PGE1 can result in subperiosteal new bone formation along the diaphysis of long bones that resembles Caffey disease but unlike Caffey disease the mandible is not involved. The other bones that can show these changes include the ribs, scapulae, and clavicles (Fig. 21.35). The development of bone changes is related to the dose and duration of PGE1 infusion. These bone changes can be seen in all children when they have received PGE1 infusion over 60 days (Woo et al. 1994) and have been reported in children with as little as 9 days of PGE1 administration (Nadroo et al. 2000). The thickness of subperiosteal new bone formation is related to the duration of therapy with PGE1, and the bones slowly revert back to normal following discontinuation of treatment.

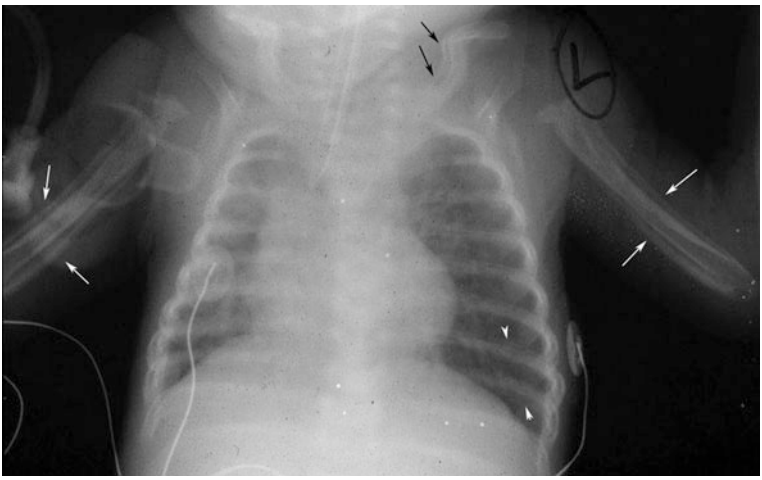

Fig. 21.35 Frontal chest radiograph in an infant with congenital heart disease who received PGE1 therapy showing subperiosteal new bone formation along the shafts of the humeri bilaterally (*white arrows*), ribs (*arrowheads*), and clavicles (better appreciated on the left side shown with *black arrows*)

12. Children with acute leukemia may present with clinically symptomatic bone involvement. On radiographs, a transverse metaphyseal band of lucency can be present. Other radiographic features include a permeative appearance of the bone with bone destruction, osteopenia, and subperiosteal new bone formation predominantly involving the metaphyseal region. Bone infiltration and osteopenia can result in pathological fractures. Vertebral-compression fractures are not uncommon. MRI can show the replacement of the normal marrow by the leukemic process. The diagnosis of leukemia may already be known or can be confirmed with other hematologic tests.
13. Metastases to the bones from neuroblastoma can result in areas of bone destruction in the metaphyses of the long bones. Bone marrow infiltration by the neoplastic process can be seen as ill-defined permeative-appearing lucencies in the bones. Like leukemia, metastatic neuroblastoma may cause pathological fractures.
14. Copper deficiency (Fig. 21.36) and Menkes kinky hair syndrome can cause osteopenia, subperiosteal new bone formation, and metaphyseal spurs with fractures like CMLs. Neurological symptoms and sparse depigmented hair help in making the diagnosis. Wormian bones are usually present in the skull.

Visceral Injuries

Intestinal and Mesenteric Injury

The intestinal and mesenteric injuries from inflicted trauma are most commonly seen in the duodenum (Fig. 21.37) and proximal jejunum. Hematomas, lacerations, mesenteric injury, and, subsequently, stricture can all result from abuse-related injury.

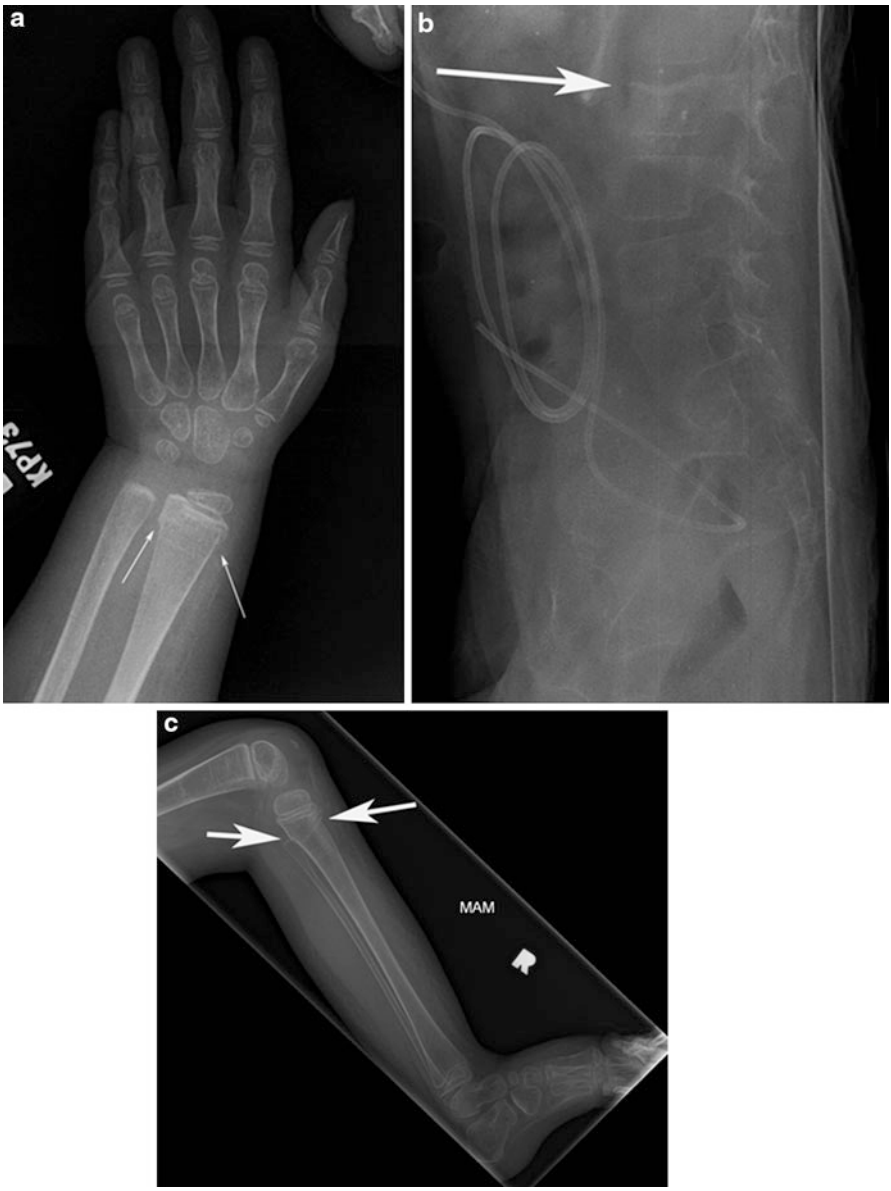

Fig. 21.36 Frontal radiograph of the left wrist (**a**), lateral radiographs of the lumbar spine (**b**) and right leg (**c**) in a 6-year-old girl with copper metabolism abnormality showing distal radial metaphyseal acute fracture (*arrows* in **a**), vertebral body compression fracture involving the superior end plate of L3 vertebra (*arrow* in **b**), and acute right proximal tibial transverse metaphyseal fracture (*arrows* in **c**) with diffuse osteopenia in the bones. These fractures are most likely insufficiency-type stress fractures due to the severe osteopenia

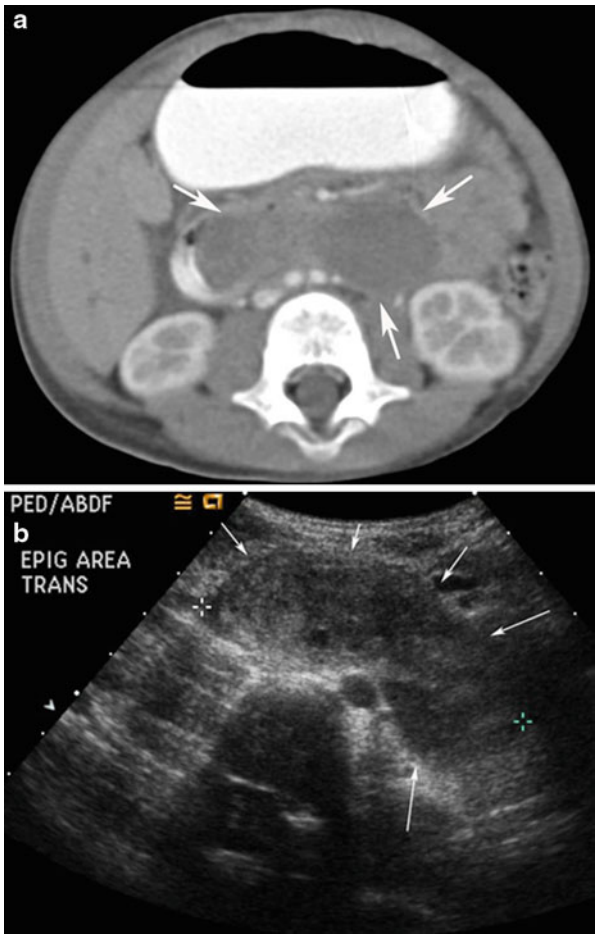

Fig. 21.37 Axial CT (**a**) and transverse sonographic (**b**) images in a 3-year-old girl with blunt abdominal injury from non accidental trauma showing a large acute duodenal hematoma in the third/transverse portion (*arrows*)

Both blunt trauma and acute deceleration of the abdomen are thought to cause most of the intestinal injuries (Lonergan et al. 2003) secondary to non accidental trauma.

CT is the best modality to evaluate intestinal and mesenteric injury (Van Rijn et al. 2010). CT findings of intestinal injury include ascites, focal submucosal mass indicative of a hematoma, or pneumoperitoneum in the setting of hollow viscus perforation. Focal mesenteric edema/fluid may suggest an isolated mesenteric injury. Ultrasound may be able to show a hematoma in the intestinal wall (Fig. 21.37b), but it is less effective than CT.

Hepatic, Splenic, and Renal Injury

As in accidental blunt abdominal trauma associated with motor vehicle collisions or falls from heights, CT (Fig. 21.38) is the modality of choice to image possible

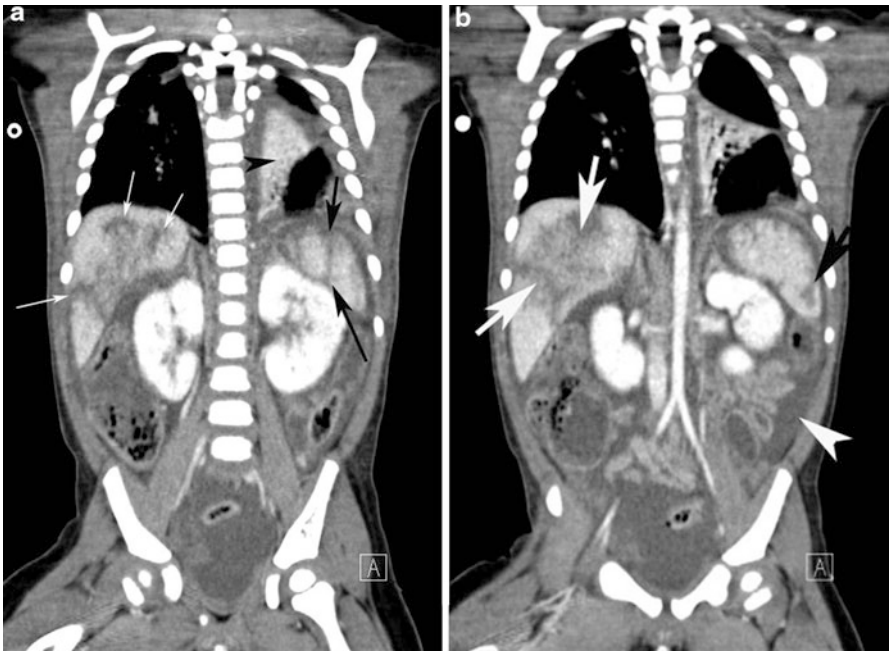

Fig. 21.38 Coronal CT images of the chest, abdomen, and pelvis in a 19-month-old male with non accidental trauma showing hepatic (*white arrows*) and splenic lacerations (*black arrows*). Collapsed left lower lobe segments are noted (*black arrowhead* in figure **a**). High-density free fluid/hemoperitoneum is also seen in the left lumbar region (*white arrowhead* in figure **b**).

visceral injuries in non accidental trauma. Subcapsular hematoma or lacerations can be seen that may or may not be associated with hemoperitoneum. Subcapsular hematoma can be seen as a rim of fluid adjacent to the liver, kidney, or spleen that tends to follow the shape of the organ. Lacerations are seen as non enhancing areas in the liver and spleen that can be linear and branching, with or without extension to the surface of these organs. Hemoperitoneum may be seen typically as high-attenuation fluid in the dependent portions of the abdomen and pelvis.

Renal parenchymal injuries result from direct blunt impact whereas injuries of the renal vasculature and collecting system can result from deceleration forces most commonly from motor vehicle collisions. Renal contusions can be seen as a focal area of non enhancement in the renal parenchyma. Perirenal hematoma with blood in the subcapsular or perinephric space can also be present. Delayed-phase CT images can show injuries to the renal collecting system causing extravasation of contrast from the renal collecting system.

CT enables grading of the intra-abdominal injuries for the surgeon and also the detection of active bleeding. CT findings provide a guide for the interventional radiologist for catheterization and selective embolization of the bleeding arteries, when clinically indicated.

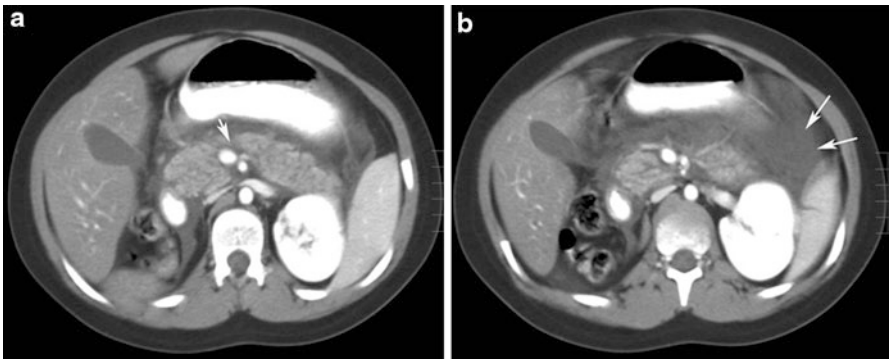

Fig. 21.39 Axial CT images in a 6-year-old child with bruises from abuse, showing pancreatic laceration (*arrow* in figure **a**) and peripancreatic hyperdense fluid/blood (*arrows* in figure **b**)

Pancreatic Injury

Pancreatic injuries are uncommon in children as compared to injuries in the liver, spleen, and kidneys and occur due to direct compression of the pancreas against the vertebral bodies. Trauma is the most common cause of acute pancreatitis in children. Blunt abdominal trauma from handle-bar injuries and motor vehicle collisions are more common causes of pancreatic injury but non accidental trauma should be considered in the differential diagnosis, in the absence of significant traumatic history. Peripancreatic edema or fluid in the lesser sac or anterior pararenal space area on CT is an indicator of pancreatic injury or contusion. Pancreatic laceration/transection (Fig. 21.39) can also occur as a result of inflicted trauma and is seen as a linear defect or non enhancing area extending across the pancreatic parenchyma. Pancreatitis and pseudocyst formation can be evaluated and followed with US, CT, or MRI.

Other Abdominal Visceral Injuries

Depending on the site and mechanism of injury, other organs in the abdomen (Fig. 21.40) can be involved in child abuse based on the site and mechanism of injury. Adrenal gland injuries or hematomas are uncommon even in accidental trauma such as motor vehicle collisions in children, and when present are usually associated with other intra-abdominal injuries. CT is usually performed based on clinical findings and can detect most of these injuries.

Visceral Injuries in the Thorax

Rib fractures are the most common injury in non accidental trauma of the chest. Associated pulmonary contusions and pleural fluid collections, usually a hemothorax,

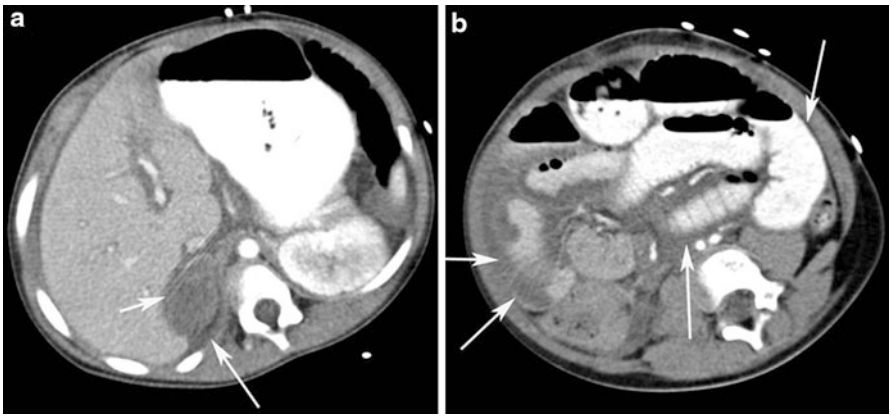

Fig. 21.40 Axial CT images in a 2-year-old with non accidental trauma showing right adrenal hematoma (*arrows* in figure **a**) and small bowel wall thickening/hematoma with bowel dilatation (*arrows* in figure **b**)

can be seen. Simple pleural effusion or chylothorax from non accidental trauma have also been reported. Pulmonary contusions are not seen on chest radiographs unless they are extensive. CT shows these contusions well as scattered focal irregular-shaped alveolar opacities due to hemorrhage with sparing of the subpleural regions. Pneumothorax or pneumomediastinum can also be present.

Cardiac injury can also result from non accidental trauma but is uncommon. Increased serum cardiac troponin I levels can be used as a marker of cardiac contusion/occult cardiac injury that may not be detected with other tests including imaging (Bennett et al. 2011). A study by Cohle and colleagues (1995) reported homicidal cardiac lacerations in six children between the ages of 9 weeks and two and a half years with five of these cases having right atrial laceration and the other case having left ventricular laceration. Cardiac rupture from blunt trauma most commonly results from compression of the heart between the sternum and vertebral column, but other factors may also be involved.

The airway and other structures in the chest can possibly be involved in injuries from non accidental trauma but these are not common.

Conclusion

This chapter discussed and illustrated fractures, soft tissue, and visceral organ injuries that can be seen in children with inflicted injury or non accidental trauma. Imaging pitfalls including normal anatomic findings that could mimic subtle fractures have been described. Other diseases that could result in multiple fractures, osteopenia, and other findings imitating metaphyseal fractures have also been discussed.

Also discussed are the imaging modalities used to evaluate children with suspected non accidental trauma including the recommended guidelines for radiographic skeletal survey by the ACR-SPR in the United States (USA) and the RCR-BSPR in the United Kingdom. Clinical correlation with the patient's age, history, and mechanism of injury is highly recommended to diagnose non accidental trauma.

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Adolescent Homicide

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Abstract

Adolescence represents a tumultuous period as the young adult strives to develop a sense of identity. While homicide has been studied extensively in the forensic pathology literature in both infants and adults over the age of 19 years, there has been a paucity of attention paid to adolescent homicide.

This chapter highlights numerous aspects of adolescent homicide, including incidence, gender and age of the victims, and the lethal method used. The manners of adolescent death, causes of adolescent homicide, and associated risk factors, including drug/alcohol use and easy access to firearms, are described. Insight is provided into the psychopathology of the offenders focusing on their psychiatric states and family dynamics. The similarities and differences in trends of adolescent homicide from an international perspective in relation to the United States are also reviewed.

The next section of the chapter discusses school shootings with a detailed analysis of the trends of school-associated student homicides, specific school shootings portrayed in the media, and characteristics of a school shooter. Hate crimes and bullying among adolescents are also addressed. Murder-suicides or "dyadic deaths" are mentioned with a particular focus on the killing of a child by a parent. Commentary is provided about two unusual "homicides," namely, hunting "accidents" and homicidal Russian roulette, in which a youth may participate.

How to determine the manner and cause of death of adolescent homicide from a forensic-pathology perspective is discussed with a focus on deaths due to firearms and sharp-force injuries. Five cases of adolescent homicide are presented including autopsy findings, scene analysis, and police evidence. Two of these cases reflect murder-suicide of a parent and adolescent.

In conclusion, numerous strategies that have been developed internationally to prevent adolescent homicide are discussed.

Introduction

Adolescence represents a transitional period as the youth matures from the childhood years and embarks on the journey to adulthood. While homicide has been studied extensively in the forensic pathology literature in both infants and adults over the age of 19 years, attention to adolescent homicide has been relatively meager. Inflicted injuries against a child or adolescent may be divided into those directed against very young children, who are unable to defend themselves against a stronger assailant, or older children, who died as a result of the same causes as adults. Pediatric homicide rates are greatest during infancy and the later teenage years, termed "infantile" and "adolescent" murders, respectively (Byard 2010).

This chapter delves into various aspects of adolescent homicide. The incidence of adolescent homicide over the decades is discussed with a focus on gender and age of this cohort as well as method used. The subsequent two sections address the manners of adolescent death and causes of adolescent homicide in the United States (USA). The landmark article by Batalis and Collins on adolescent death in South Carolina between 1989 and 2003 constitutes an exhaustive summary and a unique view of adolescent homicide (Batalis and Collins 2005). The most common causes of adolescent homicide include firearm, stabbing, strangulation, or motor vehicle hit-and-run incidents (Byard 2010; Batalis and Collins 2005; Coyne-Beasley et al. 2003). In particular, a total of 82 % of the adolescent homicides were due to firearms in Batalis and Collins' study (Batalis and Collins 2005). Additionally, black males were the most common victims, accounting for more than 60 % of the cases and representing the highest percentage of death in any demographic group regardless of manner (Batalis and Collins 2005).

Risk factors associated with adolescent homicide include drug/alcohol use or abuse, easy access to firearms, and distinctive characteristics of perpetrators. Of particular focus is the psychopathology of the offenders with emphasis on their psychiatric states and family dynamics. Insight into the similarities and differences in trends of adolescent homicide from an international perspective in relation to the USA provides a unique opportunity to appreciate how various countries address the myriad aspects of adolescent homicide including causes of death, methods utilized, and psychological traits of the offenders.

The next section of the chapter covers the shocking nature of school shootings. Detailed analysis uncovers trends in school-associated student homicides, specific school shootings portrayed in the media, and characteristics of a school shooter. Determination of manner and cause of death of adolescent homicide is in accord with widely adopted guidelines among forensic pathologists. The two most common causes of adolescent homicide in the USA, specifically, are death by firearm and sharp-force injury. Correlation of critical findings at autopsy with thorough scene and historical investigation facilitates confirmation of manners and causes of death.

Presented are representative investigations exemplifying five cases of adolescent homicide with autopsy findings, scene analysis, and police evidence. Two of these cases reflect murder-suicide involving a parent and an adolescent. All postmortem examinations were conducted at the Associate Chief Medical Examiner's Office in Frankfort, Kentucky, USA.

In the wake of this significant public health concern, numerous strategies have been developed internationally to prevent adolescent homicide. A host of interventions have been proposed and instituted to combat various aspects of adolescent homicide, including decreasing the availability of guns to adolescents, enhancing family values, and opening lines of communication between students and educators in an effort to discover warning signs that a student may exhibit prior to a school shooting. Homicide prevention programs have proven effective in helping high-risk adolescents and their families develop the knowledge, skills, and support to avoid violence (Centers for Disease Control and Prevention 2004).

Table 22.1 Homicide injury deaths and rates per 100,000, USA, all races, both sexes, ages 10–19

Year	Number of deaths	Population	Crude rate	Age-adjusted rate
1981	2,329	38,840,939	6.00	5.73
1990	3,376	34,962,628	9.66	9.49
2000	2,145	40,747,962	5.26	5.27
2009	2,105	41,511,401	5.07	4.90

Incidence of Adolescent Homicide

The incidence of homicide in the adolescent has been gradually decreasing over the past 30 years (Table 22.1). Incidence trends of adolescent homicide (between ages 10 and 19) since 1981 reveal an increase in the number in 1990 with a subsequent decrease (Centers for Disease Control and Prevention 2012). The age-adjusted rate of homicide per 100,000 in 1981 was 5.73, which spiked to 9.49 in 1990. The rate reached its lowest in the past 30 years with 4.9 in 2009.

In 2007, homicide, strictly speaking a manner of death, was the third leading cause of death for ages 10–14 and was the second leading cause of death for ages 15–18 in the USA (Centers for Disease Control and Prevention 2012). Unintentional injury ranked first in both age groups. Firearms were utilized in 85 % of teen homicides in 2007. Males aged 15–19 years are at least six times more likely to die from homicide compared to females (17.6 compared with 2.8 per 100,000, respectively) (Child Trends Data Bank 2012). Males of this age cohort are also eight times more likely to die from a firearm-related injury: In 2007, 21.9 per 100,000 males died by firearms, compared with 2.6 per 100,000 females. In 2007, the homicide rate for black male teens was 67.1 per 100,000, nearly 20 times higher than the rate for white males (3.4 per 100,000). Among females, black and Hispanic teens had the highest homicide rates in 2007, at 6.9 and 2.8 per 100,000, respectively, and 1.8 per 100,000 for white females.

The reason for the decline in adolescent homicide is unknown; however, several factors such as changing demographics, improved policing, more jailed offenders, maturing drug markets, greater safety consciousness, and a stronger economy have been proposed (Cheng et al. 2001; Cole 1999).

Manners of Adolescent Death

Batalis and Collins conducted a comprehensive review of 537 adolescent deaths (ages 10–19 years) in South Carolina between 1989 and 2003 (Batalis and Collins 2005). They catalogued many variables, including manners and causes of death as well as age, gender, and race of the victims. The manners of death were as follows: accident (36 %), homicide (34 %), suicide (16 %), natural (12 %), and undetermined (2 %). The authors divided the adolescent period into two distinct groups, specifically ages 10–14 and 15–19 years. The homicidal findings differed

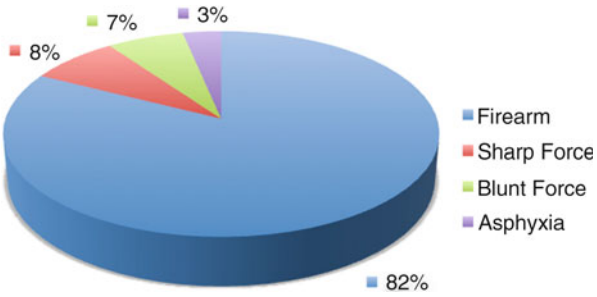

Fig. 22.1 Distribution of causes of death in adolescent homicides (Adapted from Batalis and Collins 2005)

between the two age groups. In the age group 10–14 years, accidental death was more common than homicide (47.4 % vs. 17.7 %). In contrast, homicide was more prevalent in the older age group of 15–19 years (38.4 % vs. 33.3 %).

Causes of Death in Adolescent Homicide

Several studies in the literature have addressed the causes of adolescent homicide (Batalis and Collins 2005; Coyne-Beasley et al. 2003). Batalis and Collins reported the causes of adolescent homicide in their study of adolescent deaths in South Carolina between 1989 and 2003 (Batalis and Collins 2005). Gunshot wound (GSW) was the leading cause of death (82 %) followed by sharp-force injury (8 %), blunt-force injury (7 %), and asphyxia (3 %) (Fig. 22.1). Furthermore, GSW comprised the majority of homicides in both age groups (ages 10–14 and 15–19 years).

Black males were the most common victims, accounting for more than 60 % of the cases and the highest percentage of death in any demographic group regardless of manner (Batalis and Collins 2005). Deaths due to blunt-force and sharp-force injuries were evenly distributed among the demographic groups. All of the strangulation victims were female. A close acquaintance or family member was the perpetrator of the homicide in both age groups: 68 % of the victims in the 10–14 year age group and 42 % of the cases in the 15–19 year age group. Of the 33 female victims ages 15–19, 10 (30 %) were killed by a boyfriend or ex-boyfriend. The location of the homicide was known to the victim in more than 60 % of the cases, including 23 % in the victim's own home or car.

Coyne-Beasley and colleagues conducted a medical-examiner study in North Carolina of female homicide victims aged 11–18 years between 1990 and 1995 (Coyne-Beasley et al. 2003). Of the 90 victims, 55 (61 %) were killed by firearms and 40 (44 %) were age-grade discrepant (behind in school). The majority (65 %) of victims were killed within a residential property and, in most cases, the victim's residence. Of the 37 cases in which police interviews were conducted, 17 (46 %) of the perpetrators were friends or acquaintances, 12 (32 %) were intimate partners, and 7 (19 %) were family members. Many of the family victims of homicide participated in high-risk behavior such as dropping out of school, running away from home, using drugs, and dating older men with criminal records.

Table 22.2 Risk factors for adolescent homicide

Male gender
Drug/alcohol use
Conflict with parents
Lack of parental affection and support
Weapon carrying
Poor school performance
Weak social ties
Risk taking
Exposure to television violence
Learning difficulties
Problems with impulse control
Previous warning of problems
Ambiguous messages containing threats
Victimization by social groups or individuals
Concern expressed by adults or peers
Changes in emotions and interests

Risk Factors for Adolescent Homicide

Adolescence is a time of exploration and experimentation of the surrounding world as the individual strives to develop a sense of self. Risk factors commonly associated with adolescent development and violent behavior include male gender, drug/alcohol use, conflict with parents and lack of parental affection and support, carrying a weapon, poor school performance, weak social ties, risk taking, involvement in gangs, and exposure to television violence (Table 22.2) (Cheng et al. 2001; Bijur et al. 1991; Douglas and Bell 2011; DuRant et al. 1997; Monsen 2007; Saner and Ellickson 1996; Shumaker and Prinz 2000; Valois et al. 1995). Assessments of adolescents with a potential for homicide should also address the following: previous warning of problems, ambiguous messages containing threats, victimization by social groups or individuals, concern expressed by adults or peers, and changes in emotions and interests (Twemlow et al. 2002). A precipitating event may also spur an adolescent to commit homicide, including loss of a relationship with a partner, family dispute, suspension from school, termination from a job, and insults by peers (Meloy et al. 2004). In addition, these individuals may have learning difficulties or problems with impulse control (Hardwick and Rowton-lee 1996).

Several protective factors against violence have been identified, including female gender, intolerant attitude toward deviance, and high intelligence quotient (IQ) (Douglas and Bell 2011). Family protective factors are a close and supporting relationship with parents and other adults as well as sufficient parental monitoring. School protective factors refer to commitment to school and involvement in activities such as organized sports and youth clubs.

Bradford and colleagues have demonstrated that the pharmacological action of alcohol and drugs increases the likelihood of impulsive aggression (Bradford 1992). A closer link exists between alcohol and violence compared with other drugs. Parker and colleagues studied the relationship between homicide and alcohol availability in the 91 largest cities in the USA from 1984 to 2006 (Parker et al. 2011). They reported that the greater number of alcohol outlets had a significant positive impact on youth homicide ages 13–17 and 18–24 years.

Ease of access to firearms tends to increase the possibility of gun violence (Hardwick and Rowton-lee 1996). There is a higher risk of homicide with gun in the home (Webster and Wilson 1994), and the prevalence of firearm ownership serves as a significant predictor of adolescent firearm mortality (Calhoun et al. 2005). Sloan and colleagues compared the suicide rate of individuals ages 15–24 between 1985 and 1987 in King County, Washington to Vancouver, British Columbia (Sloan et al. 1988). The suicide rate was higher in King County, marked by a tenfold higher suicide rate by handguns. The authors of this controversial study attributed the increased rate to the less restrictive firearm laws in the USA compared to Canada.

Perpetrators of Adolescent Homicide

Cornell and colleagues classified juvenile homicidal offenders based on the circumstances of the offense and adolescents' state of mind at the time of the offense (Cornell et al. 1987). The perpetrators were divided into the following groups: (1) psychotic, (2) conflict (those who kill acquaintances or family members in a moment of interpersonal tension), and (3) crime (in the midst of committing a crime) (Cornell et al. 1987). A minority of offenders were psychotic at the time of the murder, and many individuals in the crime group were intoxicated.

Several studies in the psychiatric literature address the psychiatric state of adolescents who kill (Cornell et al. 1987; Labelle et al. 1991; Myers and Kemph 1990; Toupin and Morissette 1990). These studies demonstrate that such individuals are primarily diagnosed with a conduct disorder, personality disorder, and substance abuse, often overlapping. Rare cases involve a perpetrator who is psychotic.

Homicidal adolescents are also likely to possess at least one of the following four features: (1) criminally violent family members, (2) gang membership, (3) severe educational difficulties, and (4) alcohol abuse (Busch et al. 1990; Zagar et al. 1990). Adolescents who kill are likely part of a family with significant psychopathology such as criminal violence and parental mental illness, including alcoholism (Corder et al. 1976; Lewis et al. 1985). The adolescent has commonly been a victim of abuse – either physically, sexually, or by neglect. Furthermore, the adolescent may also experience intense feelings of helplessness and hopelessness after losses in interpersonal relationships or self-esteem (Malmquist 1971).

The number of juveniles (< age 18) arrested for murder tripled between 1984 and 1994; the juvenile arrest rate for weapons-law violations increased by 103 % from 1985 to 1994 in the USA (Gest and Pope 1996). Several studies have

addressed the issue of adolescent perpetrators of homicide (Adeagbo et al. 2008; Coyne-Beasley et al. 1999; Crespi and Rigazio-DiGilio 1996; Walsh-Brennan 1974). Adeagbo and colleagues, looking at homicide committed by youth assailants between 1991 and 2006 in South Carolina (Adeagbo et al. 2008), report that a majority of perpetrators were men (97 %), black (83 %), and between the ages of 15 and 19 years (90 %). In every age range, there were more male victims than females, especially between the ages of 10 and 19 years (38 %). Most of the victims were black male acquaintances who were engaged in an argument with the assailant. The most common cause of death was cerebral laceration in 22 (31 %) victims, most likely due to firearms (68 %). Of the 60 victims who underwent toxicology testing, 39 (74 %) had positive drug panels. While cocaine, marijuana, and alcohol were commonly detected in the older age groups, most of the victims aged 10–19 years had a negative toxicology (55 %).

Coyne-Beasley and colleagues analyzed homicides committed by adolescents aged 11–18 years in North Carolina from 1990 to 1995 (Coyne-Beasley et al. 1999). Of the 419 adolescent homicide victims aged 11–18 years, most of the victims were aged 15–18 years (85 %), male (79 %), black (76 %), and from urban areas (72 %). Approximately half (48 %) of the victims were age-grade discrepant, and only 32 % of the 18-year-old victims had graduated from high school. Perpetrators were primarily at least 2 years older than their victims (55 % were over 18), male (92 %), and a friend or acquaintance (57 %). Firearms were utilized in 83 % of homicides. According to police reports, a criminal record (primarily drug-related) was noted in 40 % of the victims and 71 % of the perpetrators. The leading motive for the homicide was drug-related (23 %) followed by altercations (20 %) and retaliations (17 %) based on police data. Of note, although firearms were used as the predominant method of suicide in both age groups, younger adolescents (ages 11–14 years) as compared to older adolescents were more likely to have fatal injuries not involving a firearm, and homicide was the result of recklessness instead of homicidal intent.

International Trends of Adolescent Homicide

The World Health Organization estimates 57,000 children die annually from fatal maltreatment; the rate is approximately 0.1–12.7 deaths per 100,000 children (Toro et al. 2010). The rate of firearm-related deaths in the USA among young males ages 15–24 years between 1992 and 1995 ranged from 4.5 times to >50 times higher than rates reported in other selected developed countries (MacKenzie 2000). The greatest differences in rates appeared between the USA and England and Wales. In addition, there has been a striking number of gunshot fatalities in the USA compared to Australia, including a much lower number of firearm deaths in children living in South Australia compared to San Diego County in the USA (Byard et al. 2009).

Table 22.3 International trends of adolescent homicide

Study	Ages of victims	Causes of death
Batalis and Collins South Carolina 1989–2003 $n = 537$	10–14 years 15–19 years	Firearm: $n = 151$ (82 %) Sharp force: $n = 14$ (8 %) Blunt force: $n = 12$ (7 %) Asphyxia: $n = 6$ (3 %)
Toro et al. Budapest, Hungary 1960–2005 $n = 363$ ($n = 96$, ages 6–20)	6–15 years 16–20 years	Victims ages 6–15: Fire: $n = 10$ (22 %) Suffocation: $n = 9$ (20 %) Blunt trauma: $n = 7$ (16 %) Sharp injury: $n = 7$ (16 %) Victims ages 16–20: Sharp injury: $n = 22$ (43 %) Blunt trauma: $n = 10$ (20 %) Suffocation: $n = 8$ (16 %) Gunshot: $n = 8$ (16 %)
Swart et al. Johannesburg, South Africa 2001–2005 $n = 304$	15–19 years	Firearm: $n = 206$ (68 %) Sharp object: $n = 69$ (22 %) Blunt object: $n = 23$ (7 %) Other: $n = 10$ (3 %)
Sauvageau and Racette Quebec, Canada 2000–2004 $n = 54$ ($n = 41$, ages 10–19)	10–19 years	Victims ages 10–14: Firearm: $n = 3$ (30 %) Sharp force: $n = 3$ (30 %) Blunt force: $n = 2$ (20 %) Victims ages 15–19: Firearm: $n = 12$ (33 %) Blunt force: $n = 9$ (25 %) Sharp force: $n = 8$ (22 %)

International trends in adolescent homicide have been reported, with respect to cause of death, method, and specific age group (Table 22.3). A study in Budapest, Hungary, reported the characteristics of homicide in infants, children, and adolescents between 1960 and 2005 (Toro et al. 2010). The authors noted a decrease in the homicide rate of infants, children, and adolescents over the course of their study period, which was attributed to the effective preventive strategies, the child protection policy, and the primary healthcare system for youth. As the current chapter devotes special attention to homicide of the older child and adolescent, the homicidal data from Hungary is limited to this age group. A total of 45 children aged 6–15 years were victims of homicide: 10 (22 %) succumbed to a fire, 9 (20 %) were suffocated, and 7 (16 %) died as a result of blunt trauma and sharp injury. A total of 51 adolescents aged 16–20 years were homicide victims: 22 (43 %) sustained sharp injury, 10 (20 %) sustained blunt trauma, and 8 (16 %) died due to suffocation and gunshot.

Swart et al. reviewed 304 homicidal deaths of adolescents aged 15–19 years in Johannesburg, South Africa, between 2001 and 2005 (Swart et al. 2008). Between 2001 and 2004, the annual adolescent homicide rate decreased from a rate of 36.69

to 24.54 per 100,000 population. Most of the victims were either aged 18 or 19 years (66.9 %) and male (83.1 %). The leading cause of death was by firearm (206 cases; 68 %) followed by sharp object (69 cases; 22 %) and blunt object (23 cases; 7 %). More than half (56.2 %) of the adolescent homicides occurred on a weekend, peaking on Saturday (21.9 %). Of the 177 adolescent homicide victims undergoing testing for blood alcohol concentration, 70 (39.5 %) tested positive. Swart and Seedat expanded their study to include the years 2001–2005 in Johannesburg, encompassing 451 adolescent homicides (Swart and Seedat 2010). Arguments (32.8 %) most commonly prompted the homicide, followed (in order) by revenge (11.3 %), robbery (10.8 %), and vigilantism (6.2 %). The authors proposed a triad for categorizing adolescent homicide: (1) male victims killed by strangers during a crime-related event, (2) male victims killed by an acquaintance during an argument, and (3) female victims.

The Canadian experience on adolescent homicide is offered by Sauvageau and colleagues in their study (2000–2004) of child and adolescent victims (Sauvageau and Racette 2008). An accidental manner of death was the most common for both age groups 10–14 years and 15–19 years (50 % and 38 %). Homicide and suicide were the second and third leading manners of death for ages 10–14 years (19 % and 14 %), while suicide followed closely by homicide ranked second and third as the most common manners of death for ages 15–19 years (25 % and 24 %). Homicide by firearm was the primary method for both age groups (ages 10–14 years, 30 %; ages 15–19 years, 22 %). Sharp-force and blunt-force injuries were also common among adolescents ages 10–14 years (30 % and 20 %) and ages 15–19 years (25 % and 22 %). Sauvageau and Racette compared their study of adolescent homicide to that of Batalis and Collins in South Carolina (Batalis and Collins 2005; Sauvageau and Racette 2008). The Canadian study reported that the homicide rate was higher in younger teens (ages 10–14 years) in Quebec compared to South Carolina while the opposite was true for older teens (ages 15–19 years).

Schlueter and colleagues highlighted trends in violent deaths among young people aged 10–24 years in Switzerland between 1969 and 1997 (Schlueter et al. 2004). Rates of violent death were much higher in males than females and increased from the age group 10–14 years to 20–24 years. In 1995–1997, violent deaths comprised 66 % ($n = 1{,}221$) of all fatalities among young people. While young people often sustained violent deaths, only 3 % of the violent deaths were homicides.

The homicide rate in Colombia, South America, is approximately ten times the rate in the USA (Brook et al. 2003, 2007). Brook and colleagues conducted a survey of 2,837 adolescents aged 12–17 years in 1995–1996 to attempt to elucidate the personality, familial, peer, and ecological/cultural factors that may contribute to the pervasiveness of violence and homicide in Colombia (Brook et al. 2003). An adolescent's violent behavior was most highly correlated with both violence directed at the adolescent and the adolescent's own drug use. Additional significant risk factors included peer drug use, peer deviance, and exposure to violence on television.

Adolescent offenders aged 15–18 years, who were accused of homicide, underwent forensic psychiatric evaluations in Finland between 1990 and 2001

(Hagelstam and Hakkanen 2006). Nine percent of homicides in Finland are committed by individuals under 18 years of age. The majority (66 %) of victims were adults compared with child or adolescent victims (>18 years of age; 22 %) or elderly victims (>65 years; 12 %). The type of victims were an acquaintance in 58 % of cases, a stranger in 28 %, a family member in 12 %, and an ex-intimate partner in 5 %. A total of 69 % of offenders were intoxicated, and 21 % were under the influence of drugs at the time of the homicide. Approximately half of the perpetrators had a history of a conduct or personality disorder, while 32 % had not been diagnosed with either a mental illness or substance abuse. Furthermore, 28 % of offenders had been placed in an institution, 54 % had parents with alcohol problems, and 32 % had witnessed or experienced physical violence at home.

The family dynamics as well as behavior and psychological development disorders were investigated among juveniles who committed homicide or attempted homicide in Split Dalmation County in Croatia between 1989 and 1998 (Britvic et al. 2006). The authors reported that physical abuse and parental rejection are both high-risk factors for the occurrence of juvenile homicide and attempted homicide.

School Shootings

School-associated student homicides are rare and represent approximately 1 % of homicides that occur among school-age youths (Centers for Disease Control and Prevention 2008; Anderson et al. 2001). During the 1990s, the rate of school-associated single-victim student homicides decreased significantly, while rates of school-associated homicides in which two or more students were killed (multiple-victim homicides) increased (Centers for Disease Control and Prevention 2008). The Centers for Disease Control and Prevention (CDC) reported that the student homicide rates in American schools in the 1990s were highest near the start of each semester (Centers for Disease Control and Prevention 2001). School-associated student homicides decreased between 1992 and 2006 and stabilized from 1999 to 2006 when 116 students were killed in 109 school-associated homicides (Centers for Disease Control and Prevention 2008).

School shootings have been portrayed in detail in the media due to their shocking nature. Parents who entrust their children to the safety of the educational system are horrified when an unthinkable school shooting occurs. The earliest known US shooting on school property was the Pontiac's Rebellion school massacre on July 26, 1764, following the French and Indian War when four Lenape American Indians entered the schoolhouse near present-day Greencastle, Pennsylvania (Anonymous 2012). The schoolmaster Enoch Brown and ten children were shot and killed.

The recent and tragic school shooting at Sandy Hook Elementary School in Newtown, Connecticut shocked the USA and the world on December 14, 2012 (Barron 2012; Associated Press 2012a). Twenty-year-old Adam Lanza fatally shot twenty children and six adult staff members after he shot and killed his mother at his home. He committed suicide by a cranial gunshot wound as first responders arrived at the school. A state court database showed no records of a criminal past (Misur 2012).

Lanza was described as "intelligent but nervous and fidgety," and there were reports that he suffered from a developmental disorder such as Asperger's syndrome (Halbfinger 2012). While known as an honors student, he was also a loner who was uncomfortable in social situations. Lanza's mother was a gun enthusiast who took her son target shooting (Alexander 2012). The Sandy Hook school shooting spurred the heated gun debate with proposed legislation that would ban the sale and manufacture of 157 types of semiautomatic weapons as well as magazines holding more than 10 rounds of ammunition (Steinhauer 2013).

Most people are aware of the horrendous school shooting perpetrated by Eric Harris, aged 17 years, and Dylan Klebold, aged 18 years, near Littleton, Colorado, on April 20, 1999 (Dedman 2006). They killed 12 students and one teacher, wounded 23 students, and killed themselves at Columbine High School. They had prepared for more destruction at the high school with the use of 31 explosive devices and had devised detailed plans, such as hand signals for "use bomb" and "suicide" (Dedman 2006). Harris had been under psychiatric care and had complained of depression, anger, and suicidal thoughts. He was treated with antidepressants, both selective serotonin reuptake inhibitors, sertraline and fluvoxamine, the latter medication being 8.4 times more likely than other medications to be associated with violence (Moore et al. 2010). Both Harris and Klebold believed they were at war against society and needed to take action toward those they hated.

The authors of this chapter are located in the state of Kentucky, the site of a devastating school shooting at Heath High School in West Paducah, Kentucky, on December 1, 1997 (Dedman 2006). Michael Carneal, aged 14 years, utilized a stolen pistol to kill three students and wound five others in a prayer group, including his ex-girlfriend. After the shooting, he was diagnosed with schizophrenia and has been since hospitalized on several occasions for psychosis.

The Virginia Tech massacre was a school shooting that occurred on April 16, 2007, on the campus of Virginia Polytechnic Institute and State University in Blacksburg, Virginia (MSNBC 2012; Virginia Tech Review Panel 2012). The offender, Seung-Hui Cho, killed 32 individuals and wounded 25 others prior to committing suicide. This massacre was the deadliest shooting event by a single gunman in the history of the USA and was the worst act of mass murder on college students since the bombing of Pan Am Flight 103 in 1988, when 36 students from Syracuse University were killed. Cho had been diagnosed with a severe anxiety disorder and had been treated with therapy and special education support, none of which had been disclosed to Virginia Tech due to federal privacy laws. He had also been accused of stalking two female students 2 years prior to the massacre and had been declared mentally ill by a Virginia special justice and instructed to undergo treatment.

Investigators of school shootings have attempted to "profile" the adolescent perpetrators; however, a school shooter does not necessarily conform to a stereotype. However, while a school shooter does not always fit a specific mold, several characteristics of school shooters have been observed (Table 22.4) (Twemlow et al. 2002; Dedman 2006; Logue 2008). The Secret Service attributes alienation or persecution to school shooters, which prompted them to violence.

Table 22.4 Characteristics of school-shooting perpetrators

Male gender
No typical profile: shooters come from many types of families, all incomes, all races, all academic backgrounds
Solving a problem, such as bullying
Friends were informed of shooter's grievances prior to killing, often knowing of planned violence
Easy to obtain weapons, often bringing them from home
Few diagnosed with mental illness or had histories of drug or alcohol abuse
Feelings of depression or desperation
Suicidal threats/attempts common
Revenge motive
Feelings of being persecuted, bullied, or threatened
Difficulty coping with a major change in a personal relationship, such as lost love
Interest in violent themes, including media, games, own writings

The Secret Service studied the cases of 41 children involved in 37 shootings at their current or former school from 1974 to 2000. The researchers discovered "that killers do not 'snap.' They plan. They acquire weapons. They tell others what they are planning. These children take a long, planned, public path toward violence" (Dedman 2006). The US Secret Service recommends that adults question their child's behavior and communication instead of focusing on specific traits as follows: "What has this child said? Does he have grievances? What do his friends know? Does he have access to weapons? Is he depressed or despondent?" (Dedman 2006).

A school-associated violent death event is defined as a firearm-related homicide or suicide in which the homicide perpetrator or the suicide victim was an elementary or secondary school student (Centers for Disease Control and Prevention 2003). During 1992–1999, a total of 323 school-associated violent deaths occurred in the USA resulting in 358 fatalities (Centers for Disease Control and Prevention 2003). Of the 218 student perpetrators involved in a school-associated homicide or suicide between 1992 and 1999, 123 (56.4 %) individuals used at least one firearm during the event. In addition, among the students who had a firearm at the time of the event, 33 (26.8 %) committed suicide, 85 (69.1 %) perpetrated a homicide, and 5 (4.1 %) perpetrated a homicide-suicide. The vast majority (115 cases, 93.5 %) of student offenders were male, and the median age of student perpetrators was 16 years (range 10–21 years). A total of 48 (51 %) firearms used in homicidal school events came from the home ($n = 22$; 23.4 %) or from a friend or relative ($n = 26$, 27.6 %) of the homicide offender.

Hate Crimes and "Bullying"

Hate crimes refer to crimes that are motivated by the offender's bias against the victim's race, religion, ethnic or national origin, gender, disability, or sexual

orientation (Steinberg et al. 2003). The Office of the Juvenile Justice and Delinquency Prevention of the Department of Justice funded the National Juvenile Hate Crime Study in 1995 (Ball et al. 1995). This study reviewed databases of juveniles and hate crime from 79 of America's largest cities. The researchers estimated that juveniles committed between 17 % and 26 % of all hate crimes (Ball et al. 1995).

Levin and McDevitt reported that the findings of the Office of Juvenile Justice and Delinquency Prevention significantly underestimated the participation of juveniles in hate crimes (Levin and McDevitt 1995). They estimated that juveniles commit approximately 70 % of all hate crimes. The largest determinant of hate crimes is race, with African Americans as the most likely target group (Steinberg et al. 2003). While gender-based hate crimes (crimes against women) are the most common form of hate crime in general, the most prevalent form of hate crime among teenagers is focused on sexual minorities (Franklin 2000).

It has been suggested that the cause of juvenile hate crime is due to two epidemics that confront youths, specifically, violence and prejudice (Steinberg et al. 2003). The school system has transformed into a festering ground of juvenile hate crime. These crimes have become more prevalent over the past 25 years due to drastic cultural and societal change, marked by a lack of a parent in the home providing guidance and poor peer selection. Prevention of juvenile hate crime requires an understanding of the hate crime perpetrator (Steinberg et al. 2003). Adolescents who instigate hate crimes are characterized by a host of features, including impulse-control problems, thrill-seeking behavior, bullying, conduct or aggression problems, an attempt to be competent, or feeling of betrayal and underlying hurt (Beck 1999). Several national educational interventions have been implemented to target juvenile hate crime in schools, including the National Center for Hate Crime Prevention and the National Bias Crime Training Project developed by the Education Development Center, Inc (McLaughlin and Brilliant 1997).

Bullying refers to physical or psychological abuse perpetrated by one powerful child upon another with the intention to harm or dominate (Englander 2012). It is a form of aggression in which children and adolescents are intentionally intimidated, harassed, or harmed (Lemstra et al. 2012). Cyberbullying, namely, bullying through an online medium, has become more common as a result of the increasing online social life shared by adolescents today. Lemstra conducted a questionnaire survey of 4,197 youth aged 9–15 years in Saskatoon, Canada (Lemstra et al. 2012). A total of 23 % of these individuals had been physically bullied at least once or twice in the previous 4 weeks (Lemstra et al. 2012). Several independent risk factors were associated with physical bullying such as (1) being male, (2) attending a school in a low-income neighborhood, (3) not having a happy home, (4) having numerous arguments with parents, and (5) feeling like leaving home. These authors reported that 80 % of the children who were physically bullied were more likely to have a depressed mood.

An adolescent victim of either physical or psychological bullying may respond to the bullying attack in one of two destructive pathways, specifically, embracing suicide as the only means of escaping the torture or plotting a homicidal rampage

against those who precipitated the bullying (Twemlow et al. 2002; Meloy et al. 2004; Brunstein et al. 2010; Hinduja and Patchin 2010; Winsper et al. 2012). Strategies that reduce peer aggression manifested by bullying may serve as valuable preventive tools in decreasing adolescent suicide and the likelihood that an adolescent may engage in homicidal behavior against a peer. The National Bullying Prevention Center has been developed in the USA to attempt to curtail the wide prevalence of bullying (The National Bullying Prevention Center 2012). Their website is http://www.pacer.org/bullying. They advocate a three-pronged approach that a parent may pursue in the realm of the school system: (1) work with your child (gather the details of the bullying including the perpetrator, location, and times), (2) work with the school (meet with your child's teacher and principal), and (3) work with district administration (advise the district superintendent about the bullying incident).

Murder-Suicide

Murder-suicides or "dyadic deaths" refer to homicide(s) followed by the suicide of the perpetrator within 1 week of the homicide(s) (Gregory and Milroy 2010). Data from the USA and internationally suggest that with a higher homicide rate, in turn, the rate of homicide-suicide is elevated (Byard 2010; Milroy 1995; Palermo et al. 1997). Furthermore, a high percentage of the fatalities result from firearms in those countries with higher rates of homicide-suicide (Milroy 1995; Centers for Disease Control 1991). Marzuk and colleagues classified homicide-suicide as follows: (1) spousal or consortial, (2) familial, and (3) extrafamilial (Marzuk et al. 1992). The most common type is spousal killing involving a man who kills his wife due to the breakdown of their relationship with ensuing jealousy and rage (Gregory and Milroy 2010; Milroy 1995; Palermo et al. 1997). Murder-suicide of the jealous paranoia type constitutes 50–75 % of all murder-suicides (Palermo et al. 1997).

Another frequently encountered type is that of the killing of the children by a parent with a sense of misplaced altruism (Milroy 1995). Byard and colleagues conducted a 29-year study of murder-suicides involving children in Adelaide, Australia (Byard et al. 1999). In general, the methods of homicide and suicide are less violent (carbon monoxide and poisoning) among female perpetrators compared with their male consort. Fathers murdered not only their children but also their wives while mothers killed only their children. Male killers who kill their entire family including the family pet have been termed "family annihilators" (Milroy 1995).

Unusual "Homicides"

Hunting "Accidents"

Hunting game is a popular activity worldwide encompassing various types of animals including deer, birds, turkeys, squirrels, and rabbits. Deer hunting is

a common sport in numerous areas of the USA. A host of weapons are used in the hunting, trapping, and killing of game. The majority of deer hunting–related fatalities are due to accidental firearm injuries (Shields and Stewart 2011). Hunters may also sustain blunt-force trauma after falling out of their elevated tree stand due to the faulty design or construction of the perch (Shields and Stewart 2011). Less commonly encountered are homicidal fatalities while hunting.

Several incidents involving teenage fatalities while hunting have been recently reported including a 14-year-old boy in Ohio who was shot in the abdomen by another 14-year-old while they were deer hunting with three adults and a 14-year-old boy in California who was shot and killed by a teenage cousin while they were hunting deer with the boy's uncle, a local hunting safety instructor (Iannelli 2012). While these cases may be initially reported as accidental, further delving into the history and scene investigation are warranted.

On October 23, 2011, a 16-year-old in Montana ventured with two teenage friends for a day of deer hunting (Tuttle 2012). While authorities initially reported his death as accidental, the manner was later determined to be homicide. His cause of death was a GSW to the posterior neck. The victim's friends altered their stories, ranging from "the victim shot himself under the chin" to "one of the friends was walking behind the victim when the friend tripped and his gun accidentally discharged" (Associated Press 2012b).

A thorough investigation is warranted following the death of an adolescent while hunting with a friend. Special attention should be focused on the location of injuries such as GSW to the back that were not readily accessible to the victim. While the shooter may provide histories of the occurrence such as the victim was mistaken for a deer or that the shooter's gun accidentally discharged, investigators should be alert to a more sinister act.

Homicidal Russian Roulette

Fatal Russian roulette denotes a death following an act of extreme bravado in which the individual spins the cylinder of a revolver loaded with at least one cartridge, aims the muzzle at the head, and pulls the trigger (Shields et al. 2008). The majority of victims are males $<$ 30 years who are under the influence of ethanol or other drugs. While the presumed intent is to survive, the manner of Russian roulette is deemed to be suicide in the majority of cases based on the inherently deliberate and volitional actions of the victim (Shields et al. 2008). Russian roulette occurs in the setting of at least two individuals, and at least ten other people may be present in the room (Shields et al. 2008).

In Abilene, Texas, in January 2011, a 16-year-old, a 17-year-old, and a man were playing Russian roulette in which they passed around a revolver containing at least one bullet, and a participant spun the barrel and pointed the gun either at another player or at their own head and pulled the trigger (Blaz 2012). The 16-year-old died during the game after being shot by the 17-year-old. The living individuals initially told the police that the gun had discharged accidentally after it fell but later admitted to playing Russian roulette. The shooter was found guilty of criminally negligent homicide but was acquitted of manslaughter (Blaz 2012).

In July 2012 in Pennsylvania, two 15-year-olds were playing Russian roulette when one individual pointed the gun at his friend's head and pulled the trigger (Cavaliere 2012). Prosecutors are considering third-degree homicide or manslaughter charges against the teen.

The investigation of a death in the setting of Russian roulette necessitates a detailed history of the incident. In most cases, the victim holds the loaded gun against his/her own head leading to a suicidal manner of death. However, homicide should be considered in the context of this game of fates when one individual holds the gun against a friend's head.

Medicolegal Investigation of Adolescent Homicide: Pathological Findings

Manner of Death: The pivotal aspect in the investigation of the death of an adolescent is to establish the accurate manner and cause of death through scene investigation, autopsy findings, and police interrogations. When an adolescent is discovered unexpectedly dead coupled with suspicious findings, the case should be considered a potential homicide (Byard 2010). The death scene may offer valuable clues that may aid in the determination of cause and manner of death. Therefore, the scene should be secured, and the location of the body in relation to the surroundings should be sufficiently documented in writing and photographically. The forensic pathologist bears the responsibility of assessing the injuries, determining a provisional cause of death, and possibly providing an estimate of time of death (Byard 2010). A host of injuries may be detected at postmortem examination which may lead to the conclusion of a homicidal death. A thorough analysis must be conducted to assess whether an adolescent's death results from homicide or suicide (Lee et al. 1999; Shields et al. 2006). The adolescent period from 10 to 19 years of age signifies a developmental stage marking the transition from typical childhood fatalities to adult types of violent deaths (Lawrence and Fattore 2004). As the most common causes of adolescent homicide are firearms and sharp-force injuries, both of these causes will be discussed with respect to autopsy findings (Table 22.5).

Firearms: GSW is the leading cause of adolescent homicide in the USA (Batalis and Collins 2005; Coyne-Beasley et al. 1999). GSW in adolescents have similar features to those found in adults with respect to the injuries determined by the type, range, and caliber of the involved weapon (Byard 2010). Distinction between homicide, suicide, or accident is the primary determination in the investigation of a death involving a shooting. The site of the entrance wound and direction of the bullet path have been used as markers to differentiate between homicidal or suicidal manners of death (Cina et al. 1999; de la Grandmaison et al. 2008; Druid 1997; Suwanjutha 1988). A distant shot could not have been self-inflicted without a device designed especially for this purpose. Pathologists focus on direction of fire and the range of fire by assessing gunpowder stippling, soot, or both around a bullet wound (Spitz 2006a). The victim's clothing over the GSW should be examined microscopically and chemically for the presence of powder residue.

Table 22.5 Autopsy findings and investigations of firearm and sharp force injury in adolescent homicide

Cause of death	Classic autopsy findings and homicide investigation
Firearm	Range of fire
	Direction of fire
	Gunpowder stippling/soot around bullet wound
	Examination of clothing for powder residue
	Number of entrance and exit wounds and their location on body
	Shape of wound (stellate, round, slit-like, or jagged)
	Diameter of the power residue deposits
	Direction of the bullet by probing the gunshot wound
	Description of the wound track internally in anatomical order
	Description of the missile path through the body in relation to the planes of the body
Sharp force injury	Incised wounds: injury longer than deep
	Stab wounds: injury deeper than long
	Homicidal cuts of the throat are often single and deep
	Defense wounds on the upper extremities (forearms, hands)
	Pattern and distribution of wounds may determine weapon
	Direction of wound by dissection of tract of hemorrhage
	Analyze victim's clothing
	Collect detailed history of event: circumstances surrounding the death and scene analysis

A GSW in an area of the body of lesser accessibility to the victim or multiple bullet wounds are suspicious of homicide. The majority of suicidal shots are of the head, specifically the right temporal region (Shields et al. 2005). Multiple bullet wounds do not rule out suicide (Shields et al. 2003), particularly if the weapon is an automatic or semiautomatic.

The determination of an accidental GSW versus a homicidal or suicidal GSW is based on the circumstances surrounding the incident (Spitz 2006a). The pathologist's findings at autopsy coupled with photographs and diagrams at the scene should be able to confirm or dispel the account of the event.

The autopsy involving a GSW victim should focus on four components: (1) description of clothing, (2) pertinent findings pertaining to bullet wounds, (3) cause of death, and (4) toxicological and serological analyses (Spitz 2006a). The entrance and exit wounds and grazes should be individually labeled using numbers or letters, and their location should be described in relation to their distance from the top of the head and from the midline of the body. With respect to the external examination, several factors should be documented, including features of the bullet wound (entrance vs. exit wound) (Fig. 22.2a, b), shape of the wound (stellate, round, slit-like, or jagged), diameter of the powder residue deposits, and direction of the bullet, in addition to inspecting the internal permanent wound cavity. The internal examination should involve a description of the wound

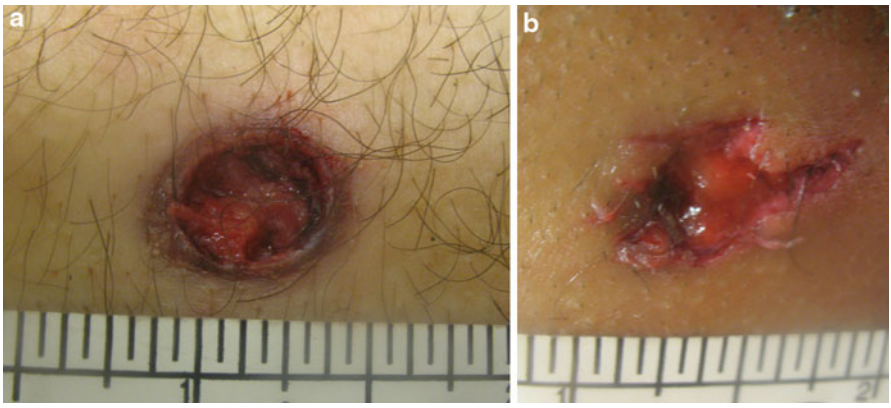

Fig. 22.2 Classic features of an (**a**) entrance and (**b**) exit wound evaluated on victim #3. Scale is in inches (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

track in anatomical order as well as the missile path through the body in relation to the planes of the body. The most common acute mechanism of death in victims of gunfire is hemorrhage. Peritonitis and pneumonia are intervening sequelae if the victim's death is delayed.

Sharp-Force Injuries: Sharp-force injuries are the second leading cause of death in adolescents in the USA (Batalis and Collins 2005). Sharp-force injuries, namely, incised wounds and stabbings, may be associated with homicidal, suicidal, or accidental manner of death. Autopsy findings are valuable in determining whether the sharp-force fatality was homicidal or suicidal. Brunel and colleagues conducted a comparative study of homicidal and suicidal sharp-force fatalities between 1986 and 2008 (Brunel et al. 2010). Homicide victims were more likely to have sustained stab and cut wounds; wounds at the head, limbs, hands, or back; the presence of bone or cartilage wounds; the presence of defensive or violence-associated traumatic wounds; and a significantly higher injury-severity score (assesses the gravity of traumatic wounds regardless of origin or cause) (Brunel et al. 2010). Conversely, several factors were predictive of a suicide, including isolated cut wounds; wounds located at the anterior trunk, neck, or forearms; the lack of bone or cartilage wounds; and the presence of "hesitation" wounds.

Incised wounds produce an injury that is longer than it is deep, while stab wounds cause a wound that is deeper than its length on the skin (Spitz 2006b). Homicidal cuts of the throat are often single and deep, and the majority of homicidal throat slashings occur when the assailant is behind the victim (Byard 2010). Defense wounds are cuts or slashes on the upper extremities, primarily the forearms and hands, and signify active resistance by the homicidal victim. Historical information of the incident is imperative, including a review of the circumstances surrounding the death as well as the scene where the body was found. The amount of force required to inflict a particular stab wound is based on two components: (1) the speed at which the knife is thrust and (2) the sharpness of

the tip of the blade (Byard 2010; Spitz 2006b). Whether the wound tract passes through bone must also be taken into consideration, with attention to the type of bone involved and its thickness.

The forensic pathologist's duty is to categorize the type of weapon utilized in an adolescent homicide by examining the wounds at autopsy. The pattern and distribution of wounds may shed light on the type of instrument used in the attack. In addition, an analysis of the direction of a knife wound is conducted at autopsy by dissection along the track of hemorrhage. The clothing should also be examined. Exsanguination is the most common mechanism of death from sharp-force injuries with bleeding primarily into body cavities.

Representative Medical-Examiner Cases of Adolescent Homicide

Five cases of homicide in which the victim was an adolescent are presented. Two of the cases reflect murder-suicide involving a parent and an adolescent.

Case #1: A 10-year-old Caucasian boy was found at a motel with three shotgun wounds inflicted by his 36-year-old mother. The mother had been diagnosed with schizophrenia and bipolar disorder. Coroner's investigation revealed that the mother had been devoted to her son, designing a classroom to homeschool him. Although she was divorced from the boy's father, who subsequently remarried, the father continued to control his ex-wife. He had told her to stop eating and convinced her to discontinue her psychiatric medications. Three weeks prior to the fatality, the boy's mother took her son and a shotgun to go hunting, bringing blankets and a picnic. The mother test-fired the gun during this outing. The mother subsequently bought another shotgun at a pawn shop. On the day of the fatality, investigators surmised that the mother had stood at the foot of the motel bed and fired three rounds into her son. She then reloaded the gun and committed suicide by a contact shotgun wound of the trunk.

The boy's autopsy demonstrated three close-range shotgun wounds of the trunk with perforations of the ribs, right 2–10 and left 1–12, skin, heart, lungs, liver, diaphragm, spleen, left kidney, aorta, and T10 vertebra. There were two coalescing shotgun wounds of the left trunk just medial and below the nipple (Fig. 22.3a, b). The third wound was located in the left upper abdominal quadrant and left lower chest. There were hemothoraces (right [250 ml] and left [100 ml]) combined with a hemoperitoneum.

Case #2: A 43-year-old Caucasian man and his 13-year-old daughter were discovered lying beside each other on a mattress in their enclosed home garage next to a vehicle which had been running. The girl had been diagnosed with Angelman syndrome, a complex neurogenetic disorder, and had mental retardation requiring a feeding gastrostomy. The man's wife had moved out of the family home, and they were in the process of getting divorced.

The girl's body was found in the prone position. Autopsy revealed cherry-red lividity of the skin, viscera, and blood with petechiae of the thymus and heart (Fig. 22.4a, b). The postmortem blood carbon monoxide saturation was 75 % total Hb.

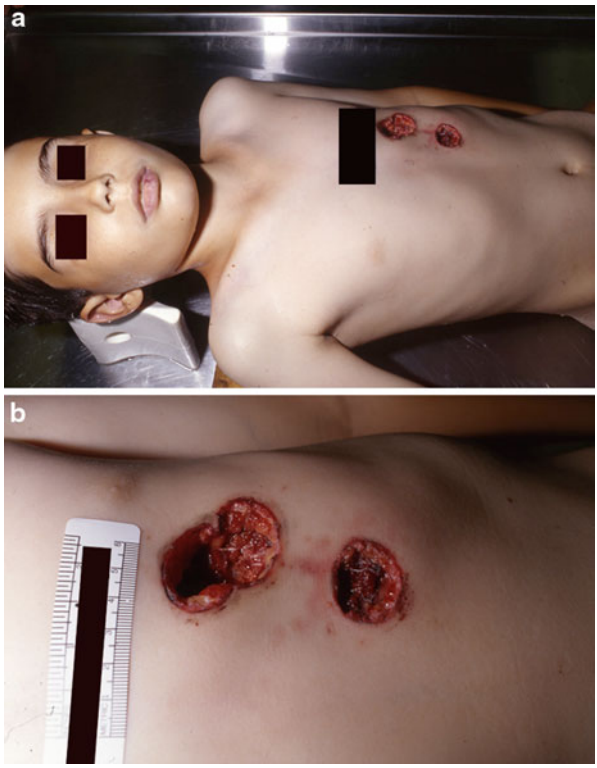

Fig. 22.3 Case #1: (**a**) Three shotgun wounds of the left trunk. Two of these wounds coalesce. (**b**) A close-up view of (**a**) (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

Indications of Angelman syndrome included short stature (4 ft 2 in. [50 in.; 127 cm] for a 13-year-old female), asymmetrical skull, extended ankles, prognathism with minimal maxillary hypoplasia, and feeding gastrostomy (Fig. 22.5). Initially described in 1965 by the English pediatrician Harry Angelman, Angelman syndrome is also known as "happy puppet" syndrome and is characterized by individuals displaying severe intellectual disability, ataxia, absent speech, jerky arm movements, and bouts of inappropriate laughter (Chamberlain and Lalande 2010). Additional criteria may include microcephaly, seizures, electroencephalographic (EEG) abnormalities, and hyperactivity (Williams et al. 2006).

The cause of death was asphyxia due to carbon monoxide intoxication complicating positional asphyxia due to the prone position of the body on the mattress.

Case #3: This case reflects drug violence associated with homicide encountered in the adolescent population. A 19-year-old Caucasian man was found lying in a parking lot with multiple perforating and penetrating gunshot wounds of the face, neck, trunk, and upper extremities. The victim sustained a total of ten gunshot wounds: head (3) (Fig. 22.6), neck (1), trunk (5) (Fig. 22.7a, b), and right extremity (1). The victim had blunt-force injuries, including a scalp abrasion of the occiput and skin abrasion of the chest.

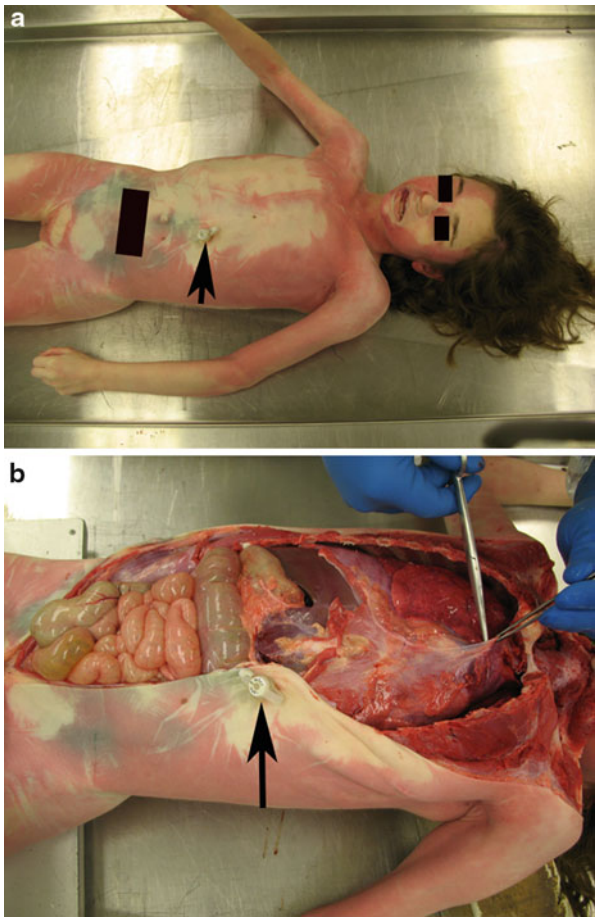

Fig. 22.4 Case #2: Carbon monoxide intoxication with cherry red lividity of the (**a**) skin, (**b**) viscera, and blood. Note the feeding gastrostomy marked by an *arrow* (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

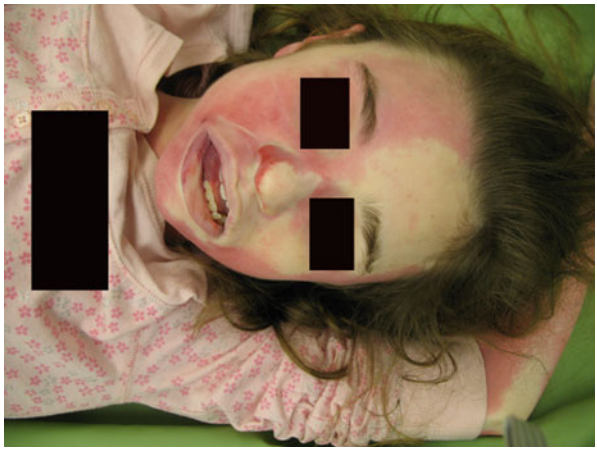

Fig. 22.5 Case #2: Carbon monoxide intoxication with cherry red lividity of the skin. There was also evidence of positional asphyxia due to the body found in a prone position on a mattress. Note the characteristic facial features of Angelman syndrome (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

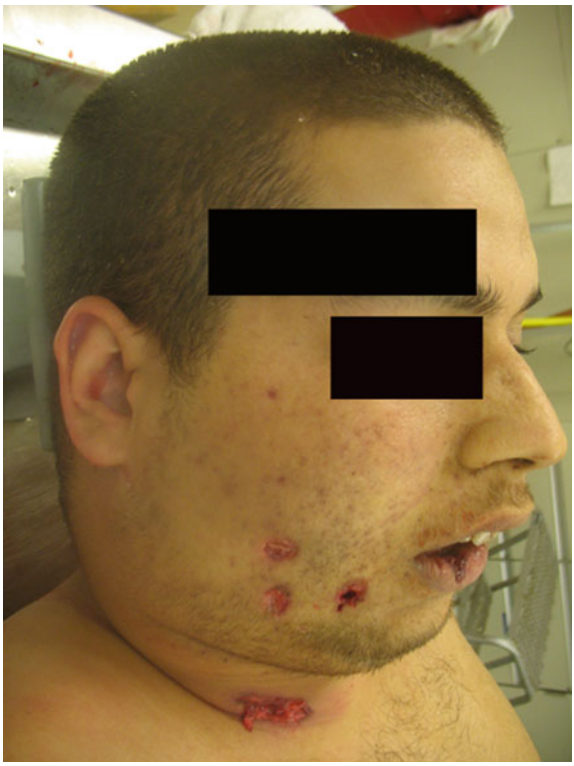

Fig. 22.6 Case #3: Facial and neck injuries resulting from multiple gunshot wounds (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

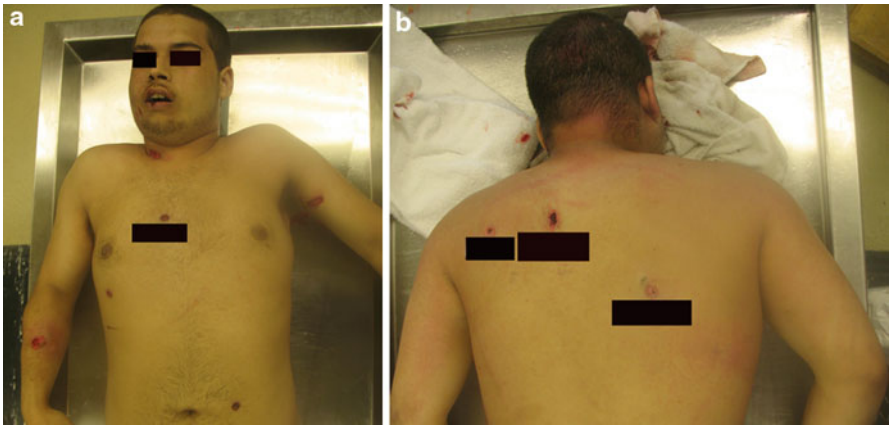

Fig. 22.7 Case #3: (**a**) Multiple gunshot wounds of the face, neck, chest, abdomen, and upper extremities. (**b**) Multiple gunshot wounds of the back (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

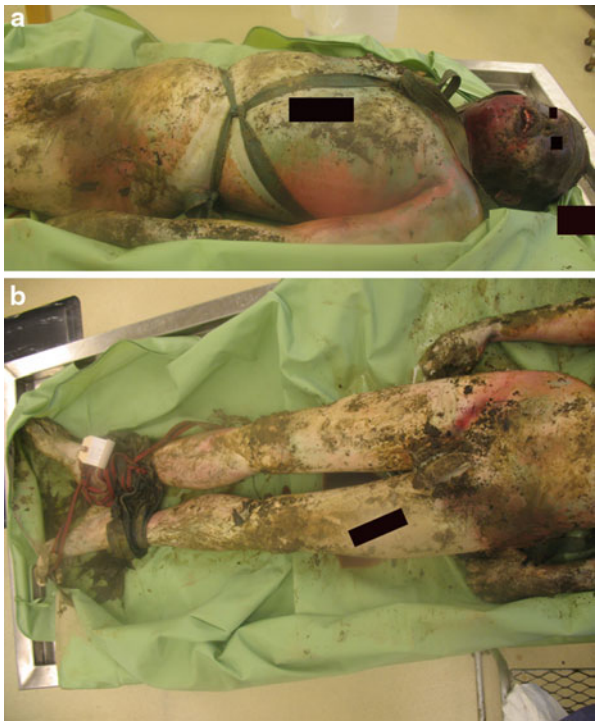

Fig. 22.8 Case #4: Decomposed body with straps tightly placed around (**a**) torso and (**b**) lower extremities. The straps were attached to concrete blocks (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

Postmortem toxicology (ng/mL) was as follows: bloody fluid of the left chest cavity (alprazolam, 14.8; THC, 21.1; THC-COOH, 53.8; ethanol, 0.038 % [w/v]), urine (carboxy-THC, 31; ethanol, 0.051 % [w/v]), and vitreous humor ethanol (0.032 % [w/v]).

A 27-year-old man, an acquaintance of the victim's, was charged with murder in this case. The offender had a history of public intoxication, possession of marijuana, and three traffic violations in the previous 2 years.

Case #4: The decomposed body of a 19-year-old Caucasian male was found submerged in a pond with straps attached to concrete blocks. The blocks had been used to weigh him down; however, his body was floating in the pond due to decomposition. He was last known to be alive 5 weeks earlier. The victim had a history of cocaine and methamphetamine use.

Two straps were tightly placed around the victim's torso and extremities (Fig. 22.8a, b). The autopsy revealed two gunshot wounds, specifically, of the head (Fig. 22.9a, b) and upper back (Fig. 22.10a, b). There was also blunt-force injury consisting of a cutaneous contusion of the right wrist. Postmortem toxicology of the decompositional fluid of the chest (ng/mL) revealed cocaine (125), benzoylecgonine (2,035), oxycodone (2,673), oxymorphone (59.4), THC-COOH (6.7), and 7-Aminoclonazepam (28.8).

The investigation of this homicide is ongoing. Persons of interest have been identified; however, an individual has not been charged.

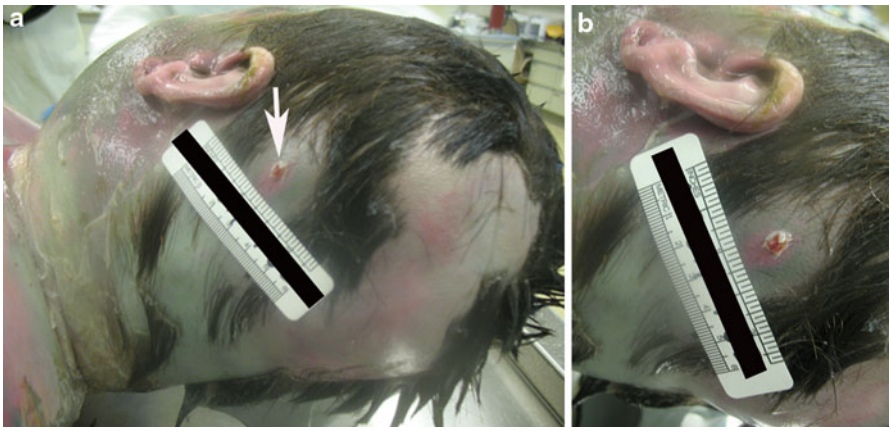

Fig. 22.9 Case #4: (**a**) Gunshot wound of the head in the left lateral occiput. (**b**) Close-up photo of (**a**) (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

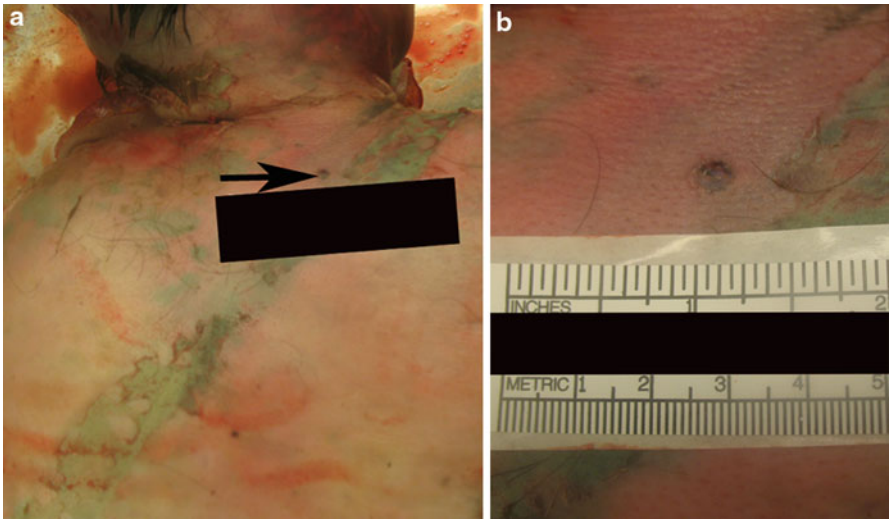

Fig. 22.10 Case #4: (**a**) Gunshot wound of the upper back. (**b**) Close-up photo of (**a**) (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

Case #5: The final case describes an adolescent homicide resulting from sharp-force injuries. A 19-year-old black male was stabbed by his first cousin and transported by a bystander at the scene via personal auto to the local hospital where he succumbed to hypovolemic shock intraoperatively. The victim and his first cousin had argued about the "quality and authenticity of a gold tooth" according to the coroner who investigated the case. The two cousins initially had a fist fight. The perpetrator subsequently left and returned with two knives. The perpetrator found the victim at his aunt's home, and the homicide ensued.

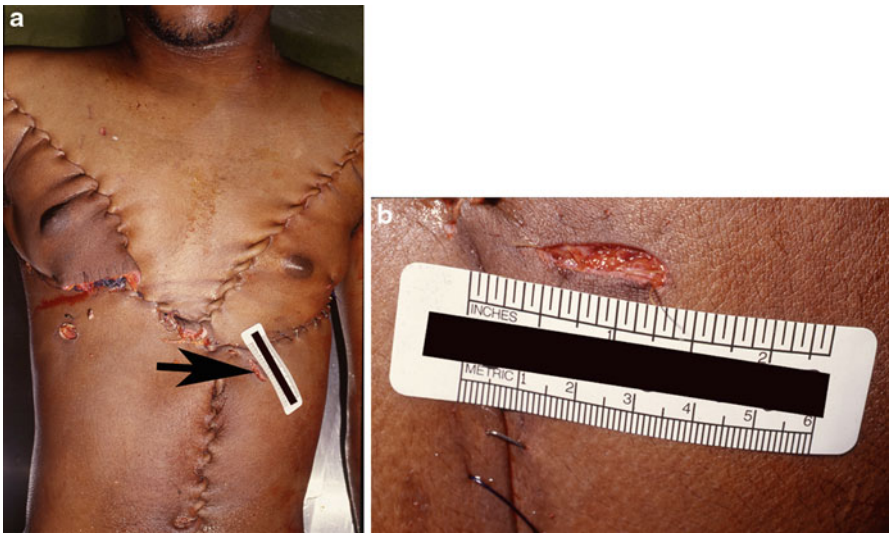

Fig. 22.11 Case #5: (**a**) A post-autopsy photo of the stab wound of the chest in the right inframammary region. Note the *arrow* marking the stab wound. (**b**) Close-up photo of (**a**) (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

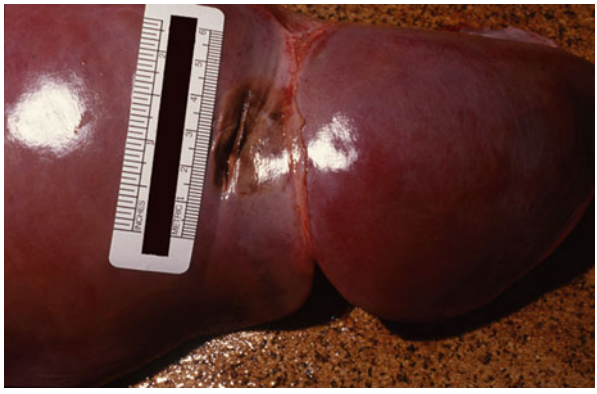

Fig. 22.12 Case #5: Penetrating wound of the liver subjacent to the stab wound of the right side of the chest (Obtained from the Office of the Associate Chief Medical Examiner, Frankfort, Kentucky)

The victim sustained acute intra truncal hemorrhage due to perforating sharp-force injuries of the right intercostal vessels, liver, and abdominal veins. At autopsy, he had evidence of stab wounds of the right inframammary region (Fig. 22.11a, b) with perforations of the right sixth costal cartilage with sixth and seventh intercostal muscle/vessels, right hemidiaphragm, liver (Fig. 22.12), and parahepatic abdominal veins. The decedent had also sustained blunt-force injuries of the head and extremities. Blood and vitreous toxicological analysis was negative.

The first cousin was charged with murder and sentenced to a maximum of 20 years in prison.

Adolescent Homicide Prevention

Adolescent homicide prevention programs are multifaceted and address the risk factors associated with homicide and stress the protective factors required to buffer against violent behavior. Several key components include increasing self-esteem (low self-esteem has been linked to bullying), establishing a close bond with the primary caregiver, and enhancing an individual's social and emotional skills (Douglas and Bell 2011). In response to school shootings, the Secret Service and Boards of Education have made numerous suggestions to schools and parents to decrease the likelihood of school shootings: (1) attempt to understand the process of violence as students do not "snap"; (2) understand that targeted violence involves the interaction between the attacker, situation, setting, and target; thus, be vigilant to these interwoven factors; (3) investigate communications among peers and encourage students to talk about their knowledge of a particular situation; (4) be cognizant of bullying situations; (5) utilize safe gun storage; and (6) increase efficiency in handling of grievances (Dedman 2006). Improvement in national, state, and local efforts are mandatory to prevent school-associated violent deaths, including a heightened focus on the cause of these deaths such as the use of firearms (Logue 2008).

The Centers for Disease Control investigated the violence-related behaviors among high school students in the USA between 1991 and 2003 (Centers for Disease Control and Prevention 2004). Over this time period, they reported that students were increasingly more likely to miss school because they felt too unsafe to attend. In 2003, nearly one in ten high school students stated that they had been threatened or injured with a weapon on school property during the preceding 12 months. To address these inflammatory statistics and to promote safety and prevent violence, they developed the School Health Guidelines to Prevent Unintentional Injuries and Violence to reduce students' actual and perceived risk of violence (Centers for Disease Control and Prevention 2004). They stressed the importance of school health nurses, counselors, and psychologists as the essential healthcare providers in the school system (Logue 2008). Homicidal prevention programs have been beneficial in aiding adolescents at high risk and their families to acquire the knowledge, skills, and support critical to avoid violence (Centers for Disease Control and Prevention 2004).

A feature of school shootings is that heavily armed students have been able to gain access to the school premises carrying undetected guns, ammunition, and explosives (Wike and Fraser 2009). Many schools have instituted routine or random searches of school bags and lockers. In addition, some schools have installed metal detectors; however, this practice has been primarily limited to large, urban schools (Wike and Fraser 2009).

Conclusion

The homicide of an adolescent is a shocking occurrence for family and friends of the victim and warrants a thorough analysis into the underlying motives, methods, and perpetrators inherent in this type of death. In the USA, the typical victim is a black

male, who is killed by a close acquaintance or family member utilizing a firearm. A host of factors are integrally associated with increasing the risk of homicidal behavior in adolescents, specifically, biological and psychological vulnerability, environmental stresses, the attitude toward violence in society, and the availability of weapons (Hardwick and Rowton-lee 1996). Risk factors potentiate each other, and youths most at risk are those with the greatest number and degree of severity of these factors. The goal is to address these risk factors and to select the most appropriate form of treatment to minimize them. For example, children with learning difficulties may be more prone to exhibit aggression and impulsivity; thus, they should be referred to interventional services who can effectively address the underlying cause of violence. In other cases, intervention may need to target the home, school, or neighborhood such as parent-empowerment training, teaching conflict resolution skills, and treatment for adolescents who have sustained violence (Hardwick and Rowton-lee 1996).

While the adolescent homicide rate in the USA surpasses the majority of other countries (Christoffel 1990), a firearm is a common theme internationally. The availability of guns for adolescents in the USA as compared to Canada (Sloan et al. 1988) and Australia (Byard et al. 2009) is reflected in the high rate of firearm death in the adolescent age in the USA. Gun control for adolescents has served as one of the preventive measures that has been investigated. In 1999, the Oakland Gun Tracing Project was developed in response to the high level of gun violence among young people in Oakland, California (Calhoun et al. 2005). They instituted evidence-based policy recommendations aimed at reducing the supply and demand for gun acquisition among urban youth. They also emphasized policy strategies, including initiating a comprehensive gun-tracing program, federal handgun registration, reporting of stolen firearms, and intervention to all juveniles when they enter the criminal justice system (Calhoun et al. 2005).

The forensic pathologist plays a vital role in the determination of the manner and cause of adolescent death. A thorough scene examination, collection of historical information regarding the incident, and a detailed autopsy are warranted in the investigation of these deaths. The five detailed cases of adolescent homicide presented in this chapter exemplify the role that the forensic pathologist has in the differentiation between various manners and causes of adolescent fatalities. The international perspective of adolescent homicide shares common trends, namely, a male victim who succumbs to a gunshot wound and perpetrators with a history of drug/alcohol use and family discord. International collaboration may shed light on the challenges facing each country and offer valuable solutions to decrease the prevalence of adolescent homicide.

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Pediatric Sexual Abuse

23

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Contents

Abstract

Child sexual abuse is a common form of child maltreatment that can leave a broad range of residual evidence. This chapter will define child sexual abuse and then will explore the various findings that should be collected as

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evidence. It will contrast the relative increasing indicia of reliability in interpreting a child's behavior, trace evidence, victim's statements, trauma, sexually transmitted infections (STIs), presence of seminal products, witnesses, suspect statement, presence of somatic DNA, presence of sperm, pregnancy, and video/photographic evidence. Suggested guidelines are offered with respect to purpose of sexual abuse exams, STI testing, and prophylaxis for possible medical consequences. Entities that may be mistaken for sexual abuse will also be discussed.

Introduction and Definitions

Sexual abuse of a child can involve exposing the child to sexualized information, behavior, and/or contact, making a concise definition difficult (Haugaard 2000). Kempe (1978) provided the foundation for the current American Academy of Pediatrics definition: "Sexual abuse occurs when a child is engaged in sexual activities that he or she cannot comprehend, for which he or she is developmentally unprepared and cannot give consent, and/or that violate the law or social taboos of society" (Kellogg et al. 2005). The Uniform Crime Report's definition of the term "rape" has recently been updated by the US Department of Justice to include, "The penetration, no matter how slight, of the vagina or anus with any body part or object, or oral penetration by a sex organ of another person, without the consent of the victim" (http://www.justice.gov/opa/pr/2012/January/12-ag-018.html). Although legal definitions vary from state to state, the key elements defining child sexual abuse generally include *lack of consent *to contact or noncontact sexual events *involving a minor *by someone significantly older.

Lack of consent can be through the use of force or intimidation, but also includes situations in which a victim is incapacitated or developmentally unable to consent. Incapacitation can occur through congenital or acquired mental defect, or by drug facilitation (poisoning or self-medication with legal or illegal substances). Most authorities agree that young age or cognitive impairment limits a victim's ability to consent, but there is disagreement on an exact age or the cognitive impairment threshold above which consent exists and below which it does not. You are advised to consult your local statutes for this information.

Contact sexual abuse involves the perpetrator using various objects, their mouth, fingers, or genitals to make lewd contact with the victim's mouth, breasts, anus, genitals, or body generally. Noncontact sexual abuse involves pornography, voyeurism, or sexual exhibitionism.

A minor is defined as a person less than the age of full legal responsibility. For most jurisdictions in the world, this age is 18 years old. For some jurisdictions, emancipation from minority status can occur at various younger ages. The legal age

to consent to sex and the actual crime a perpetrator can be charged with varies among jurisdictions and depends on the age difference and relationship between perpetrator and minor victim.

Classification of Findings

Most physical evidence can be classified as to its scientific significance in specifying child maltreatment. Various classification systems have been proposed over time (Muram 1989; Bays and Chadwick 1993; Adams et al. 1994; Myhre et al. 1998; Slaughter and Brown 1992; Adams 2011). A classification system is useful to quickly communicate the relative scientific specificity of physical evidence. A simple five-point classification system built on these prior efforts has served this author well over time and is explained below. Subjective evidence such as a victim's statement can be used to corroborate physical evidence, but should not be used to change the classification of the physical evidence. For example, a nonspecific finding (defined below) does not become more specific just because it is congruent with the victim's statement.

Normal Findings

A normal finding means that nothing abnormal was found. A normal examination may indicate that no abuse took place, but there are also many abusive sexual acts that do not leave evidence. A common mistake is to think that the absence of evidence is evidence of absence. A normal finding neither confirms nor refutes prior sexual abuse.

Nonspecific Findings

A nonspecific finding is an abnormal finding noted during the investigation, and the finding either scientifically occurs in both the abused and nonabused populations, or its scientific prevalence in both populations is unknown. A common example is anal fissures. There are many causes of anal fissures including traumatic bowel movements due to constipation, diarrhea, infection, autoimmune disease, dehydration, etc., as well as traumatic consensual or nonconsensual sexual contact (Myhre et al. 2013). Therefore, anal fissures as an isolated finding are "nonspecific" in defining the etiology. Some recent classification schemes include an indeterminate class in which the specificity for abuse is unknown due to insufficient scientific study or consensus. To maintain simplicity, findings of indeterminate significance are included in the nonspecific class until science justifies otherwise.

Concerning Findings

A concerning finding is an abnormal finding noted during the investigation, and the scientific literature shows this finding to occur more frequently in the abused population, but it also shows it can sometimes occur in the nonabused population. A common example of this is genital warts caused by the human papillomavirus. A major mode of transmission of this virus is sexual, but inoculation by nonsexual transmission such as during birth is possible. Another example are deep notches in the posterior rim of the hymen. Again, this finding has an association with sexual abuse, but has been rarely described in the non-abused population. Concerning findings are important in that they include items which should raise the suspicion of sexual abuse and should provoke questions about whether sexual abuse is present.

Suggestive Findings

A suggestive finding is an abnormal finding noted during an investigation, and the scientific literature shows this class of finding to occur almost exclusively with abuse in specific contexts, but scientific thought can explain nonabusive ways in which this finding might exist. Examples of these types of findings include the residual of most penetrating anogenital trauma including abrasions, lacerations, and scars. The reason is that although there are some injuries that frequently are due to abuse, scientists can think of accident mimics. Indeed, various case studies of accidents have reported rare events mimicking anogenital findings seen in abuse (Boos et al. 2003). Fortunately, accidents are usually well defined and the events are known to most caregivers.

Definitive Findings

A definitive finding is an abnormal finding noted during an investigation, and the scientific literature shows this finding to occur exclusively with abuse; scientists cannot think of nonabusive ways or can reasonably exclude non abusive ways in which this finding might exist. Examples of definitive findings are pregnancy, sperm, or semen in a nonconsensual-age child or adolescent that has been proven by DNA to belong to an abuser by virtue of age or relationship.

Evidence

Given the wide range of acts defining child sexual abuse, the consequent evidence of that abuse is similarly wide ranging. Table 23.1 lists the types of evidence used to define sexual contact or abuse. Note the evidence types with an asterisk reflect those items available to be collected by the forensic medical examiner. Evidence types are arranged loosely by relative indicia of reliability with the most reliable at the top

Table 23.1 General interpretation of evidence in suspected child sexual abuse cases

Mandatory Reporting Threshold →

Relative Indicia of Reliability ↑

Evidence	Normal	Nonspecific	Concerning	Suggestive	Definitive Sexual Contact
Video/Photo	|-------Surveillance or other images proving general contact or location of individuals---------|	|----------Pornography used to seduce----------|	|----------Surveillance depicting abuse/assault ----------|	• Lewd images of victim or children • Images of inflicted injury
Pregnancy[a]					• Sex act and donor identity
Sperm in/on Victim[a]					• Sex act and donor identity • Positive Y-STR from female anogenital samples
DNA Somatic[a]	|----------Donor Identity (category depends on other facts) ----------|				
Suspect Statement	|---------- Bribes ----------|			• Threats • Suspect admissions	• Suspect confession
Witness	|---------- Witnessed abusive act (category depends on detail, clarity, credibility and context) ----------|				
Seminal Products[a]			• Acid phosphatase	• PSA/p30 • Semenogelin • MHS-5	
STI[a]	• Physiologic vaginal leukorrhea	• Vaginal discharge or anogenital inflammation or redness • HPV or Chlamydia trachomatis (< 3 yo) • HSV type I or II • Bacterial vaginosis or *Candida albicans* • Lice, Scabies, Crabs anogenital ulcers • Urinary tract infection (non-STI)	• HPV (≥ 3 yo)	• *Trichomonas vaginalis* (non-neonatal)	• Donor identity - HIV and *other STI in future* • HIV or Hepatitis B (non-neonatal, non-transfusion) • *Treponema palidum* (non-neonatal) • *Neisseria gonorrhea* (non-neonatal) • *Chlamydia trachomatis* (> 3 yo)

Trauma[a]	• Variant anatomy
	  • Hymen (see text)
	  • Periurethral or vestibular bands
	  • Linear vestibularis
	  • Perineal body protrusions
	• Nevi
		• Congenital conditions
		  • Failure of midline fusion
		  • Diastasis ani
		• Medical conditions
		  • Labial adhesions
		  • Lichen sclerosis
		  • Urethral prolapse
		  • Anal fissure(s)
		  • Peri-anal venous pooling
		  • Anal skin tags
		  • Anal dilatation
		• Anogenital trauma with clear accidental history
		• Hymen narrowing
			• Hymen deep notches posteriorly
			• Non-penetrating anogenital trauma without clear accidental history
				If accidental trauma can be excluded:
				• Acute hymen, vaginal, penile, scrotal, rectal or anal injury
				• Hymen transection of posterior rim
					• Inflicted trauma not necessarily sexual
					  • Slap pattern
					  • Human bite pattern
					  • Loop/strap pattern
					• Human bite on genitalia or breast

Victim Statement[a]			• Vague history of assault	• Clear but not detailed history of assault	• Clear and detailed history of assault
Trace Evidence[a]		• See text; assist in defining crime scene			
Behavior[a]	• Sexual curiosity • Masturbation	• Demeanor • Emotional congruence • Aggression • Regression • Avoidance of suspect	• Promiscuity • Prostitution • Excessive masturbation • Adult sexual acts by children		

[a]Evidence available to forensic medical examiner

Table 23.2 Purpose of forensic medical examination of the living child in order of priority

1.	Reassurance of normality and safety, if possible
2.	Diagnosis and treatment of medical and psychological problems
3.	Collection of forensic evidence

and least reliable at the bottom. This is not meant to discredit a lower-ranking evidence type from being self-sufficient. It does mean, however, that evidence with lower relative indicia of reliability should be scrutinized prior to reaching a final conclusion. Movement to the right in the chart indicates evidence categories which better specify sexual contact or sexual abuse.

Following an abuse concern, most investigations begin by collecting statements from the child, suspect, and witnesses. Statements should be documented as verbatim as possible. Ideally, digital voice and video recorders offer highest documentation fidelity (Lamb et al. 2000; Cauchi et al. 2010). Some nuances to collecting these various statements are examined later in this chapter.

All children suspected of being sexually abused should undergo a comprehensive forensic medical examination by an examiner experienced and comfortable with the task. A forensic medical examination is similar to the usual general pediatric examination and should be conducted only with proper legal consent. When able, the competent minor's assent for this examination should also be sought. The purpose of this examination in order of priority should be focused on providing reassurance of normality and safety as well as diagnosing and treating medical and psychological problems and then collecting forensic evidence. See Table 23.2. With these priorities in mind, most children do well with this examination (Palusci and Cyrus 2001; Allard-Dansereau et al. 2001; Prior 2001; Waibel-Duncan and Sandler 2001, 2002; Waibel-Duncan 2001; Davies and Seymour 2001; Mears et al. 2003; Duncan and Sanger 2004; Gulla et al. 2007; Walsh et al. 2007; Marks et al. 2009; Leventhal et al. 2010; Scribano et al. 2010). The procedure should involve a thorough inspection of all skin surfaces with particular attention to those areas often associated with sexual assault. Those areas include the oropharynx, breasts, and anogenital area. The use of sedation is rarely needed and should only be used for cases in which the extent of the trauma cannot be otherwise visualized and/or the trauma needs to be repaired. All abnormalities should be photographically documented, including those areas that appear normal but are complained about as abnormal. Standard photographic documentation should also be performed of the anogenital examination to prevent the need for repeat examination and to permit peer review even if the examiner believes that the findings are normal. Biological and trace-evidence collection is described later.

Varying the position of the female child and vulva during the exam can assist in performing a full inspection of the vaginal vestibule and in some cases vaginal contents (Boyle et al. 2008; McCann et al. 1990a). Labial separation, labial traction, and perineal lift permit movement of the vulva from obstructing the view of the vestibular contents while also putting tension on the hymen to best expose the

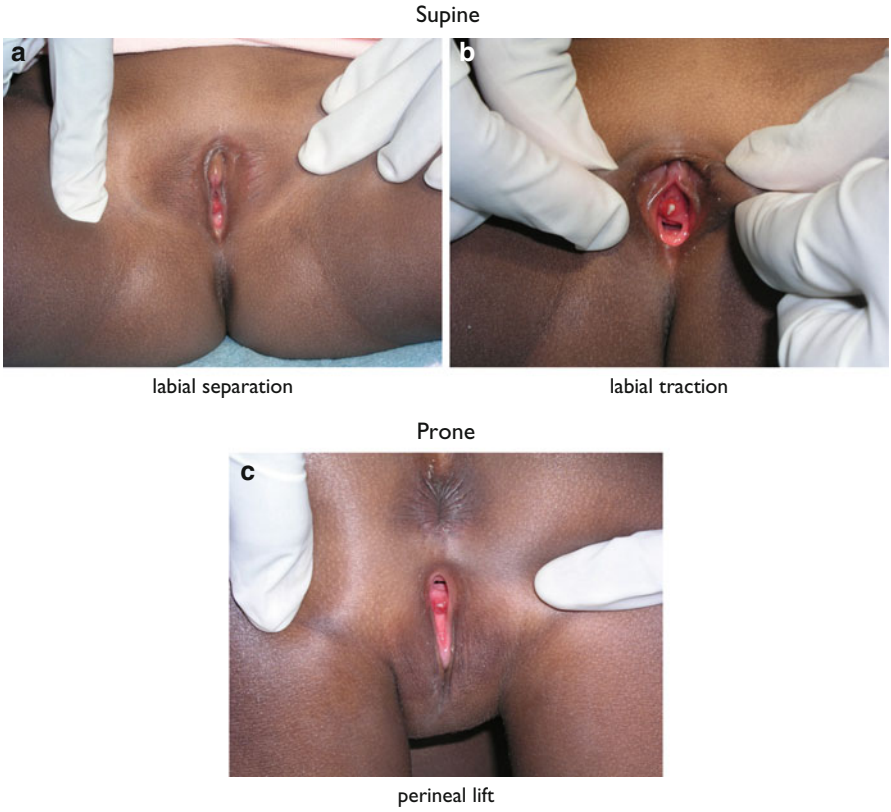

Fig. 23.1 Use of labial and overall positioning aids in viewing the vestibular contents. Figure is of a prepubertal female demonstrating the various techniques to visualize the vestibule. (**a**) Child is supine and the examiner is separating the labia. (**b**) Child is supine and examiner is placing traction on the labia toward the examiner and laterally toward thighs. Careful attention should be paid to the posterior fourchette or any labial adhesions as this technique can cause injury through excess tension. (**c**) Child is in the knee-chest prone position with the examiner pushing the perineum in the direction just lateral to the anus

hymen's posterior rim. The use of supine versus prone knee-chest positioning takes advantage of gravity to aid in putting tension on the hymen (Fig. 23.1). Abnormal findings in the supine position should be confirmed in the prone position.

In the older female child, the hymen has a natural redundancy and various techniques have been described to aid in its examination. A well-tolerated technique involves the use of a Foley catheter (Ferrell 1995; Persaud et al. 1997; Jones et al. 2003a) (Fig. 23.2). A less expensive method is to use Q-tips to stretch the hymen tissue so that the edges can be completely examined (Fig. 23.3).

The remainder of this chapter will explore each of the evidence types. Table 23.3 is a checklist that can be employed to avoid missing evidence.

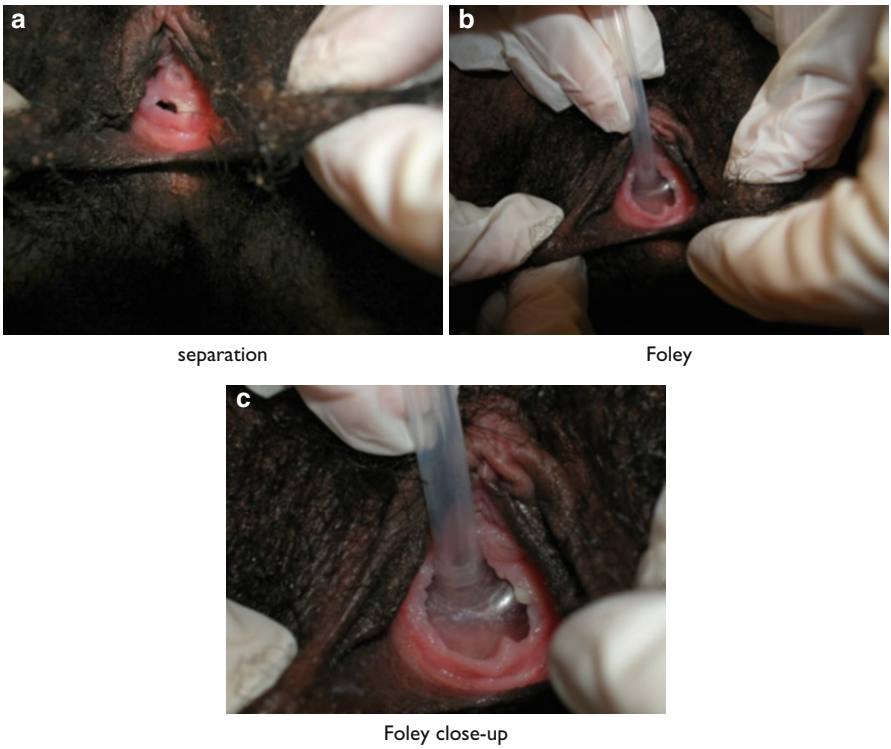

Fig. 23.2 Foley catheter technique. Examination of the pubertal hymen is often complicated by the redundancy of tissue. All images are of the same pubertal child in the supine position. (**a**) Separation alone often does not adequately expose the hymen. (**b**) and (**c**) Use of the Foley catheter technique is demonstrated. A Foley catheter is inserted into the vagina past the hymen, inflated, then gently pulled to distend the hymen. (**c**) Close-up of (**b**) with residual septum noted a 5 o'clock position

Video/Photographic Evidence

This type of evidence has high indicia of reliability. It includes images of the criminal act, images corroborating contact between suspect and victim, images showing injuries to the victim or suspect, and images of the crime scene.

We are entrenched in the digital age, and the ability to create pornography is within reach of most in our society. Images capturing the criminal act of child pornography are coming to law enforcement attention with greater frequency (Cooper 2011). Cameras are smaller and less expensive than ever before, and image production no longer requires specialized technical skills. Additionally, surveillance cameras are common both inside and outside homes.

Introducing pornographic images to children is a common grooming and desensitizing method used by sexual abusers (Kaufman et al. 1998; Prat and Jonas 2012). When able to, ask all children about being photographed, videotaped, or being shown pornographic images.

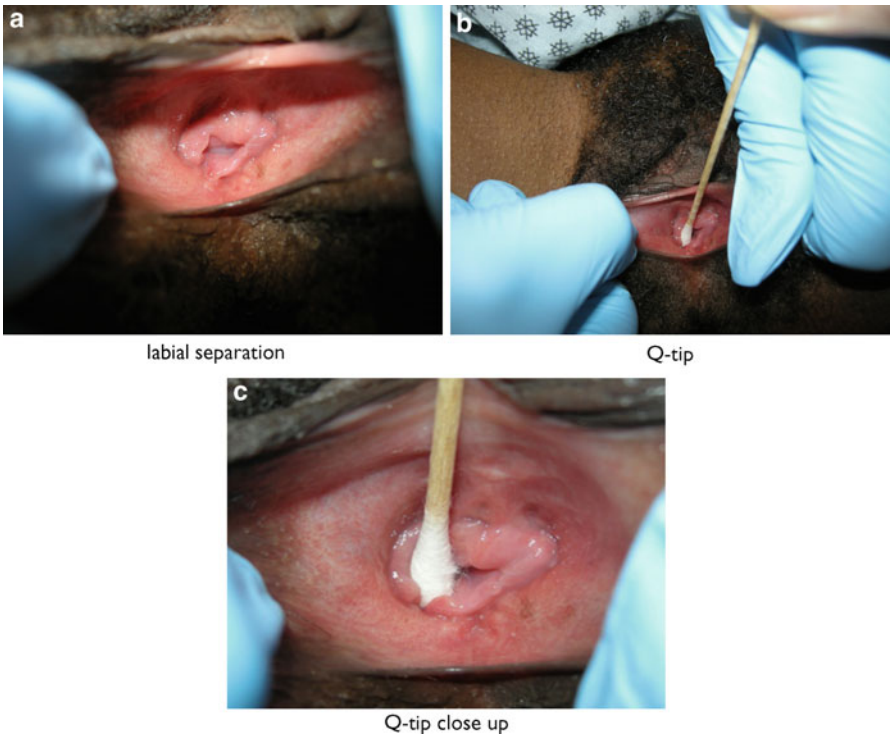

Fig. 23.3 Q-tip technique. Foley catheters are expensive and Q-tips can be used to resolve the tissue redundancy. (**a**) The labial traction technique to separate the labia. (**b**) and (**c**) The use of the Q-tip technique to highlight the transection of the hymen

Consider the existence of overt or covert surveillance. With the wider use of "nanny cams," abuse is being recorded with greater frequency. Traffic cameras, ATMs, security cameras, etc., are additional sources of imaging evidence. An attempt to recover these images should be made.

Photographs or videos should be taken of all alleged crime scenes even if temporally remote from the incident. Photograph implements suspected of being used in the abuse, including weapons, restraints, medications, objects used to inflict pain, etc. These images can be used to establish what the victim saw, to refresh the victim's memory, and to corroborate elements of the victim's statements or physical findings.

Biological Evidence: Pregnancy, DNA, Sperm, Seminal Products

Biological evidence should be sought from all involved persons, their clothing, and from the incident scene. The presence of foreign DNA, sperm, and semen where they do not belong can provide evidence of general contact or of a sexual act.

Table 23.3 Evidence checklist

Victim(s)
Statements
First reporter hearsay
Child Advocacy Center
Medical hearsay
Diary
Scene
Video/images used to desensitize
Items establishing proximity of perpetrator to victim
Overt or covert surveillance
Victim's tampons or menstrual pads
Items in contact with semen
Computers/phones used between perpetrator and victim
Messaging/e-mail
Voicemails
Telephone records
Photographs of all incident scene(s)
Lubricants or similar
Sex toys
(Child) pornography
Items used to bribe/seduce
Weapons
Restraints
Medical exam(s)
Trauma
Sexually transmitted infections
Pregnancy
Semen
Sperm
DNA
Toxicology
Trace evidence
Suspect
Trace evidence
Unique identifiers
Legal and illegal pharmaceuticals inventory
Toxicology
Prior bad acts showing system, motive, and intent
Check DHS records
Check criminal background

(*continued*)

Table 23.3 (continued)

Suspect statements
Formal
Pretext
Against interest
Witness(es)
Other victims of suspect
Examine all children in contact with suspect

DNA can provide donor identity, and biological evidence with DNA provides higher indicia of reliability than evidence without DNA.

Biological evidence is best found proximate to the incident time. DNA, sperm, and semen degrade quickly if deposited within a person, and evidence via "sexual assault kit" should be gathered quickly. The chance for recovery diminishes after 24 h in prepubertal children and after 72 h in adolescents (Palusci et al. 2006; Christian 2011; Young et al. 2006). In the deceased child, where sexual abuse is suspected, collection should occur regardless of time delay (Collins and Bennett 2001).

Pregnancy provides definitive evidence of a sex act and paternity. All females with a sexual maturity rating of III or above should be tested for pregnancy both acutely and 2 weeks after a sexual act. Paternity testing of conception products should be pursued in every pregnancy thought to be the result of sexual abuse or assault.

Samples of biological materials should be obtained from body areas likely to contain evidence and from contact areas identified by the victim. The use of nylon versus cotton swabs helps with subsequent efficient elution for DNA typing (Benschop et al. 2010). The mouth, penis or vagina, perineum, and anus are sites often sampled routinely, but consider adding routine collection from the "3 B's": breast, "belly button," and "butt crack" (gluteal cleft). The posterior fornix of the vagina in one study was the most sensitive site sampled (Astrup et al. 2012). An older study suggests longer sperm survival in the cervical os (Morgan 2008). All areas which were licked, sucked, or bitten by a perpetrator should also be sampled (Myers and Adkins 2008). Particular attention should be paid to the victim's fingernails and suspect's penis and fingernails. Lastly, additional areas to sample can be identified by fluorescence under ultraviolet light (Wawryk and Odell 2005).

All surfaces, clothing, and other materials possibly in contact with saliva or ejaculate/semen should be collected or sampled. Semen in the dry state on fabrics can last a long time (Lachica and García-Ferrer 1998). As above, timely sampling increases successful recovery.

Laboratory testing of collected samples often proceeds with biochemical screens for semen looking for acid phosphatase, prostatic-specific antigen (PSA or p30) (Sato et al. 2002; Levine et al. 2004), semenogelin (Pang and Cheung 2007;

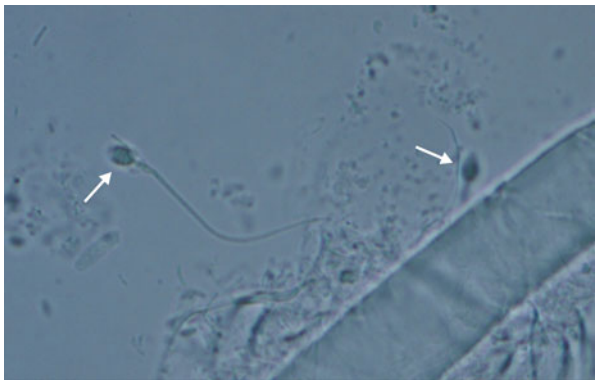

Fig. 23.4 Human sperm from vaginal saline wet mount (*arrows*)

Sato et al. 2007), or MHS-5 (Herr et al. 1986; Keil et al. 1996). This is followed by microscopy (saline wet mounts, gram stain, PAP stain, Christmas-tree stain) (Fig. 23.4) (Romero-Montoya et al. 2011). Lastly, testing is performed for the presence of male and female DNA by Y-STR profiling, Fluorescence in situ hybridization (FISH), and/or DNA STR profiling (Romero-Montoya et al. 2011; Mayntz-Press et al. 2008; Delfin et al. 2005; Johnson et al. 2005; Hall and Ballantyne 2003; Sibille et al. 2002; Tsuji et al. 2001; Prinz and Sansone 2001; Dekairelle and Hoste 2001; Rao et al. 1995; Collins et al. 1994; Murray et al. 2007; Collins et al. 2000; Cina et al. 2000a, b; Farmen et al. 2012). The absence of semen/sperm findings after a history of sexual contact may result from the lack of ejaculation, a vasectomy, condom use, or sperm/semen degradation before evidence collection.

In familial abuse cases, a finding of foreign somatic DNA needs careful interpretation due its prevalence in the victim's environment. In nonfamilial and stranger assault cases, where the victim is not supposed to have had contact with the perpetrator, finding foreign somatic DNA can help confront alibis.

Suspect Statements

Collect and consider all statements of suspects from all sources. When suspects make voluntary, noncustodial statements against their interests, whether by admissions or confessions, those statements are generally admissible at trial as an exception to the usual evidentiary rule of excluding hearsay /see Federal Rules of Evidence 804(3)(A) and (B)/. Law enforcement, with the victim's cooperation, should examine all of the victim's e-mail accounts, personal webpages, text messages, written letters, and diaries for communication which would tend to incriminate the suspect. Preserve all statements which indicate lustful predisposition, solicitation, or coercion toward silencing the victim. Gifts and special treatment of the victim should be documented, and their existence can help to counter later false assertions of a revenge motive by the victim. Whenever such communications

are identified by laypersons, notify the law enforcement agency involved so they may recover the information to maintain the integrity of the evidence.

One technique used by law enforcement to document voluntary statements about a suspect's relationship and actions with a victim is through pretext calling. This technique is used before a victim's allegation becomes generally known. It involves either the victim, or someone known to the victim and suspect, calling the suspect while the call is audio recorded. The caller engages the suspect about their prior sex acts or threatens imminent disclosure of the acts and the suspect's responses are recorded. Examples include a victim calling to say, "I'm pregnant, what are we going to do?" "My mom saw us and she is mad," "My mom found my diary where I wrote about having sex with you," or "I don't think what we are doing is right," etc. Examples of nonvictim, pretext calls include, "Do you know what your daughter just told me?" "Your granddaughter is pregnant," or "I found your son's diary."

Witnesses

Although it is rare for a sexual perpetrator to victimize a child with witnesses, it does occur. The most common occurrence is among other victims or other perpetrators. Consider all child contacts and former child contacts of an alleged perpetrator as either potential witnesses or former victims. All children should be asked about being potential witnesses. Maintaining secrecy is common, and other victims may remain silent unless asked. Child witnesses should be interviewed by those with expertise and experience in interviewing children.

Sexually Transmitted Infection (STI)

The diagnosis of an STI suggests that a child has experienced sexual contact and may provide source identification. The broader context of age, parties' relationship, and situation is needed to differentiate nonsexual, nonconsensual, or abusive sexual contact. The main forensic considerations in evaluating a child with possible STI are deciding whom to test, confirming the diagnosis, surveying for other STIs, and identifying the transmission mode(s) and source(s).

Children with STIs often present with no symptoms, nonspecific symptoms (sore throat, pruritus, dysuria, painful defecation, etc.) and/or nonspecific signs (odor, inflammation, skin rash or ulcers, warts, discharge, or bleeding) (Girardet et al. 2009). These signs and symptoms in the proper context should prompt an exploration for STIs. See Table 23.4 for contexts where STI testing is indicated (Atabaki and Paradise 1999; Pickering 2012). Table 23.5 outlines a testing and prophylaxis strategy based in part on the 2010 CDC (Workowski et al. 2010) and the AAP Committee on Infectious Diseases (Pickering 2012) recommendations. Local STI prevalence rates and antibiotic susceptibility can be used to further modify these recommendations.

Overall, the prevalence of STI in the pediatric population is low and reflects the relative prevalence of STI in the adult population (Pickering 2012;

Table 23.4 Children suspected of being sexually abused who should be tested for STIs (Kellogg et al. 2005; Workowski et al. 2010)

History of potential contact with infected secretions (ejaculate, oral or vaginal secretions, and blood)
History of any other household member with an STI
History of child sexual abuse albeit less than clear and detailed, and there is a need for antibiotics to treat another infection that may prevent STI recognition
History of prior consensual sexual contact
History of suspect having STI
Parental or patient concern regardless of any other indicator
Physical findings of oral or anogenital trauma, inflammation, discharge, or other STI
Physical examination of sexual maturity rating > Tanner III

Table 23.5 Suggested STI testing and prophylaxis strategies

Acute (incident < 72 h)
Urine (dirty) – NAAT for GC/CT; wet mount for Trichomonas
Blood – RPR or VDRL, HIV and (Hepatitis B, if unvaccinated)
Pharynx – GC culture
Urethra (male) – GC/CT culture
Vagina/cervix (cervix preferred if Tanner III+) – GC/CT culture
Vagina – wet prep/KOH – Trichomonas culture (if available)
Rectal – GC/CT culture
Ulcer – scrape base and submit for viral culture
Post-exposure prophylaxis:
Bacterial: Tanner III and above, and symptomatic Tanner I & II
If ≥ 45 kg
Ceftriaxone 250 mg IM × 1 or cefixime 400 mg PO x 1
Azithromycin 1 g PO × 1 or doxycycline, if > 8 yo, 100 mg PO BID x 7 days
Metronidazole 2 g PO × 1
If < 45 kg
Ceftriaxone 125 mg IM
Azithromycin 20 mg/kg (max 1 g) PO × 1 or erythromycin base or ethylsuccinate 12.5 mg/kg PO QID × 14 days
Metronidazole 5 mg/kg PO TID × 7 days; max 2 g
HIV antiviral – call CDC HIV hotline 1-888- HIV-4911 to get latest updates and guidelines for the specific case
Hepatitis B: Begin or complete Hepatitis B virus immunization series if not fully immunized
Tetanus toxoid: Begin or update as if tetanus prone wound
Pregnancy: levonorgestrel, ulipristal, or Yuzpe method (consider up to 5 days post incident)
Acute + 2 weeks
Pharynx – GC culture
Urine – NAAT GC/CT probe
Vagina/cervix – GC/CT probe
Rectal – GC/CT culture

(*continued*)

Table 23.5 (continued)

Acute + 6 weeks
Blood – RPR or VDRL and HIV
Acute + 3 months
Blood – RPR or VDRL, HIV and (Hepatitis B, if unvaccinated)
Acute + 6 months
Blood – RPR or VDRL, HIV and (Hepatitis B, if unvaccinated)
Notes:
If timing is unknown, start as if presenting for 2-week visit
Note you can batch the CT culture from two sources (vagina/cervix and rectal) to save cost

NAAT = nucleic-acid amplification test
GC = gonococcus
CT = *Chlamydia trachomatis*

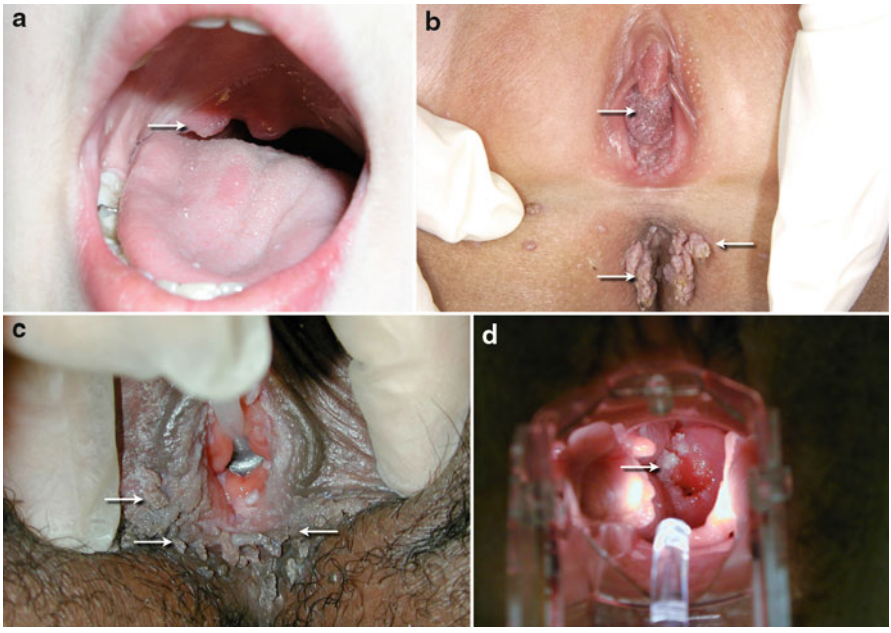

Fig. 23.5 Condyloma acuminata (*arrows*) (**a**) soft palate (**b**) prepubertal female with periurethral and perianal condyloma accuminata (**c**) pubertal female with numerous perineal condyloma. Note Foley catheter intravaginal to exposure posterior rim of hymen (**d**) puberal female with lighted plastic speculum placed in vagina with candyloma of uterine cervix

Workowski et al. 2010). Culture technique remains the gold standard but is inherently insensitive and requires more intrusive sampling (vaginal, cervical, or urethral swabs). The low prevalence rate of STI in prepubertal children has an adverse effect on the positive predictive value of any screening test (Girardet et al. 2009). In an effort to promote a less intrusive and cost-effective visit, the use of

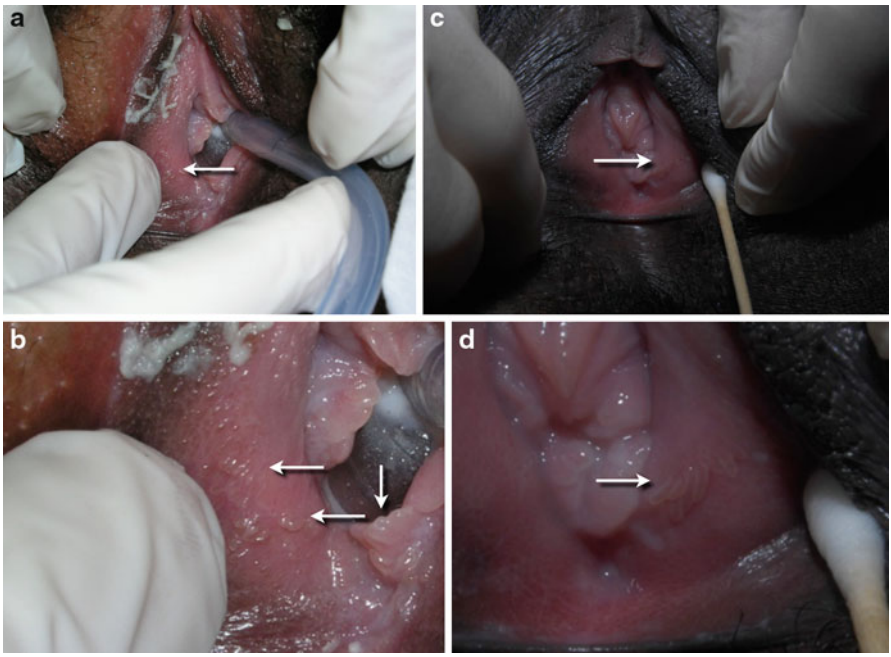

Fig. 23.6 Vestibular papillomatosis (*arrows*). (**a**) Overview of pubertal female with Foley catheter in the vagina and distending the hymen which has a transection between 7 and 9 o'clock. (**b**) Close-up of (**a**) and (**c**) Overview of pubertal female with Q-tip moving left labia minora laterally. (**d**) Close-up of (**c**)

nucleic-acid amplification tests (NAATs) for gonorrhea, Chlamydia, and other infections has become more common. Positive NAAT results require confirmation with a probe for a different part of the bacterial genome or by subsequent culturing for the organism directly (Workowski et al. 2010).

To acquire an STI, a child must have contact with infectious material which generally includes vertical and horizontal modes of transmission. Vertical transmission involves both transplacental and perinatal inoculation. Horizontal transmission can be from either sexual or nonsexual contact with infectious material. Nonsexual transmission includes autoinoculation (e.g., a nongenital site to a genital site of same person), heteroinoculation (e.g., contact between persons during diapering or other hygiene activities), and by fomites contaminated with infectious material.

All STIs have vertical modes of transmission, and their diagnosis in the neonatal period is nonspecific for sexual abuse. Human papillomavirus (HPV) (Myhre et al. 2003a) and *Chlamydia trachomatis* (Bell et al. 1992) can have long asymptomatic latencies after acquisition, and their diagnosis should be interpreted cautiously in children up to 3 years old (Fig. 23.5). Evidence of STI after appropriate treatment with antibiotics should raise the concern for a horizontal mode of contact with infectious secretions.

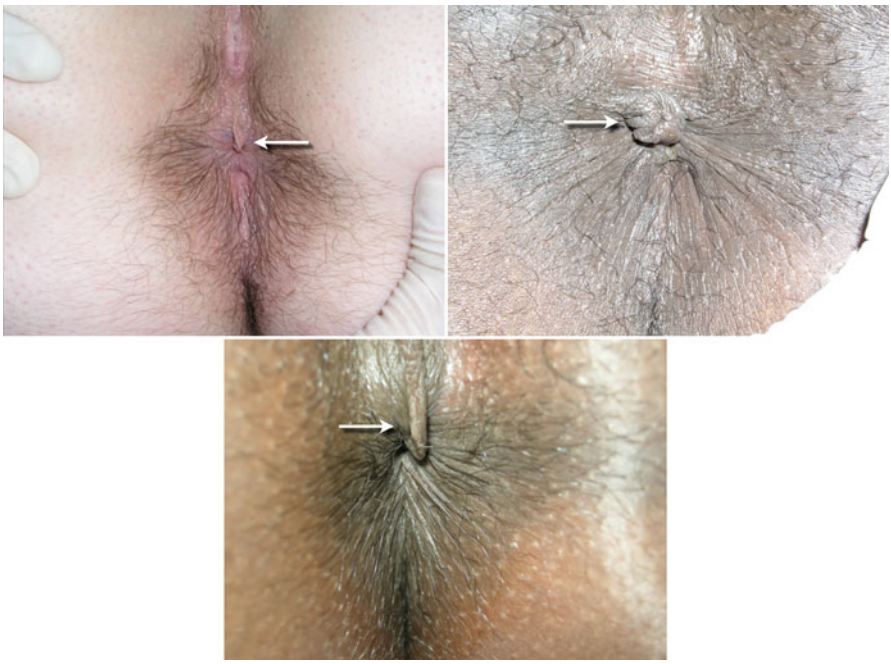

Fig. 23.7 Midline perineal body protrusion (*arrows*) is a common normal variant of the posterior perineum seen in both genders, but more common in females. It is often misdiagnosed as an anal skin tag or scar from trauma

The issue of fomite transfer was given more consideration in the older literature when the sexual abuse of a child was not as well recognized. There are case reports of STI survivability on various fomites, but infectivity does not have clear scientific evidence (Kramer et al. 2006; Reading and Rannan-Eliya 2007; Novak et al. 1995; Lo et al. 2010; Srivastava 1980; Dayan 2004; Gutman et al. 1993).

In the normal state, the pharynx and anogenital area should be without inflammation or signs of infection. There are some anatomic variants that may cause confusion with STIs. These include penile pearly papules (Watanabe et al. 2010; Körber and Dissemond 2009; Agrawal et al. 2004; Neri et al. 1997; Oates 1997; Neinstein and Goldenring 1984; Rehbein 1977), vestibular benign papillomatosis (Sarifakioglu et al. 2006; Sangueza and Saenz 2007; Pao et al. 1994; Prieto et al. 2004; Chan and Chiu 2008), midline perineal body protrusions (Kayashima et al. 1996; Cruces et al. 1998; Miyamoto et al. 2004; Hernandez-Machin et al. 2007; Kim et al. 2007; Mérigou et al. 1998; Fleet and Davis 2005; McCann et al. 1989; Konta et al. 2000; Patrizi et al. 2002), diastasis ani, median raphe, anal tags, and posterior anal protrusions (Leung 2010) (Figs. 23.6–23.10).

There are many nonsexual causes of infection of the pharynx and anogenital area. As a group, these infections when present are nonspecific in defining sexual abuse.

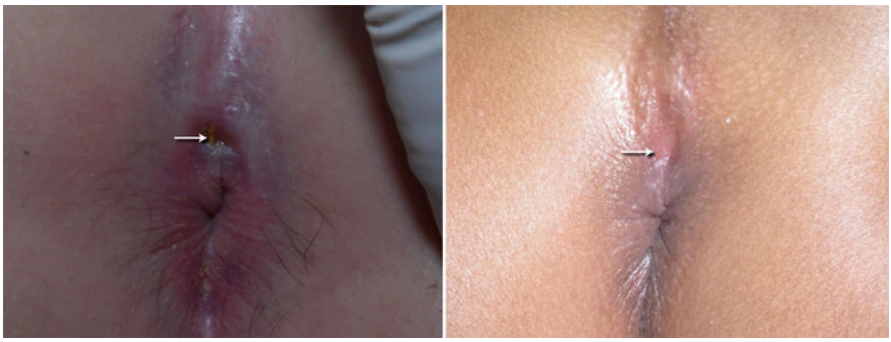

Fig. 23.8 Diastasis ani (*arrows*) is an anatomical variant reflecting the incomplete embryological merging of the underlying midline structures

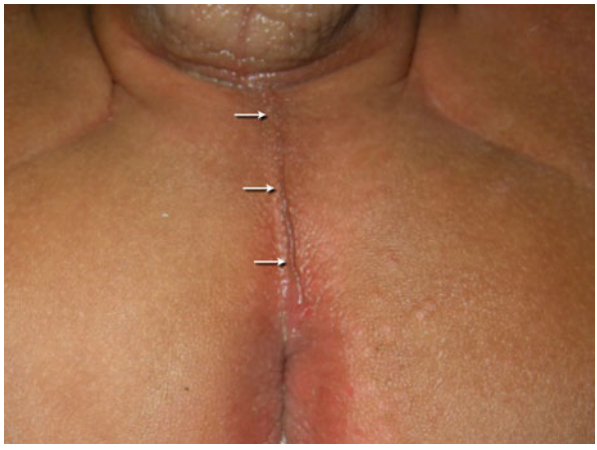

Fig. 23.9 Median raphe (*arrows*) is a common anatomical variant seen in both genders but more common in males. In males, this ridge of skin can extend all the way to the base of the penis

These include group A streptococci, *Escherichia coli* and other enteric bacteria, *Molluscum contagiosum*, lice, scabies, crabs, and herpes simplex virus (HSV) (Fig. 23.11).

The diagnosis of HIV, Hepatitis B or C, *Treponema pallidum* (syphilis), *Neisseria gonorrhoea*e, *Chlamydia trachomatis*, *Trichomonas vaginalis*, human papillomavirus (HPV), or herpes simplex virus (HSV) outside the neonatal period should prompt consideration of sexual contact and begin a search to identify the source. While witnesses and the child's statements can be used to direct this investigation, testing of all significant contacts and caregivers may be necessary. Suspects transmitting infection may test negative if treated previously with an antibiotic, if time elapsed and infection naturally cleared, or if the test

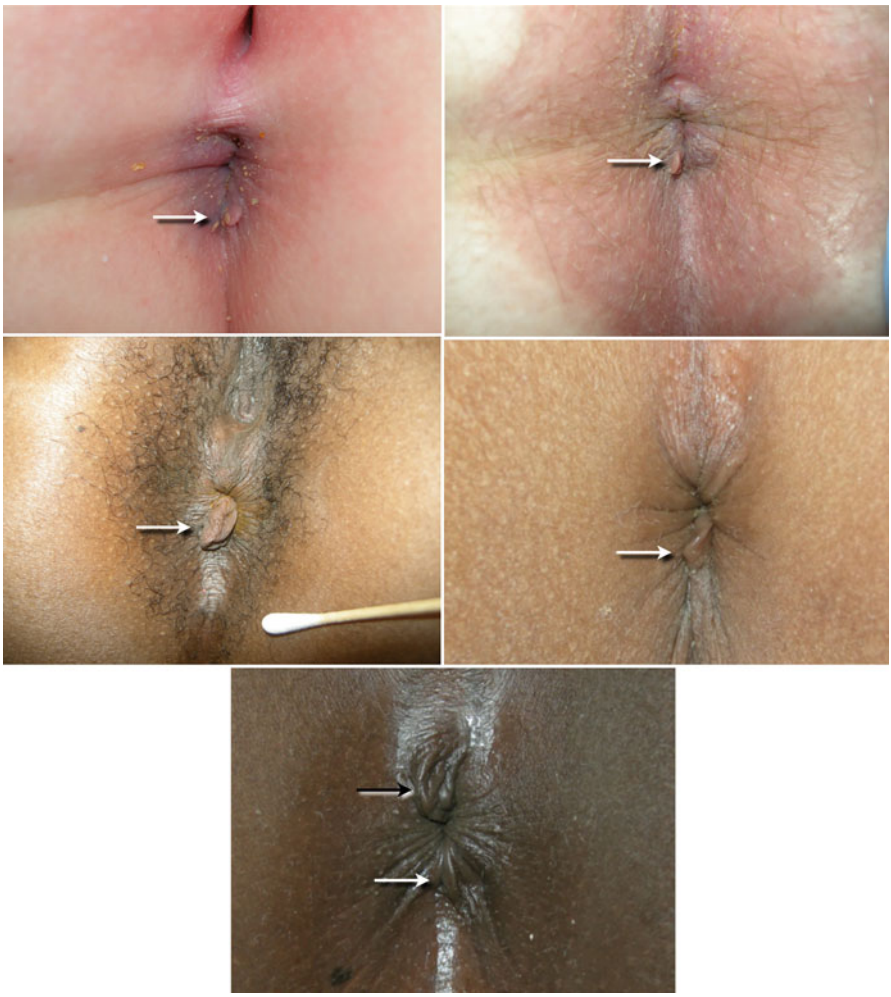

Fig. 23.10 Anus tag posterior (*white arrows*). Anal tags in the midline are generally nonspecific in defining prior trauma or sexual contact. *Black arrow* with *white shadow* is a midline perineal body protrusion

result was falsely negative. The index patient should also be tested for all other STIs. Table 23.1 and 23.5 shows how the various STIs when found are categorized.

The subset of HIV, Hepatitis B, *Treponema pallidum* (syphilis), *Neisseria gonorrhoea*e, *Chlamydia trachomatis*, and *Trichomonas vaginalis* with rare exception are sexually transmitted and, when found, indicate intimate contact with infected secretions (Pickering 2012; Workowski et al. 2010).

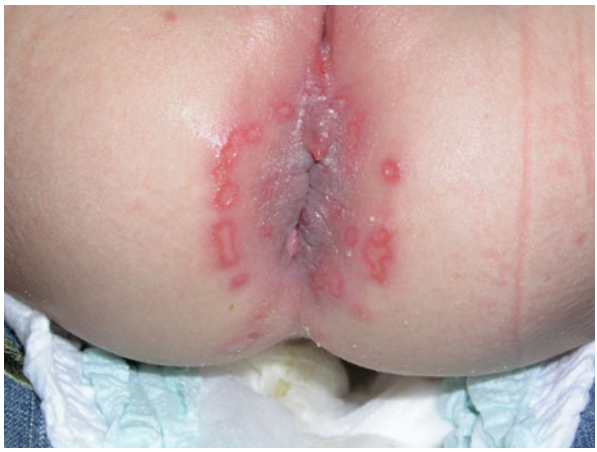

Fig. 23.11 Herpes simplex. Image is of the perianal area of a prepubertal female depicting numerous ulcers which were painful. Confirmation of the diagnosis requires scraping of the ulcer base and submission for testing

Advancing DNA technology has seen various STIs' genomes used to understand the epidemiology of STIs. The forensic application of this technology is in its infancy but has been used in limited cases involving HIV (Scaduto et al. 2010). Epidemiologists are using similar techniques for *Neisseria gonorrhoea*e (Abu-Rajab et al. 2009) and *Chlamydia trachomatis* (Yang et al. 1993) which may eventually lead to forensic uses.

Post-exposure prophylaxis (PEP) for infection is available to victims who present within 72 h of exposure. Bacterial post-exposure prophylaxis is reserved for victims who have a sexual maturity rating of III or greater. Females with lesser maturity ratings have a lower risk of acquiring infection and of having disseminated infection, and have a greater risk from the effects of bacterial prophylaxis (Workowski et al. 2010). HIV PEP may be warranted for all victims within 72 h of a sexual assault causing anogenital injury or when the suspected perpetrator has risk factors for having HIV (Workowski et al. 2010). Hepatitis B PEP by vaccination is recommended for victims without previous vaccination (Workowski et al. 2010).

Trauma

The scientific study of anogenital trauma began with descriptions of the trauma or trauma residua in children where other evidence existed to diagnose sexual abuse. This led to an elaboration of findings that were purported to define sexual abuse. As is often repeated, correlation is not causation. It took researchers to revisit these findings by comparing anogenital examinations in children screened as nonabused (McCann et al. 1989, 1990b; Berenson et al. 1991; Kellogg and Parra 1991;

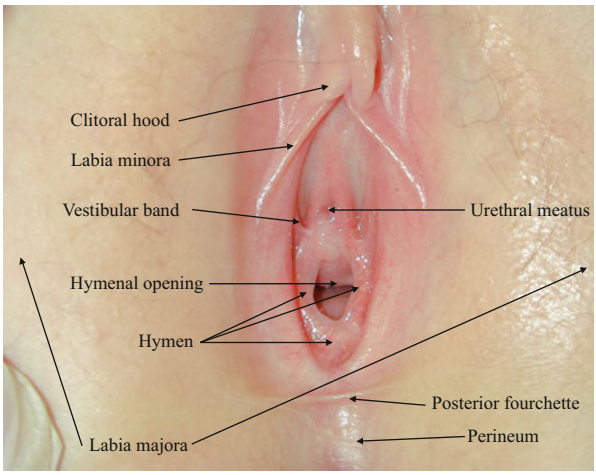

Fig. 23.12 Normal prepubertal female anatomy

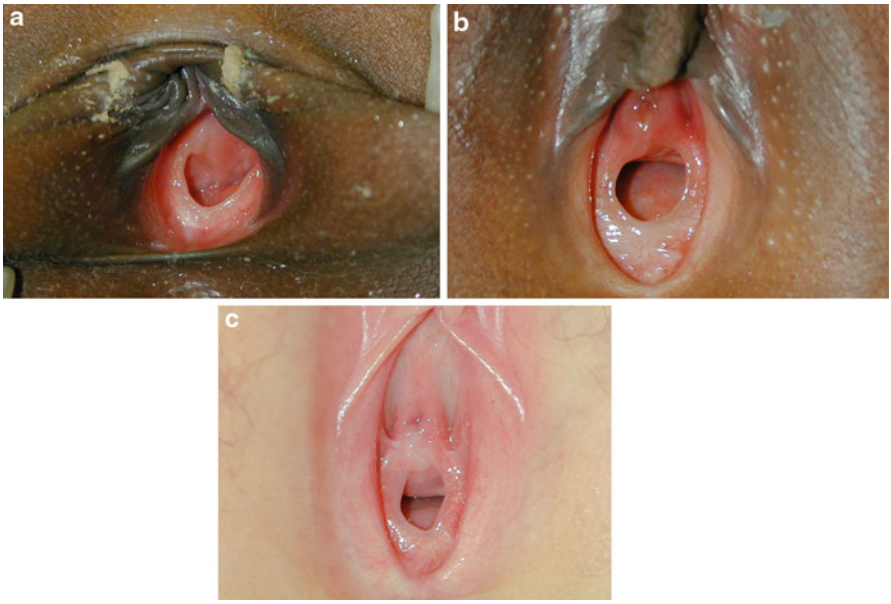

Fig. 23.13 Common hymen shapes. (**a**) Crescentic shape with the hymen inserting anteriorly at the 11 o'clock and 2 o'clock positions (*arrows*). (**b**) and (**c**) Annular-shaped hymen where the innermost ring forms a complete circle

Gardner 1992; Berenson et al. 1992, 1993; Berenson 1993, 1995; McCann et al. 1996; Myhre et al. 2001; Berenson and Grady 2002; Heger et al. 2002a; Myhre et al. 2002, 2003b; Adams et al. 2004). Normal and nonspecific findings have reached general consensus especially for the younger children. Given children's tendency to

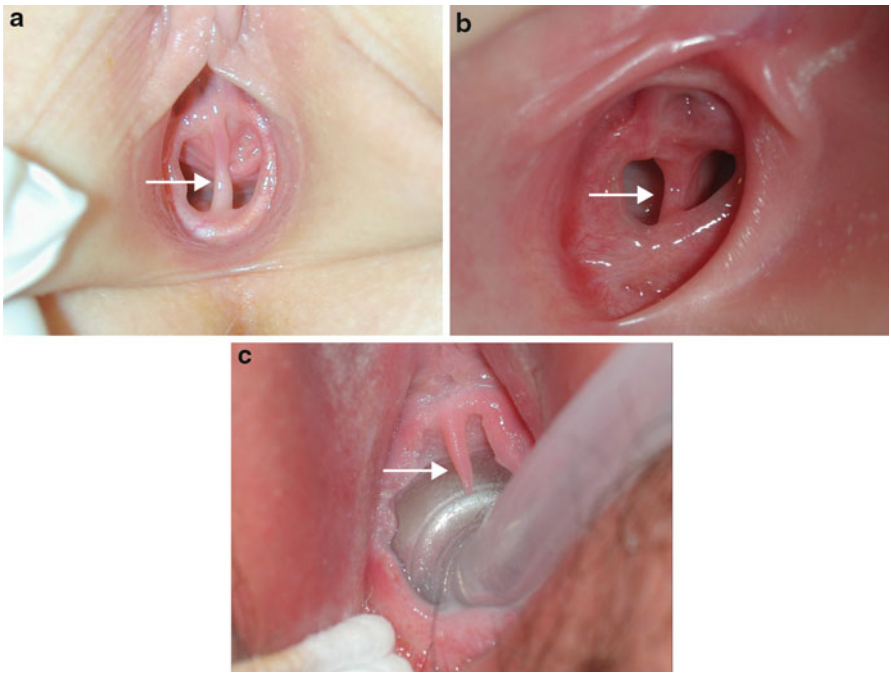

Fig. 23.14 Uncommon hymen shapes. (**a**) and (**b**) Vertical septa (*arrows*) creating two opening through the hymen into the vagina. (**c**) The hymen being distend with Foley catheter technique and with a septal remnant noted at 12 o'clock (*arrow*)

secrecy about sexual abuse and consensual sex and reluctance to be examined, it is more difficult to screen for nonabuse and define sexual abuse as the child ages.

In females, the genitalia include the labia majora, labia minora, posterior fourchette, clitoral hood, clitoris, vestibule, fossa navicularis, urethra, and hymen (Fig. 23.12). Normally the hymen has a single opening, usually anteriorly displaced, with the two most common configurations being crescentic and annular (Fig. 23.13). Occasionally, two or more openings occur congenitally (Fig. 23.14). The level of estrogen changes from newborn to latency age to puberty. Higher levels of estrogen are associated with hymens that are thickened and more elastic and cause natural lubrication from the induction of the mucous glands.

The following findings are found in the nonabused population and should not be confused with trauma residua: hymen mounds (Fig. 23.15), linear vestibularis or midline avascular areas (Fig. 23.16), median raphe (Fig. 23.9), diastasis ani (Fig. 23.8), periurethral or vestibular bands (Fig. 23.17), minimal or no visible hymen in the superior half of the vestibule, pigmentation of the labia or perianal area, labia minora adhesions (Fig. 23.18), labia minora tags (Fig. 23.19), and prominence of the urethral opening (Fig. 23.20). Urethral prolapse and perianal

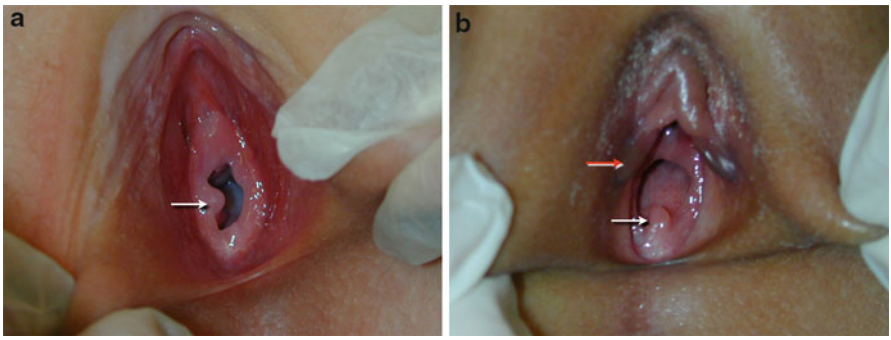

Fig. 23.15 Hymen mounds (*white arrows*) are a normal variant as is the asymmetrically pigmented labia minora (*red arrow* with *white shadow*)

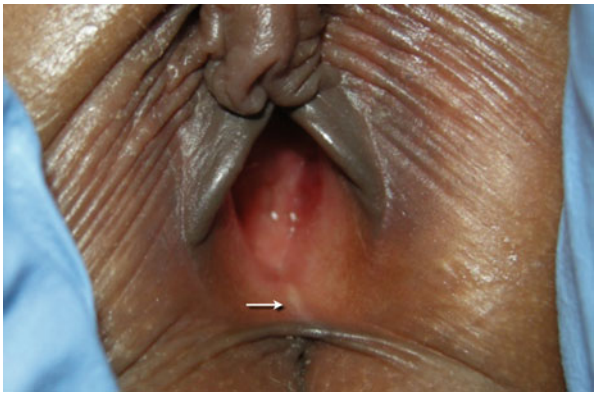

Fig. 23.16 Linear vestibularis represents a hypopigmented to avascular area that runs in the 6 o'clock position from the base of the hymen to the posterior fourchette. It is a nonspecific finding that is sometimes misdiagnosed as a scar from trauma

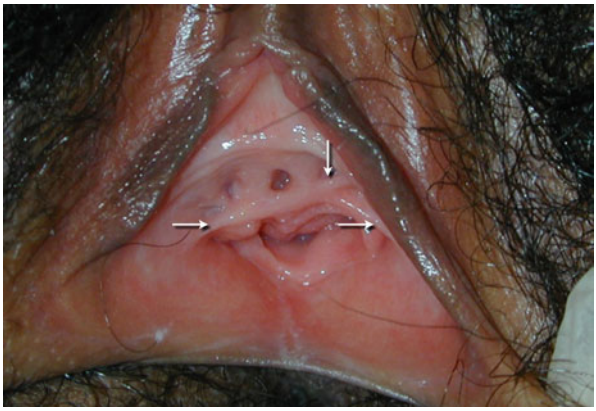

Fig. 23.17 Vestibular bands (*arrows*) are ligaments that extend from the vestibular walls to the urethra (*arrows*) and also to various points on the hymen especially posteriorly. These bands are normal findings that sometimes are misdiagnosed as scars

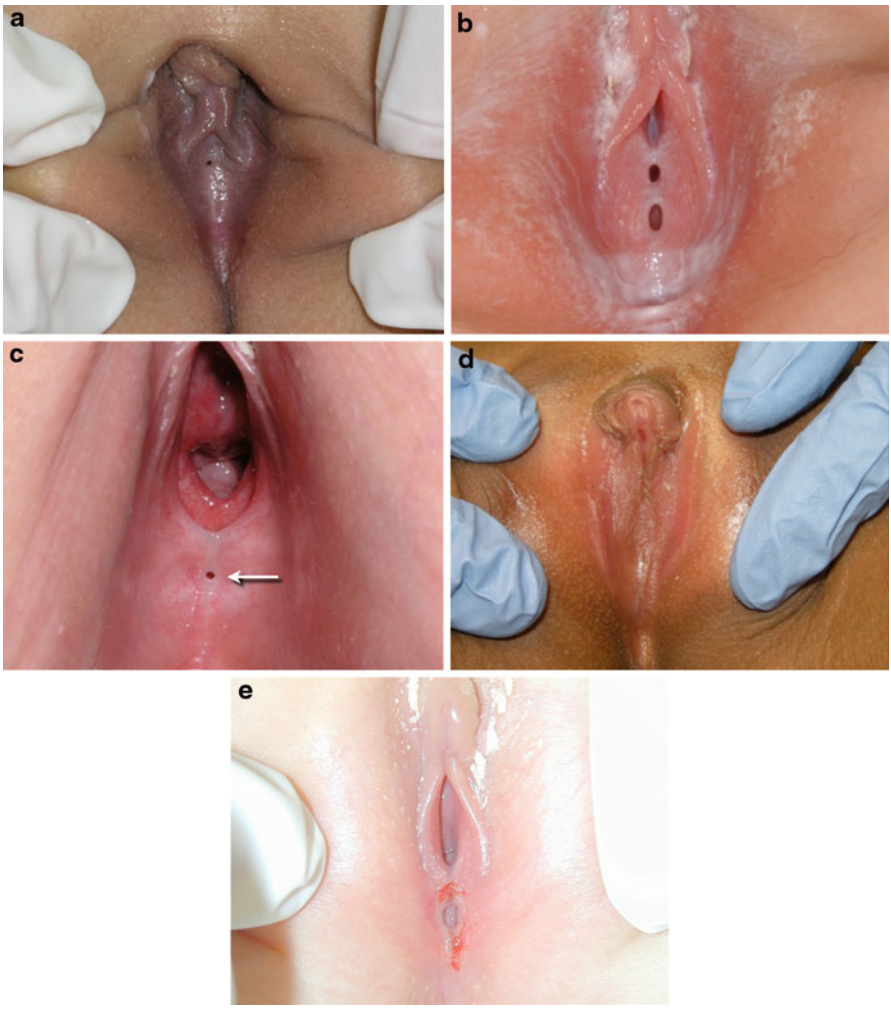

Fig. 23.18 Labia minora adhesions are thought to occur as a consequence of labia irritation, inflammation, or trauma in combination with low levels of estrogen. They are seen almost exclusively in the prepubertal latency age female. The degree of adhesion can be such that the vestibule is almost completely covered (**a**, **b**, **d**, **e**) or just partially (**c**). In (**c**), the *arrow points* to a dehiscence with in the posterior labia minoral adhesion. Most adhesions are treated successfully with topical estrogen creams

venous pooling can mimic bruising (Figs. 23.21–23.22). Blanching to compression, or having the child walk around, can help to differentiate venous pooling.

The impact of tampon usage has had limited study with some agreement that there is a possible association with hymen clefts but not hymen transections

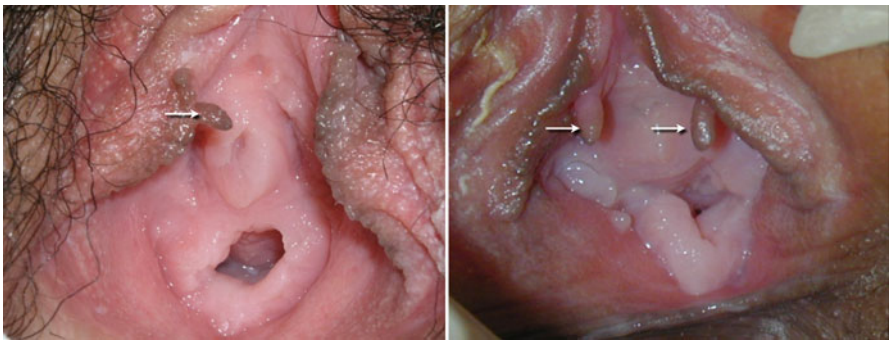

Fig. 23.19 Labia minora tags (*arrows*) reflect an uncommon normal anatomic variant. They can be confused with traumatic laceration of the inferior labia minora during blunt penetrating trauma (not depicted)

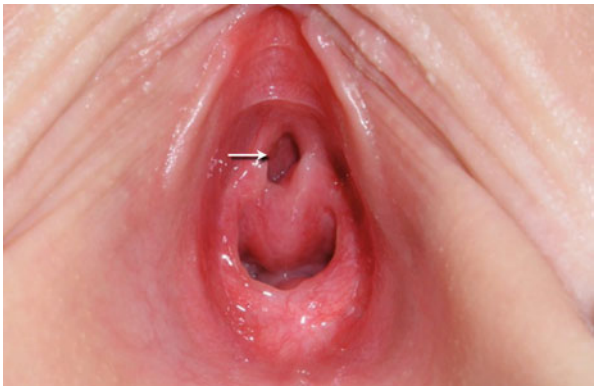

Fig. 23.20 Prominent urethra (*arrow*). This finding is often misdiagnosed as a urethral dilation. Urethral dilation is differentiated by the continuous leak of urine that accompanies these findings, but it is not present in this image

(Emans et al. 1994; Goodyear-Smith and Laidlaw 1998; Edgardh and Ormstad 2002; Adams et al. 2004). Hymen clefts have been described in the nonabused pubertal population and therefore are nonspecific in defining abuse.

Failure of midline fusion, fissures of the anal verge, anal dilatation, (McCann et al. 1996), vulva vitiligo, and lichen sclerosus et atrophicus (Isaac et al. 2007) represent abnormal findings that are nonspecific in defining abuse (Figs. 23.23–23.27). Anal Crohn disease can mimic injury (Fig. 23.28). Deep notches of the hymen and posterior hymenal narrowing have been variously attributed to previous trauma, but at present the science is indeterminate, making these findings also nonspecific.

Until recently, a normal hymen has been used worldwide to define female virginity. The first opinion in the literature that challenged this concept did not

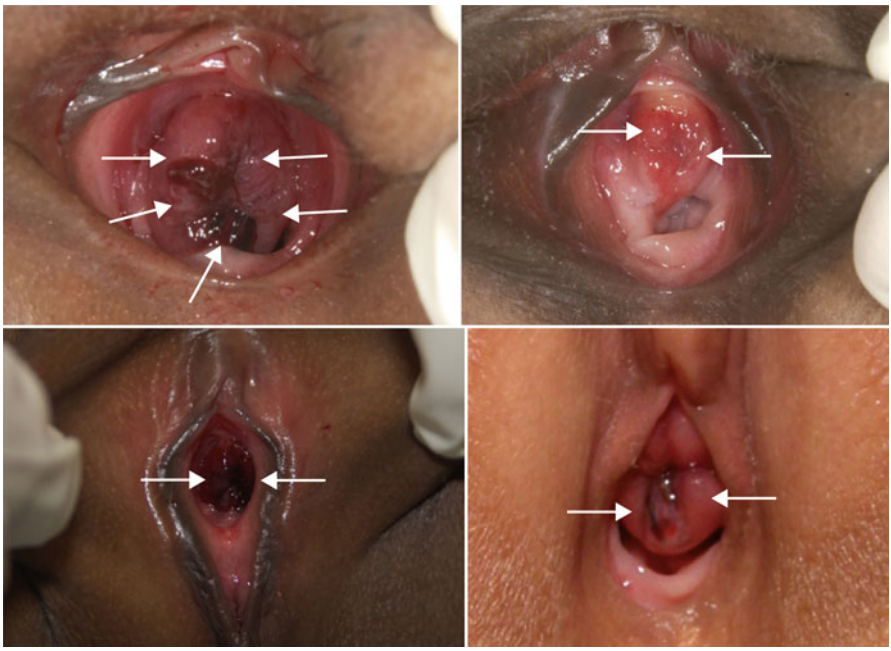

Fig. 23.21 Urethra prolapse (*red arrows*) occurs as a consequence of urethra irritation or infection in females along with low levels of estrogen. It is seen mostly in the black race but has been described in other races. Most urethra prolapses are treated successfully with topical estrogen creams

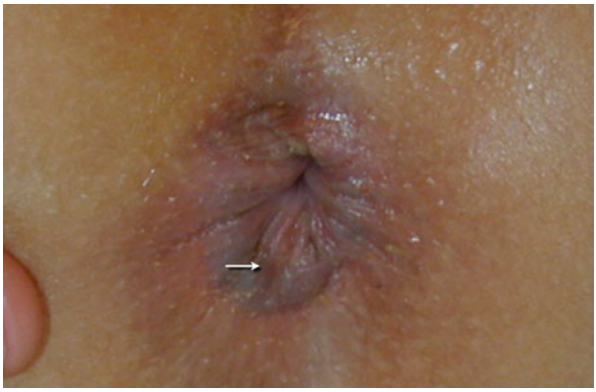

Fig. 23.22 Venous pooling of the hemorrhoidal vessels (*arrow*) creates a bluish tinge to the perianal and anal skin. This finding is often confused with bruising and can be differentiated by having the child stand and walk around

appear until 1978 when Underhill and Dewhurst wrote their editorial, "The doctor cannot always tell. Medical examination of the 'intact' hymen" (Underhill and Dewhurst 1978). The same year, Whitley published a survey of 100 women about their first coital experience challenging the necessity of pain and bleeding (Whitley 1978).

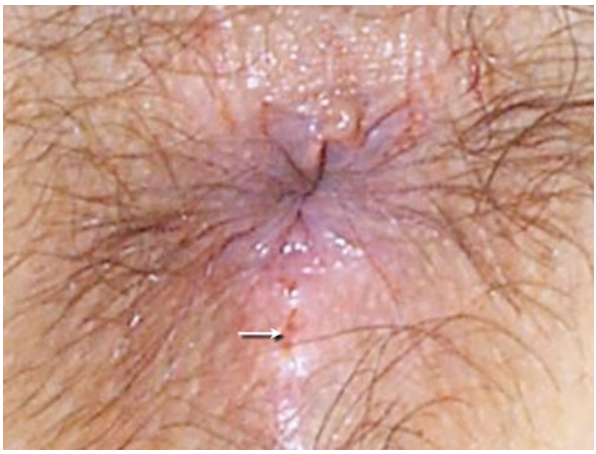

Fig. 23.23 Anal fissures (*arrow*) reflect superficial breaks in the anal skin that are caused by constipation, anal sphincter tone, irritants, inflammation, trauma, and immune factors

In that survey, 32 % of the women denied pain and 44 % reported no bleeding with their first coitus. In 1989, Muram used perpetrator confessions to categorize the findings in 31 female victims. While the article's focus was on abnormal findings, in 18 of the 31 victims in which the perpetrator admitted vaginal penetration, 7 of the 18 victims had normal or nonspecific findings (Muram 1989). In 1994, Adams and Harper used perpetrator convictions for sexual abuse to study the findings in 236 victims (Adams et al. 1994): 77 % of the victims had normal or nonspecific hymenal or vaginal examinations, and 99 % had normal anal examinations. In 2002, Heger and colleagues studied 2,384 children referred for possible sexual abuse and found that 96.3 % had normal examinations (Heger et al. 2002b). After isolating those children who provided a history of penetration, 94 % of the females and 99 % of the males had normal findings on examination. The next blow to a normal examination defining the virginal state came in Kellogg and colleagues' 2004 study of pregnant adolescents (Kellogg et al. 2004). These authors examined 36 pregnant adolescents and noted only 2 of them had definitive findings of sexual penetration. It is accepted that a normal anogenital examination cannot be used to disprove other credible evidence of sexual abuse. A child can undergo a normal examination despite having been sexually abused (Table 23.6).

There are three categories of trauma to the anogenital area: accidental, nonconsensual, and consensual injuries. Accidental anogenital trauma is usually a consequence of straddle injuries (Fig. 23.29), sharp penetrating injuries (Fig. 23.30), rapid leg abduction, or rapid, severe abdominal or pelvic compression. Forcible retraction of the penile foreskin by caregivers ignorant of proper penile hygiene can cause frenulum breve (Fig. 23.31). Falling toilet seats can cause bruising and injury to the penis (Gazi et al. 2001; Widni et al. 2011). Straddle injuries (Dowd et al. 1994) occur when a child impacts the perineum with their legs straddling an object such as a bicycle bar, balance beam, or cabinet door. These injuries usually cause injury at the site of bony prominences including the pubic

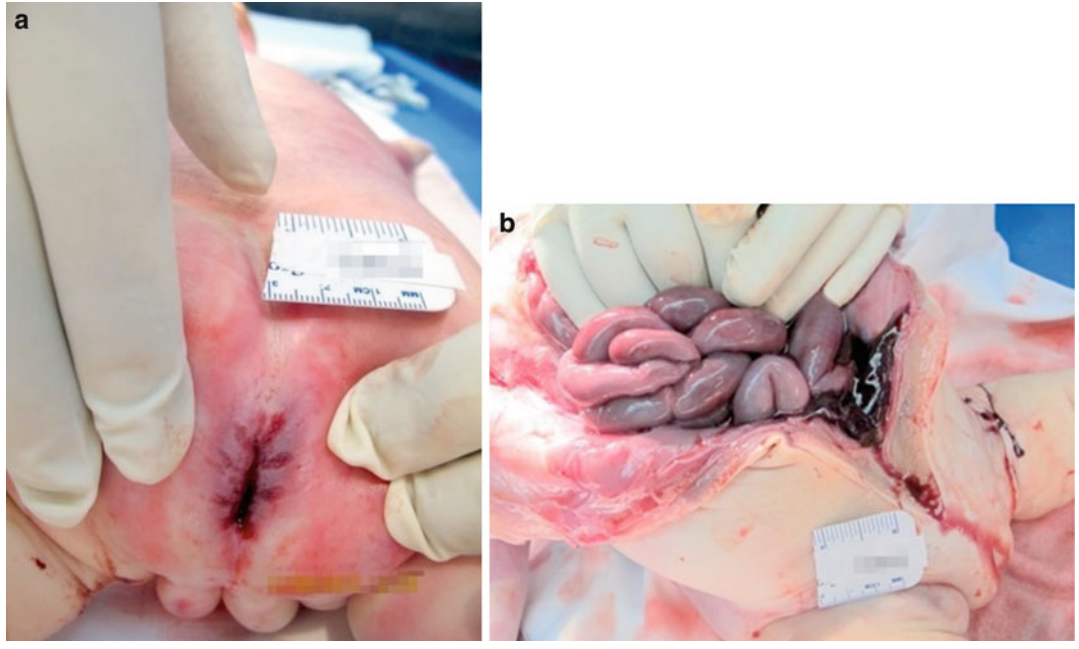

Fig. 23.24 Four-month-old female whose homicide death was either from strangulation or exsanguination. Known child sex offender implicated. (**a**) demonstrates multiple superficial lacerations around the anal verge. (**b**) shows hemoperitoneum. Also present but not shown is rectal laceration. [Photos courtesy of Mary Case, MD, St. Louis, MO]

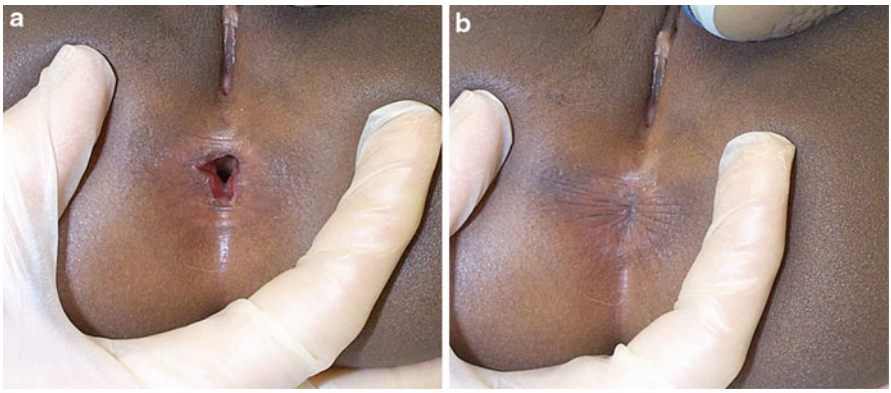

Fig. 23.25 Image is of a prepubertal female in the supine position with the vulva midline 12 o'clock and the anus centered. Anal dilatation (**a**) is a finding that has been described in children selected for non-abuse, and in children with stool in the rectal ampulla. The literature shows an association with sexually abused children, but at present the science has not settled the interpretive significance. Both (**a**) and (**b**) are of the same child minutes apart

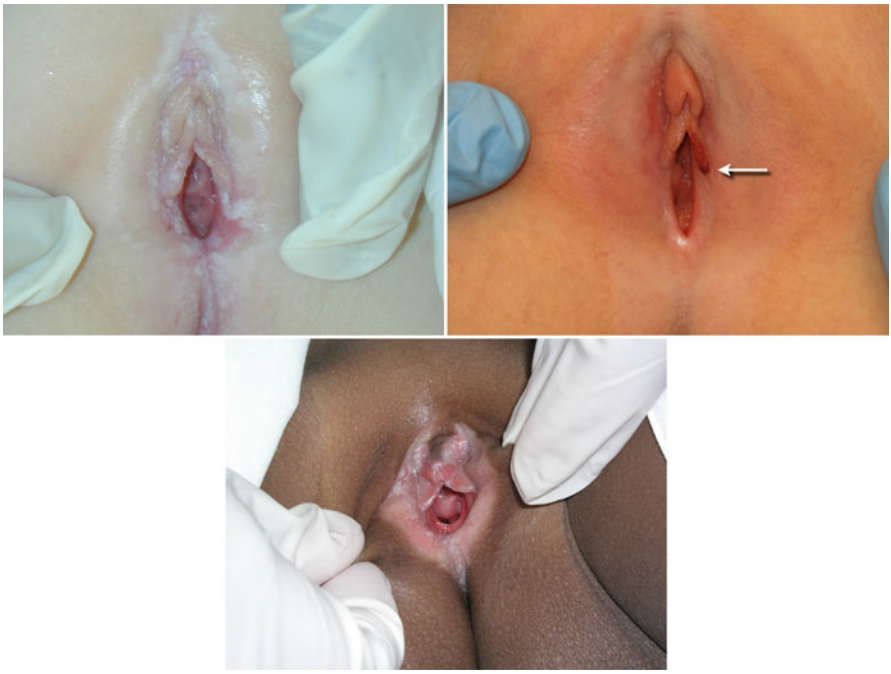

Fig. 23.26 Images are of three different prepubertal females with lichen sclerosis. Each presented with genital itching and discomfort and caregiver observation of chronic genital touching by patient. Until pointed out to caregivers, the hypopigmented skin was not known. The timing of onset to present state as depicted in each photograph is unknown. Lichen sclerosus is one of the vulvar dystrophies that can be seen in childhood. This finding can have subepidermal ecchymoses (*arrow*) creating concern for trauma. This finding is nonspecific in defining sexual abuse

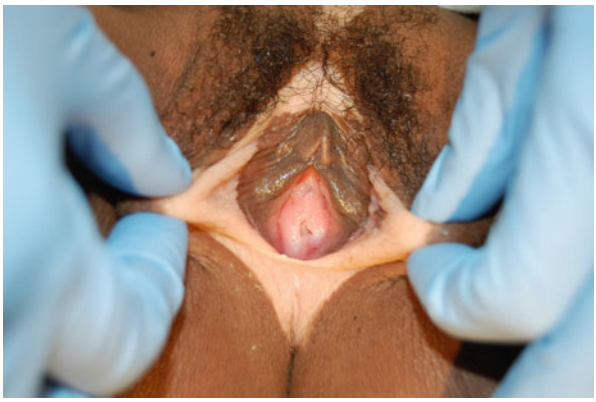

Fig. 23.27 Vulva vitiligo reflects a loss of pigment and does not have an association with sexual abuse

symphysis and the coccyx. Bruising in the periclitoral area with occasional lacerations are often seen (Fig. 23.32). The more internal soft structures such as the hymen are rarely involved in these cases, as they are free to move internally without impingement. Sharp penetrating injuries include impalement on various protruding objects (Sugar and Feldman 2007) such as dive sticks (Soto and Saltzman 2003), inline skates (Herrmann and Crawford 2002), Barbie dolls (Boos et al. 2003), toilet brushes (Rothämel et al. 2001), etc. These injuries mostly have an external-to-internal path which may include the clothing being torn. Recreational water sports can also cause water intrusion injury in the vagina and rectum, mimicking assault (Rudoff 1993; Smith 1996; Freeman et al. 2012; Parsons et al. 1999; Descottes et al. 2003; Di Flumeri et al. 2009). Rapid leg abduction was the mechanism of injury to perineum and hymen in one case (Bond et al. 1995). Severe abdominal or pelvic compression from motor vehicle pedestrian incidents can also cause anogenital injuries mimicking penetrating trauma (Boos et al. 2003; Gabriel et al. 2009).

Very rarely hair thread tourniquet syndrome occurs in which human hair, cotton, or similar filaments strangle genital structures. The syndrome has been reported in both males (Badawy et al. 2010) and females (Kuo et al. 2002; Serour et al. 2007; Alverson 2007). While this finding is usually felt to be a consequence of benign factors, one article advances that abuse should be considered in each case and that assigning an accidental label to an indeterminate situation should be avoided (Klusmann and Lenard 2004).

Injuries to the anogenital area, without an appropriate history of accidental trauma or consensual sex, are highly suspicious for sexual assault (Figs. 23.33–23.38). More external injuries such as to the penis, scrotum, vulva, or perineum are less specific for sexual assault. Healing of acute anogenital trauma is often complete in both accidental and nonaccidental settings (Heppenstall-Heger et al. 2003). Infection, repetitive trauma, and deep trauma will rarely contribute to poor healing and scarring. Most traumas observed from sexual assault have also been observed in consensual settings (Norvell et al. 1984; Lincoln 2001; Jones et al. 2003b; Ahmed et al. 2006; Omo-Aghoja et al. 2009; Zink et al. 2010).

Table 23.6 Lay explanation for lack of trauma findings despite history of abuse

Injury is minimal or none
1. Oral and anogenital anatomy designed for penetration without injury
The mouth, vagina, and anus evolved for eating, sexual intercourse, and defecation. This evolved anatomy includes self-lubrication, rich vascular supply, and quick recuperation from trauma. It is a myth and common misconception that damage must occur with first sexual penetration. The hymen in 98 % of females has a "donut" shape with a central hole. The hymen is elastic and can be stretched significantly. Slight penetration, which does not contact the recessed hymen, should not be expected to cause trauma to the hymen
"Labial coitus" involves the penis or fingers entering the vulval cleft such that the child may perceive penetration, but penetration may not contact the hymen which is recessed partially into the vagina. While the child may describe penetration, the "uninitiated" has no concept of "full penetration" as a reference until that occurs
2. Lubricants used
Lubricants assist in allowing penetration without trauma. Lubrication can be from the vaginal glands of the child who is sexually aroused or under stress or externally introduced by the perpetrator (Vaseline, K-Y jelly, lotions, saliva, etc.)
3. Drug facilitation
Sexual abusers may use alcohol, prescription and/or illicit sedatives, hypnotics or painkillers to "relax" or overcome victim inhibitions. Perpetrators may also attempt to mask findings by giving sedatives, painkillers and/or even illicit drugs to calm or quiet injured children. Consider toxicology testing as indicated
4. Sexual perpetrator gentle
Most perpetrators of child sexual abuse are well-known to their victims. They frequently are in positions of authority and have easy access. Child sexual abuse is usually a seduction and not a violent act (child usually complies with requests and does not fight or resist). Perpetrators know that discovery will occur quickly if the child is injured such that medical care is required or if the attention of a non-offending caregiver is required
Injuries heal rapidly and often completely
1. Genital area usually heals
When trauma occurs, healing is rapid and often complete. The lining of the vagina and hymen is called "mucosal" tissue. This is the same type of skin lining the mouth, digestive tract, and the female genital tract (Bit cheek analogy). As with all other types of trauma, there are always instances of more severe trauma where residual of that trauma can be seen
2. Pubertal transition can mask old injury
The ovaries producing estrogen mark the onset of puberty. Estrogen affects the hymen and vagina – causing the tissue to thicken, the genital glands to function and specific to the hymen to enlarge such that previous injury can be masked

Patterned skin trauma may be helpful in identifying how an injury was sustained, for example, patterned bruises or burns, human bite marks, ligature marks, skeletal fractures, and some internal injuries (Fig. 23.38). See ► Chap. 12, "Skin Conditions Mimicking Pediatric Inflicted Injury," for further extragenital trauma interpretation. Extragenital trauma may help to corroborate the nonconsensual nature of a sexual act.

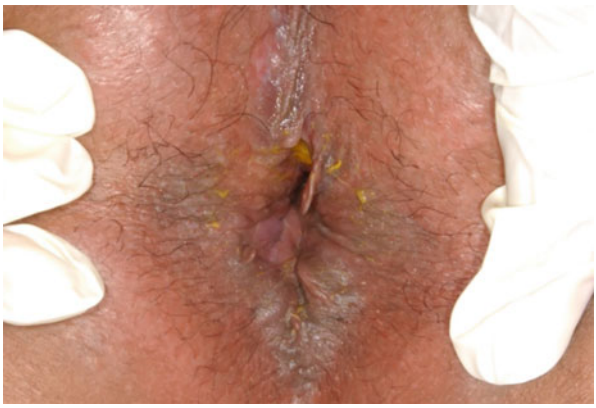

Fig. 23.28 Anal Crohn disease can result in tags, fissures, and other distortions of the anus that may initially be confused with trauma

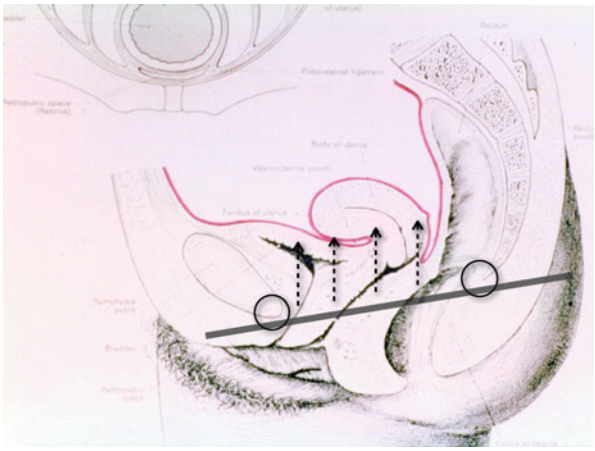

Fig. 23.29 Straddle injuries (*represented by bar*) generally impose impact trauma to the skin overlying the pubic symphysis and coccyx (*circles*), while the soft tissues in between are free to move inward toward the peritoneum (*dashed arrows*). As such, straddle injuries rarely cause injury to the hymen and vagina

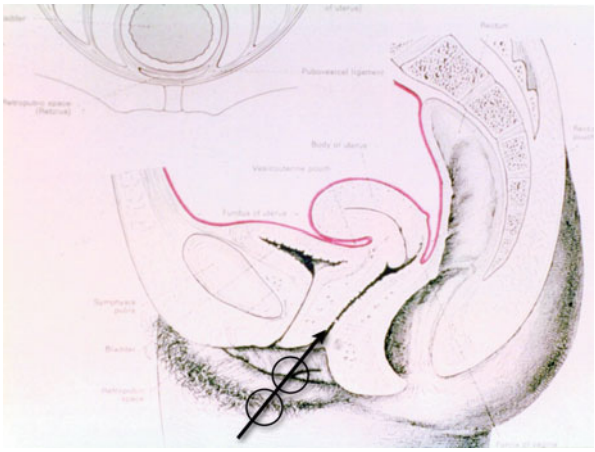

Fig. 23.30 Sharp penetrating genital injuries (*represented by arrow*) may cause internal injury but are accompanied by trauma along the entire path of intrusion (*circles*) including the clothing. This is in contrast to blunt penetrating trauma associated with sexual assault, which often has isolated deep trauma

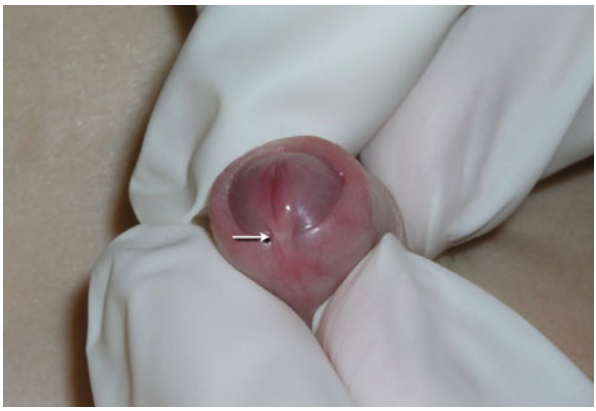

Fig. 23.31 Penis frenulum breve (*arrow*) is a consequence of irritation and inflammation from forceful foreskin retraction. Since this can occur through ignorance of proper hygiene of uncircumcised infants and abuse, it is a nonspecific finding

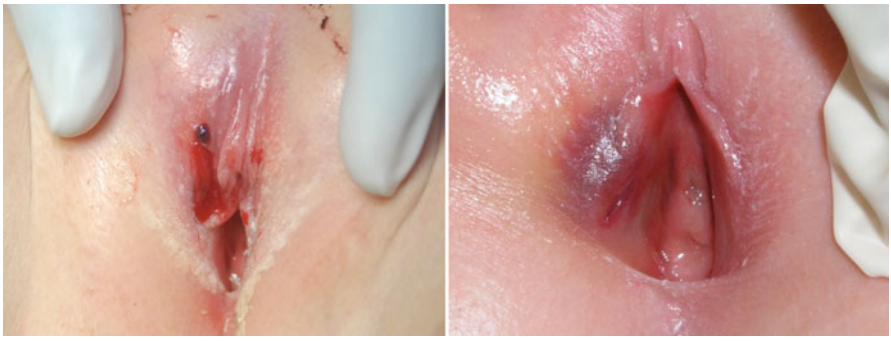

Fig. 23.32 Straddle injury is depicted in these images of two prepubertal girls. Note the superficial and asymmetric laterality of the finding. Involvement of the peri-clitoral and anterior labia minora is expected given the underlying association of the pubic symphysis

History

Disclosure

The process of disclosing abuse has been studied. Interviewers should be well versed in the dynamics of abuse disclosure, developmental communication, and avoidance of memory-contaminating questioning. If possible, children's history should be obtained in private by a community's most experienced interviewers and reproducibly documented. Child Advocacy Centers in the United States (USA) have evolved a model to bring best practices to the community. The National Institute of Child Health and Human Development (NICHD) sponsored numerous studies to determine best practices in forensic interviewing of children (Lyon et al. 2009; Dion and Cyr 2008; Lamb et al. 2007, 2008; Hershkowitz et al. 2007a, b; Orbach et al. 2000). Lyon produced a practical synopsis of desirable

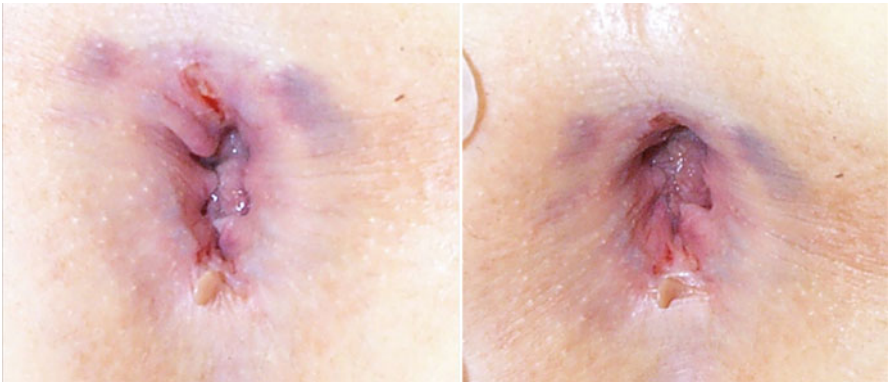

Fig. 23.33 Anus acute injury is depicted in this prepubertal male with history of gang sodomy. Note the partial laxity of the external anal sphincter, fissures at 12, 5, and 7 o'clock, and the 7 o'clock anal tag. The blue discoloration noted at 11 and 2 o'clock around the anus is prominence of the hemorrhoidal veins and can be confused with bruising. The persistence of this finding helps to rule out bruising and may necessitate serial exams

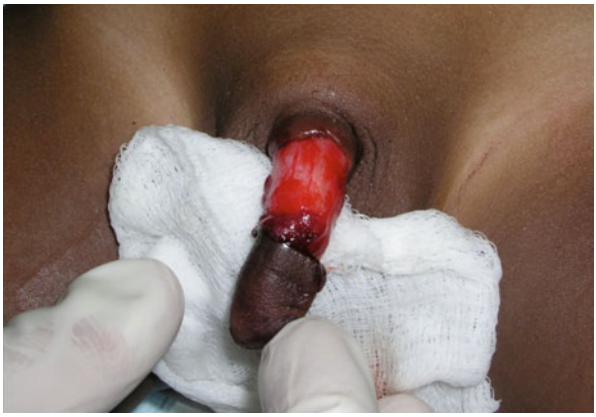

Fig. 23.34 Penis acute injury manifest as a degloving of the penile shaft skin. This finding reflects abusive injury by forceful traction or pulling of the penile shaft skin

techniques derived from this research, see http://works.bepress.com/thomaslyon/5/. The range of demeanor and emotions expressed when recounting incidents is broad. It is important to note that demeanor and affect are poor measures of truthfulness. Historians should refrain from making any credibility opinions based solely on demeanor or affect congruence with victim statements in isolation of other facts.

Idiosyncratic detail in a child's abuse history that cannot be known without personal physical experience should be sought and documented. These details lend credibility to their disclosure. Examples include histories describing dysuria as a component of their sexual abuse disclosure (DeLago et al. 2008, 2012). Always consider that consensual sexual experiences could be a confounder.

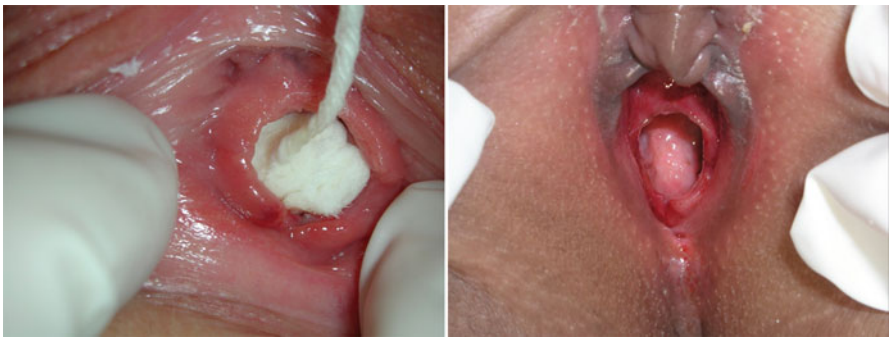

Fig. 23.35 Hymen acute injury is manifest in both images by bruising of the hymen. The image on the left is of a pubertal female. The white object is a vaginal tampon. The right image is of a prepubertal female

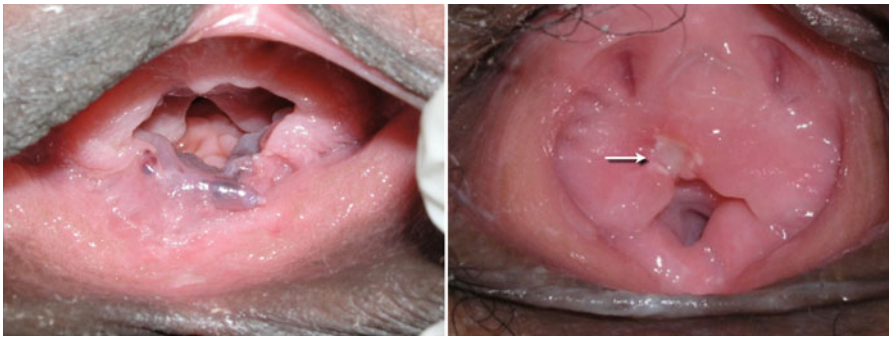

Fig. 23.36 Hymen subacute injury is seen as submucosal hemorrhage and resolving laceration in the right image (*arrow*)

Delayed Disclosure

Most victims of child sexual abuse delay in disclosing their abuse often until they are adults (Hershkowitz et al. 2007b; Hébert et al. 2009; Schönbucher et al. 2012; Goodman-Brown et al. 2003; Schaeffer et al. 2011; Hershkowitz 2006; Somer and Szwarcberg 2001; Smith et al. 2000; Kogan 2004; Kellogg and Huston 1995; Sjöberg and Lindblad 2002; Arata 1998). The definition of disclosure is variably defined in the literature, but for this chapter, disclosure is defined as occurring when a child relates an abuse incident to a person with authority to alter the course of that abuse. For example, telling a peer-aged friend would not count as a disclosure, but telling a schoolteacher would. The concept of delayed disclosure is not widely known among the public and consequently can cast unwarranted doubt on a child's (or later as an adult) credibility (Hébert et al. 2009; Yozwiak et al. 2004).

There are multiple factors which influence whether a child will disclose sexual abuse or not. This author has routinely asked children the reason for their delay in disclosing. The reasons can be grouped into three main categories: naïveté, external factors, and internal factors.

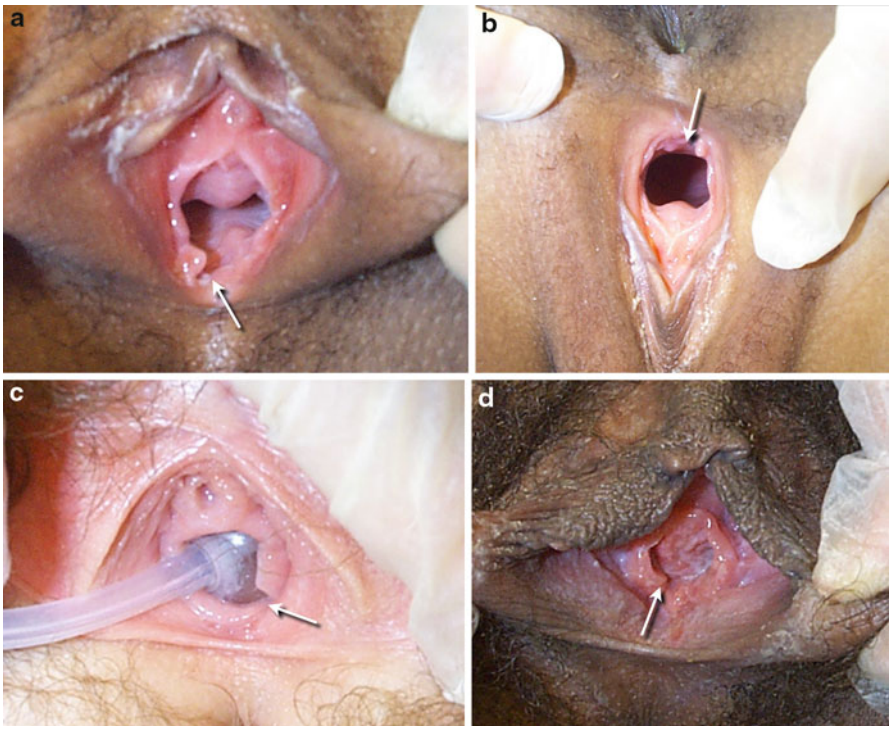

Fig. 23.37 Hymen injury residua. All images reflect discontinuity of the posterior hymenal rim (*arrows*). These findings are the consequence of transections caused by previous blunt penetrating trauma. (**a**), (**c**), and (**d**) are in the supine position. (**b**) Is in the prone knee-chest position. (**a**) and (**b**) are of the same child. (**c**) demonstrates the use of the Foley-technique to highlight the transection

Fig. 23.38 Neck acute injury is noted in these two females as a consequence of a perpetrator sucking on the neck. Recognizing this pattern is important in that swabs of the area may permit DNA identification of the suspect perpetrator through saliva left behind

Naïveté

In order for children to disclose, they have to first recognize that they are being abused and have something to disclose. Secondly, they then need to know to whom to disclose. Children are born naïve to moral concepts and will assume their abuse experiences are common to the moral experiences of all children. Even when a child gains external moral knowledge, the abuser is often someone the child knows, loves, and trusts and is in a position of authority. This means that the abuser is a person to whom a child would normally turn when reporting abuse. Two main variables predicting naïveté are the age at onset of abuse (Schönbucher et al. 2012; Goodman-Brown et al. 2003; Smith et al. 2000; Kogan 2004) and being developmentally delayed or cognitively impaired.

External Factors

The external factors fostering delayed disclosure include threats (Kogan 2004), bribes, relationship to perpetrator (familial versus extrafamilial versus stranger) (Schönbucher et al. 2012; Goodman-Brown et al. 2003; Smith et al. 2000; Kogan 2004; London et al. 2008), and the disparity in age between perpetrator and victim (Schönbucher et al. 2012).

Internal Factors

Children are observant of their communities' response to other's disclosures. As such, they can perceive negative consequences if they should disclose (Schönbucher et al. 2012; Goodman-Brown et al. 2003; Somer and Szwarcberg 2001). These perceptions include fear of nonoffending parent's/significant other's negative reaction (Schönbucher et al. 2012; Bolen and Lamb 2004), loss of relationship with perpetrator, removal from family, loss of economic status if perpetrator is the breadwinner, social rejection by peers, disgust for type of sex act touching>vaginal>anal>oral, and homosexuality (Valente 2005). As children age into adolescence, embarrassment becomes a major source of inhibition (Kellogg and Huston 1995; Bonanno et al. 2003; Fleming 1997). Often children erroneously believe they had control of their own abuse both in their participation in the act and in maintaining secrecy. Their self-blame and perceived responsibility for abuse is another common adolescent factor inhibiting disclosure (Goodman-Brown et al. 2003). Summit began the search for characterizing the dynamic of child sexual abuse and elaborated his concept of the child sexual abuse accommodation syndrome noting that many children simply accommodated to their abuse (Summit 1983). Child sexual abuse can lead to psychological trauma including post traumatic stress disorder and major depression. This psychological trauma can inhibit disclosures (Ruggiero et al. 2004).

Disclosure Type

The manner in which a child discloses is important both for their mental health and in assessing motivations behind disclosing. Sexual abuse disclosures can be divided into six main types: accidental, purposeful, intentionally withheld disclosure,

prompted/elicited, behavioral and indirect verbal attempts, and disclosure triggered by recovered memories (Alaggia 2004).

Accidental disclosure occurs when a child is caught with evidence of their victimization. Examples include a nonoffending caregiver witnessing an abusive incident, a child going to the doctor for dysuria that is later attributed to an STI, or a sexual offense that causes trauma prompting the attention of a nonoffending caregiver. The lack of intent to disclose can also be seen as corroborating a lack of motive to fabricate.

Purposeful disclosures are those where the child has decided to tell someone about their abuse and does. These disclosures can include written statements left for others to discover and verbal statements to a caregiver, teacher, or emergency telephone line.

Intentionally withheld disclosures are when the child denies or minimizes abuse in face of direct or indirect evidence to the contrary.

Prompted/elicited disclosures occur when the child is questioned by caregivers, counselors, and interviewers or is encouraged to disclose by discussions of sexual abuse, for example, through classroom presentations or television talk shows. This category often creates concerns correlated to the degree in which the questions or exposures are leading in nature.

Disclosure by behavioral and indirect verbal attempts include "... attempts to tell through behavior, non-verbal communication, or indirect verbal hints" (Alaggia 2004).

Disclosures triggered by recovered memories – there are two and possibly three modes of recovered memories (Raymaekers et al. 2012). The first are memories recovered during therapy. This type of disclosure is controversial and is often accompanied by concerns for credibility of the memories recovered and the degree to which mental-health professionals may unknowingly contribute to their fabrication. The second mode includes spontaneously recovered memories. A third mode involves a reinterpretation of existing memories recognizing abuse not previously acknowledged.

Trace Evidence

Trace evidence includes any item which may have been transferred to the victim from the crime scene or vice versa. Examples include dirt, gravel, oils, leaves, grass, insects, etc. These items may assist in defining the crime-scene location or may help include or exclude possible suspects. Interpreting this type of evidence is beyond the scope of this chapter.

Behavior

Sexual behaviors when observed in young children provoke understandable anxiety in their guardians about whether the child has been abused. As with trauma findings, several studies characterize nonabused children's sexual behaviors

(Friedrich et al. 1991, 1998, 2001; Schoentjes et al. 1999; Larsson and Svedin 2001). These studies show that children have a natural curiosity that extends to nudity, interest in differences between males and females, and will touch their own or other's genitals if given the opportunity. Those behaviors involving others regress after age 5 and reemerge with the onset of puberty. Self-stimulatory behaviors continue but become less public. Physiologically, children have a normal sexual response when their genitals are stimulated. This response can include penile and clitoral erections from birth throughout the life span. As such, masturbation can be seen in both normal and sexually abused children.

Abnormal childhood behaviors hint at problems in their environment and often warrant closer evaluation. The environment, which produces abnormal behaviors, is often quite complex. While fear, anxiety, aggression, depression, suicidal ideation, substance abuse (Kendler et al. 2000), post traumatic stress disorder, and secondary incontinence (Mellon et al. 2006) have been observed in sexually abused children, they are nonspecific in diagnosing sexual abuse in isolation. Each case has to be examined individually. A child's avoidance of, or willingness to go with, a specific person is a poor measure of prior maltreatment and also should not be used without other supporting data.

Children are not born with innate knowledge of adult sexual behavior, and therefore that behavior has to be learned. Children engaged in coercive or adult sexual behaviors suggest either vicarious exposure to adult sexual behavior or intentional exposure by sexual abuse, physical abuse, or neglect (Merrick et al. 2008). An excellent synopsis of sexual behaviors in children was published by the AAP Committee on Child Abuse and Neglect (Kellogg et al. 2009). Checklists have been developed to evaluate children's problematic and sexual behaviors (Schoentjes et al. 1999; Friedrich et al. 2001; Sim et al. 2005).

Toxicology

Drug-facilitated sexual assault should be considered in all patients who have unexplained acute anogenital signs or symptoms of sexual contact. Toxicology testing should be ordered in those cases and also considered when patients are intoxicated, unconscious, or reporting altered consciousness. Blood and urine samples should be obtained. See ► Chap. 29, "Pediatric Toxicology," on interpreting toxicology studies.

Conclusion

Justice depends on the thorough consideration, collection, and interpretation of all evidence. An understanding of normal anatomy and entities, organic and traumatic, which can mimic sexual abuse is crucial. Where the evidence tends to define child sexual abuse, it is equally important to identify and treat the mental and physical consequences that often accompany this abuse.

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Starvation, Malnutrition, Dehydration, and Fatal Neglect

24

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Contents

Abstract

Fatal starvation is a rare cause of death in industrialized countries but may be of major medicolegal importance if death results from deliberate withholding of

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food, especially in infants. Normally, the diagnosis of death as a result of starvation is a simple prima facie diagnosis. However, underlying diseases as causes of emaciation and concurrent diseases have to be ruled out. In cases of physical neglect, the forensic pathologist must not only clarify the cause of death but also give an expert opinion on the degree and duration of starvation. Several classification systems have been developed to estimate protein-energy-malnutrition (PEM) in third-world countries, especially the Waterlow classification. Following the Waterlow classification, a "stunted" (i.e., reduced weight for height) physical condition is calculated by using the ratio of the measured body height to the one expected for the actual age. Body weight can be used as a sign of acute malnutrition ("wasting"). However, body weight should be related to the expected weight for the actual height. The application of the Waterlow classification will be demonstrated using the author's cases and on cases from the literature. The Waterlow classification is not only of importance for grading the final stage in cases of fatal starvation but also for the chronological development of the nutritional status if weight and height records of children are available. The diagnostic process both in deceased and living children will be addressed.

Acute dehydration may be also seen in young children due to physical neglect. In addition to classical autopsy findings such as poor skin turgor and sunken eyes, vitreous-humor chemistry may be helpful in making the diagnosis.

Useful Definitions

Cachexia	General wasting and emaciation, usually associated with severe chronic disease or malnutrition
Dehydration	Reduction or complete loss of water content
Failure to thrive (FTT)	Children whose weight is significantly lower than the norms for their age and gender; chronic FTT may result in low height for age
Fatal starvation	Death after long-standing food deprivation
Hypernatremic dehydration	Loss of body water that is not accompanied by a compensatory sodium loss
Kwashiorkor	A severe form of malnutrition, characterized by edema, anemia, and impaired growth; edematous protein-energy-malnutrition
Malnutrition	Any disorder resulting from a deficiency (or an excess) of one or more essential nutrients causing unbalanced diet or inability to absorb or metabolize any nutrient
Marasmus	Nonedematous protein-energy-malnutrition
Undernutrition	Inadequate nutrition due to a failure to ingest, absorb, or assimilate nutrients in adequate quantities

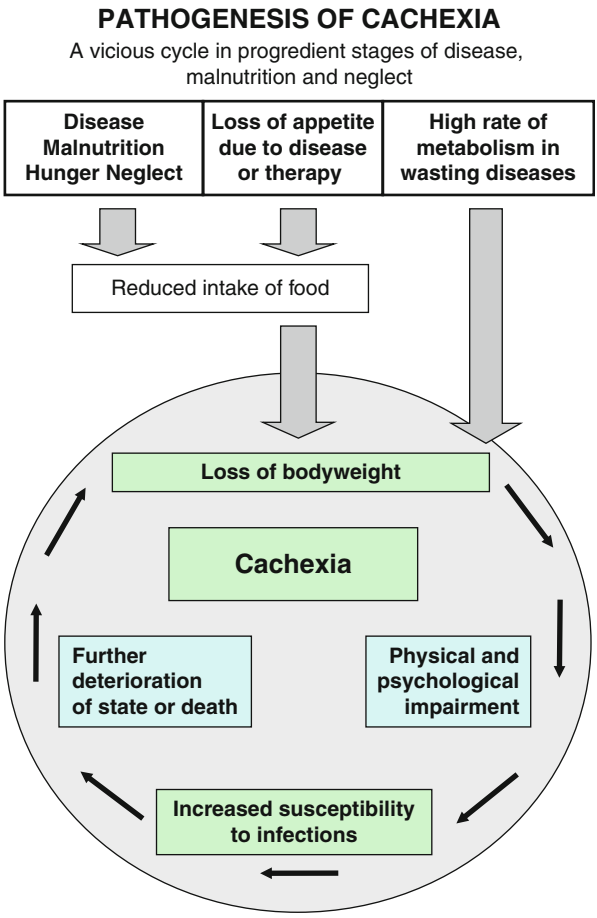

Fig. 24.1 Pathogenesis of cachexia: a vicious cycle in the stages of disease, malnutrition, and neglect

Introduction

Starvation is a rare cause of death in industrialized countries that may occur as a result of child abuse, fasting to death, or in mentally ill persons. Worldwide, starvation is one of the most frequent causes of death. According to United Nations estimates, 25,000 people die daily due to starvation and intercurrent diseases. Starvation may become of major medicolegal importance if death results from deliberate withholding of food, especially in infants.

The diagnosis of death as a result of starvation is normally a simple prima facie diagnosis, the visual features of starvation being known from contemporary famines. If there is enough circumstantial evidence, the definite diagnosis of starvation will not be in doubt.

Internal as well as external factors may point to cachexia (Fig. 24.1). Therefore, in criminal acts related to starvation in which the cause of loss of body weight is suspected to be the result of deliberate withholding of food

(e.g., in the course of neglect of infants), the forensic pathologist must collect as much evidence as possible because it is the underlying cause of starvation (i.e., "deliberate withholding of food or neglect"), and not the diagnosis of starvation itself, that will be questioned in later legal proceedings. The distinction between cause and effect is of great importance when criminal charges are filed.

Child Abuse: Types and Definitions

Today, seven types of child abuse are recognized (Hobbs et al. 1999; Madea et al. 2011; Reece 2009):

- Physical abuse
- Nonaccidental head injury
- Physical neglect, deprivation
- Nonorganic failure to thrive
- Emotional abuse
- Sexual abuse
- Fabricated and induced illness

Definition

In the United States (USA), child abuse is defined by the Child Abuse Prevention and Treatment Act (CAPTA) of 1974 as follows: "Any recent act or failure to act on the part of a parent or caretaker which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm" to a child under the age of 18 years. Child abuse is not only an intentional act but might also be the result of carelessness by a parent or caretaker.

The German Bundestag issued the following definition of child abuse: Abuse is intentional conscious or unconscious physical or mental harm which is occurring in families or in institutions, thus, in systems of cohabitation, and which is causing damage and/or arrested development or even death and, thus, detracts from or menaces the welfare and the rights of a child.

In the United Kingdom, child abuse was formally defined in the 1999 Department of Health guidelines and redefined in 2000 (Department of Health 2000):

- Physical abuse involves hitting, shaking, throwing, poisoning, burning or scalding, drowning, suffocating, or otherwise causing physical harm to the child which is actual or likely.
- Fictitious (or factitious) illness by proxy is also included under physical abuse.
- From a clinical perspective, the severity of the injury, the number of injuries, the age of the child, and any previous injuries and other abuses (neglect, child sexual abuse, emotional abuse) are all part of the jigsaw which leads to a diagnosis of physical abuse.

According to statistics, physical child abuse is an apparently uncommon type of crime, however, the estimated number of unreported cases is very high (e.g., for Germany 95 %) (Madea et al. 2011). In the USA, 16.5 children per 1,000 were found to be victims of abuse in 2005. Child neglect was the most frequent form of abuse, followed by physical abuse in 16.6 % of all reported cases.

The reasons for the high number of unreported cases include (Hobbs et al. 1999; Madea et al. 2011; Reece 2009):

- Child abuse is a familial incident with no independent witnesses
- Lack of awareness of witnesses and treating physicians
- Children's dependence on their parents
- Abused children are usually too young to report what has happened

Physical neglect is defined as deprivation of necessary care, including sufficient nourishment and hydration. The incidence of physical neglect is not known. In most cases of physical neglect, the perpetrators are female since it is usually the mother who cares for the child. Unwanted children or children of ill mothers (with addictive or psychiatric disorders) are particularly at risk.

According to another definition, pediatric neglect is a failure of a caregiver to adequately meet a child's basic needs, which include physical safety and protection, food, clothing, shelter, education, medical/dental care, and supervision (Collins 2010). Neglect is three times more common than physical abuse. For further classification of neglect, the terms *active* and *passive* are used (Block and Krebs 2005; Reece 2009). This classification is based on the intentions and actions of a caregiver. Active neglect is the deliberate withholding of care, whereas passive neglect occurs when a caregiver inadvertently does not provide for a child because his/her focus is elsewhere (Collins 2010). While physical neglect of children is the most common form of child abuse, lethal neglect is a rare event, and it is mostly seen in the form of starvation and/or dehydration.

Worldwide, malnutrition remains one of the most common causes of morbidity and mortality among children. Approximately 9 % of children below 5 years of age suffer from wasting (weight-for-height below −2 standard deviations [< −2 SD] of the National Center for Health Statistics [NCHS]/WHO reference values) and are at risk of death or severe impairment of growth and psychological development (WHO 1999). Under- and malnutrition are the end result of chronic nutritional and frequently emotional deprivation by caregivers who, because of poor understanding, poverty, or family problems, are unable to provide a child with the nutrition and care that he or she requires (WHO 1999). Undernutrition is inadequate nutrition due to a failure to ingest adequate quantities. Malnutrition is any disorder resulting from a deficiency of one or more essential nutrients. The prevalence of acute malnutrition of children admitted to hospital is still considerably high (Joosten and Hulst 2008); for example, among a group of 475 unselected children admitted to a university hospital in Germany, 6.1 % of the children were malnourished (weight-for-height <80th percentile). With respect to age, the highest risk of malnutrition was found in infants (7.1 %) and young children aged 2–5 years (4.3 %). Similar prevalence rates of 7.1 % and 8 % were reported for other countries.

Malnutrition can be of the acute, chronic, or mixed type. Acute malnutrition is the type that usually occurs in illness. Children with underlying chronic diseases present with chronic malnutrition (Joosten and Hulst 2008).

Energy Requirements

The daily energy requirement of humans above the basic metabolic rate mainly depends on physical activity (Table 24.1). Formulas for calculating the basic metabolic rate are:

- Harris-Benedict formula:
  - Men: Basal metabolic rate in kcal/day = 66.47 + (13.7 × body weight in kg) + (5 × body height in cm) – (6.8 × age in years)
  - Women: Basal metabolic rate in kcal/day = 655.1 + (9.6 × body weight in kg) + (1.8 × body height in cm) – (4.7 × age in years)
- Empirical formula:
  - Basal metabolic rate in kcal/day = body weight in kg × 25

Energy requirements in healthy children are age-dependent (Table 24.2). Energy requirements for boys and girls during the first year of life are presented in Tables 24.3–24.6 (Koletzko et al. 2008).

For normal growth, the following simple rules of thumb can be used (Koletzko et al. 2008):

- Approximate average expected *weight* gain for a healthy term infant:
  - 200 g/week in the first 3 months
  - 130 g/week in the second 3 months
  - 85 g/week in the third 3 months
  - 75 g/week in the fourth 3 months
  - Birth weight usually doubles by 4 months and triples by 12 months
- Length:
  - Increases by 25 cm in the first year
  - Increases by 12 cm in the second year
  - By 2 years, roughly half of adult height is attained
- Head circumference:
  - Increases by 1 cm/month in the first year
  - Increases by 2 cm in the whole of the second year
  - Will be 80 % of adult size by 2 years

(Note that, as growth rates vary considerably between children, these figures should be used in conjunction with growth charts.)

Insufficient caloric intake compared to requirements results in a negative energy balance with resultant loss of body weight. Malnutrition must be differentiated from undernutrition. Undernutrition is the intake of an insufficient quantity of food, whereas malnutrition is defined as feeding of inadequate quality.

The more or less constant symptoms of starvation develop in a characteristic chronological order (Madea 2005; Madea and Banaschak 2004):

1. Loss of well-being with hunger, hunger pangs, and craving for food
2. Apathy and fatigue

Table 24.1 Daily energy requirement of calories in humans

Mode of energy turnover	Energy exchange	
Basic metabolic rate (body weight 70 kg)	F 6,300 kJ/day	1,500 kcal/day
	M 7,100 kJ/day	1,700 kcal/day
Basic metabolic rate plus leisure time requirement	F 8,400 kJ/day	1,900 kcal/day
	M 9,600 kJ/day	2,300 kcal/day
Basic metabolic rate for heavy workers	F 15,500 kJ/day	3,700 kcal/day
	M 20,100 kJ/day	4,800 kcal/day

F female, *M* male (According to Bürger et al. 1969)

Table 24.2 Energy requirements in healthy children

Age	kcal/kg and day Male/Female
0 to <4 months	110
4 to <12 months	95
1 to <4 years	100
4 to 7 years	90
7 to <10 years	75
10 to <13 years	60/55
13 to <15 years	55/45
15 to <19 years	45/40

Table 24.3 Energy requirements of boys during the first year of life

	1985 FAO/WHO/UNU		2004 FAO/WHO/UNU		
Age months	kJ/kg/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
0–1	519	2.166	518	473	113
1–2	485	2.387	570	434	104
2–3	456	2.494	596	397	95
3–4	431	2.38	569	343	82
4–5	414	2.546	608	340	81
5–6	404	2.674	639	337	81
6–7	397	2.73	653	329	79
7–8	395	2.845	680	330	79
8–9	397	2.936	702	330	79
9–10	414	3.058	731	335	80
10–11	418	3.145	752	336	80
11–12	437	3.243	775	337	81

3. Weight loss, more rapid in the first 6 months of starvation than afterward
4. Pigmentation change, cachexia, and hypothermia
5. Extreme lethargy, mental retardation
6. Nutritional edema
7. Suppression of the immune system and secondary infections; reduced resistance to infections in general; and development of diarrhea and tuberculosis, or other secondary infections

Table 24.4 Energy requirements of girls during the first year of life

	1985 FAO/WHO/UNU		2004 FAO/WHO/UNU		
Age months	kJ/kg/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
0–1	519	1.942	464	447	107
1–2	485	2.162	517	421	101
2–3	456	2.301	550	395	94
3–4	431	2.245	537	350	84
4–5	414	2.389	571	345	83
5–6	404	2.507	599	341	82
6–7	397	2.525	604	328	78
7–8	395	2.63	629	328	78
8–9	397	2.728	652	328	78
9–10	414	2.828	676	331	79
10–11	418	2.902	694	331	79
11–12	437	2.981	712	331	79

Table 24.5 Energy requirements of boys at 0–18 years of age, computed for a moderate level of physical activity

Age	1985 FAO/WHO/UNU		2004 FAO/WHO/UNU		
years	kJ/kg/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
1–2	439	4.0	950	345	82
2–3	418	4.7	1,125	350	84
3–4	397	5.2	1,250	334	80
4–5	397	5.7	1,350	322	77
5–6	377	6.1	1,475	312	74
6–7	377	6.6	1,575	303	73
7–8	326	7.1	1,700	295	71
8–9	326	7.7	1,825	287	69
9–10	326	8.3	1,975	279	67
10–11	267	9.0	2,150	270	65
11–12	267	9.8	2,350	261	62
12–13	228	10.7	2,550	252	60
13–14	228	11.6	2,775	242	58
14–15	200	12.5	3,000	233	56
15–16	200	13.3	3,175	224	53
16–17	186	13.9	3,325	216	52
17–18	186	14.3	3,400	210	50

Fatal Starvation

Most victims of fatal starvation are under the age of 1 year, however, older children may be involved, particularly disabled children. Children below the age of 3 years have only a limited ability to obtain food or drinks (Collins 2010; Madea 2005; Madea et al. 1994).

Table 24.6 Energy requirements of girls at 0–18 years of age, computed for a moderate level of physical activity

	1985 FAO/WHO/UNU		2004 FAO/WHO/UNU		
Age years	kJ/kg/day	MJ/day	kcal/day	kJ/kg/day	kcal/kg/day
1–2	439	3.6	850	335	80
2–3	418	4.4	1,050	339	81
3–4	397	4.8	1,150	322	77
4–5	397	5.2	1,250	310	74
5–6	356	5.6	1,325	301	72
6–7	356	6.0	1,425	289	69
7–8	280	6.5	1,550	280	67
8–9	280	7.1	1,700	268	64
9–10	280	7.7	1,850	255	61
10–11	227	8.4	2,000	243	58
11–12	227	9.0	2,150	230	55
12–13	189	9.5	2,275	218	52
13–14	189	10.0	2,375	205	49
14–15	173	10.2	2,450	197	47
15–16	173	10.4	2,500	188	45
16–17	167	10.5	2,500	184	44
17–18	167	10.5	2,500	184	44

The main autopsy finding is extreme emaciation with loss of body and organ weights (Fig. 24.2, Table 24.7). Loss of body weight mainly results from the loss of subcutaneous adipose tissue and adipose tissue surrounding internal organs, atrophy of internal organs, and atrophy of muscles. Nearly all organs except the brain are reduced in weight (Table 24.8). The different rates of organ-weight loss represent an "order" in which organs are used for energy production (adipose tissue, muscles, liver, heart, spleen, kidney). Due to brain edema, the weight of the brain might even be increased. Also quite characteristic is the loss of the buccal fat pad (Bichat's fat pads). Due to the loss of subcutaneous adipose tissue the skin is wrinkled. In dehydration, sunken fontanelles and wrinkling of the skin, especially of the neck pad, can also be found (Fig. 24.3, a, b).

The loss of about 35–50 % of body weight may cause death. Atrophy of endocrine and reproductive glands (testes) is quite characteristic. In infants, complete atrophy of the thymus is characteristic, along with diminution in the size of the lymph nodes.

The gallbladder is commonly distended as a result of the absence of food as the natural stimulant of bile excretion. Stomach and small bowel are normally empty, but the presence of extremely dry stool in the colon is another characteristic finding. Even foreign bodies may be found in the colon, indicating that the starving person tried to eat everything accessible prior to death (Adelson 1963; Byard 2010; Collins 2010; Davis et al. 1984; Meade and Brissie 1985; Tanegashima et al. 1999).

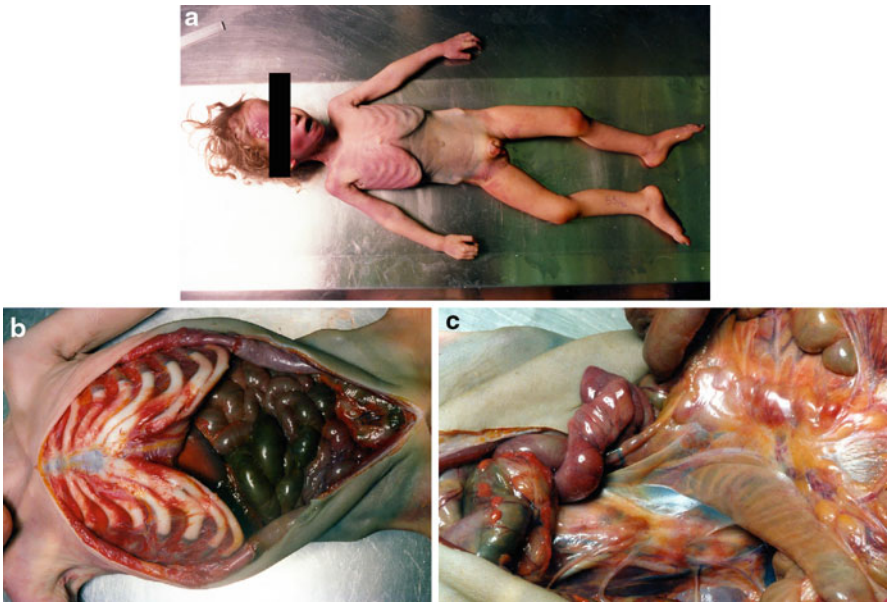

Fig. 24.2 Typical autopsy findings in starvation are: (**a**) emaciation with protruding ribs; (**b**) loss of subcutaneous adipose tissue; (**c**) loss of adipose tissue in the mesentery

Histology

Histological investigations are important in cases of starvation to exclude concurrent causes of death or underlying diseases (e.g., malabsorption) as causes for malnutrition. In cases of pediatric starvation, histological findings are nonspecific. Often, hepatic microvesicular steatosis due to protein deficiency is found (Fig. 24.4).

In addition to thymic involution, microscopic findings of a "starry sky" background, calcification of Hassall's corpuscles, and fibrofatty replacement have been described (Collins 2010; Tanegashima et al. 1999). Furthermore, secondary siderosis due to protein deficiency in the spleen and liver can be found (Fig. 24.5). Secondary siderosis is due to fatty liver disease with decreased protein synthesis and deficient apoferritin in undernutrition.

To rule out concurrent causes of death in cases of pediatric starvation, postmortem biochemical investigations of vitreous humor (see below), toxicological investigations, microbiology and virology studies, and metabolic screening must be carried out.

Metabolic Diseases

For the postmortem investigation of a possible underlying metabolic disorder at autopsy, blood and bile spotted onto filter paper should be collected.

Table 24.7 Gross autopsy findings in pediatric starvation/malnutrition

Decreased body weight
Decreased adipose tissue
Decreased visceral adipose tissue
Atrophied skeletal muscle
Decreased organ weights
Blue pallor of the skin, pale "semi-translucent" skin, thin sketched skin over the face
Pressure sores
Areas of hypopigmentation
Dental caries
Brittle hair
Alopecia
Protruding occiput
Thin neck
Sunken eyes
Sunken cheeks/decreased buccal fat
Depressed fontanelles
Protruding ribs
Protruding vertebrae
Protruding iliac crests
Winging of the scapulae
Prominent knees and joints
Scaphoid abdomen
Wrinkled skin over the joints and extremities
Wrinkled skin and subcutaneous tissue over the buttocks
Thinned walls of the stomach and intestines
Empty gastrointestinal tract
Distended and filled gallbladder
Dehydrated feces, fecoliths
Thymic involution
Dry serosal surfaces
Tenting of the skin with dehydration
Diaper rash
Secondary infections

From Collins 2010 (modified)

Table 24.8 Loss of body weight and loss of weight of internal organs (%) in relation to normal weight values for the respective age group; five cases of fatal pediatric starvation

Case no.	Age	Body weight	Heart	Liver	Spleen	Kidney	Lungs	Brain
Case 1	3 months	53.3 %	7.4	25	68.7	40.4	36	+13
Case 2	2.3 years	54	37	37	24	46	30	+10
Case 3	2.5 years	60	25	54	57	45	—	15
Case 4	2.5 years	55	30	40	51	69	39	11
Case 5	2.5 years	52	46	46	43	33	52	10

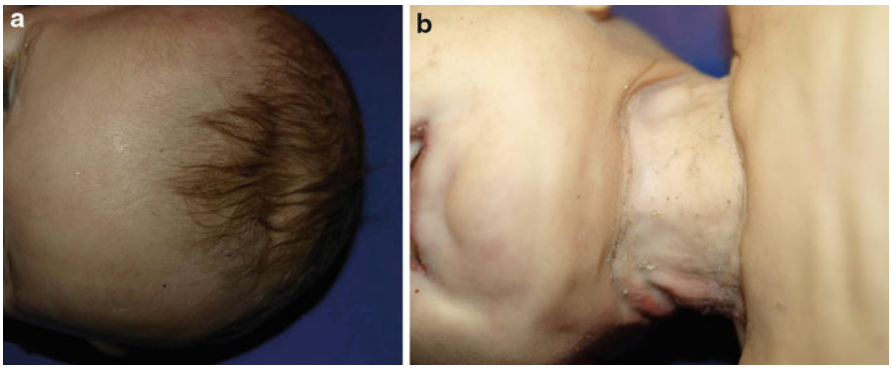

Fig. 24.3 (**a**) Sunken fontanelles, (**b**) wrinkling of skin of the neck

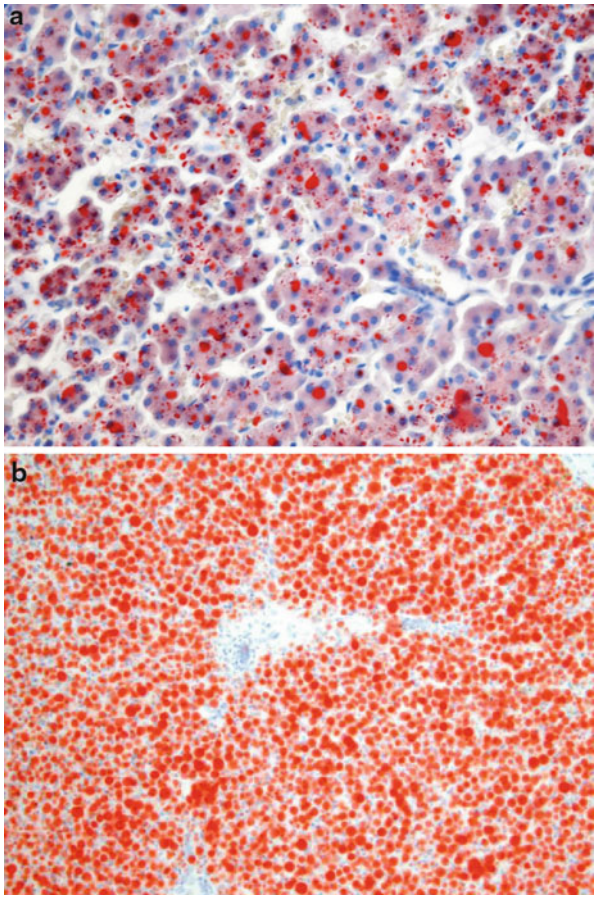

Fig. 24.4 (**a**) Hepatic microvesicular steatosis; (**b**) massive steatosis (oil red-O staining × 100)

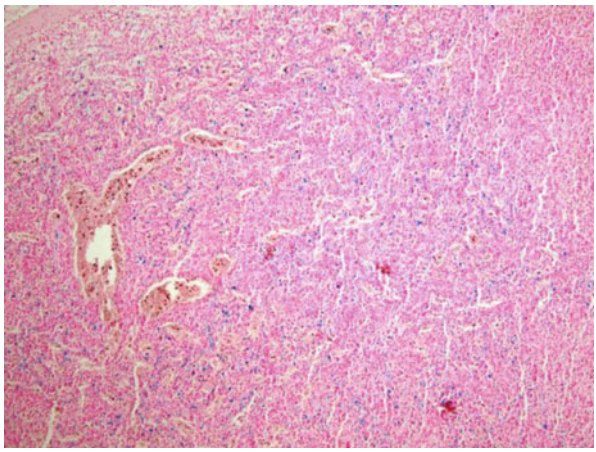

Fig. 24.5 Secondary siderosis (spleen) (Perls stain ×40)

Blood specimens are collected in heparin-containing tubes. Furthermore, a liver specimen of approximately 1–5 g should be collected and frozen as soon as possible at −70 °C. Skin/tendon specimens should be collected and placed in culture media for fibroblast culturing (Rinaldo 2010).

Investigation of Pediatric Starvation and Malnutrition

In all cases of pediatric starvation, a scene investigation must be carried out. An interview with the caregivers concerning a personal history of abuse, eating disorders, psychopathology, and alcohol and drug use is necessary. The caregiver also must be interviewed concerning feeding history, formula preparation, and the medical history of the child (Table 24.9) (Collins 2010; Hobbs et al. 1999; Reece 2009).

WHO has recommended a checklist for taking a child's medical history and conducting a physical examination that is useful for the examination of cases of malnutrition in developing countries (Table 24.10). Some laboratory tests are useful in the investigation of cases of pediatric malnutrition (Table 24.11). There is a large list of diseases that may mimic pediatric dehydration and starvation, and that must be investigated thoroughly (Table 24.12). Organic diseases as causes of malnutrition and dehydration must be ruled out. The medical history of the case should be studied, and histological investigations are of the utmost importance (Table 24.12).

For inexperienced and socially isolated mothers, malnutrition and failure to thrive may be unintentional (Table 24.13).

Unintentional failure to thrive may be seen in cases of inadequate nutrition, prolonged breast-feeding without adequate supplementation, overdilution

Table 24.9 Investigation of pediatric starvation and malnutrition

Investigation of pediatric starvation/ malnutrition	Medical investigation of pediatric starvation/ malnutrition
Interview of caregivers (personal history of abuse, eating disorders, psychopathology, alcohol and drug use, domestic violence, social skills)	Medical history (genetic conditions, growth history, endocrine disorders, caregivers' knowledge of normal growth and development, eating pattern, types of food available in the house)
Feeding history	Well-baby pediatric clinic records
Formula sample	Women, infants, children (WIC) records
Manufacturer of formula for content and concentration	Charting of body measurements over time
Interview of siblings	Development over time
Interview of neighbors and family	Comparison of growth and development with family/social history
Determination of any changes in household (e.g., financial, new partner, drugs, etc.)	
Social service records or social history	
Medical history	
Birth records	
Well-baby pediatric clinic records	
Home visit by health professional	

From K.A. Collins, 2010 (modified)

of formulas, milk-free diets that are low in protein, homemade formulas with inappropriate composition, and cult diets (Block and Krebs 2005; Byard 2010).

Classification of Protein-Energy Malnutrition

Anthropometrical data for starved persons and the organ weights should be routinely compared to those of a reference population. These data are the essential basis for the diagnosis of starvation. However, comparison with reference values or percentile charts alone does not permit grading of the degree or stage of malnutrition.

Several classification systems have been developed to estimate PEM in third-world countries (Gomez et al. 1955; Waterlow 1972, 1973; World Health Organization 1999). Especially for forensic pathologists, these classifications are superior to percentile charts because anthropometrical data allow also an estimate of the degree of malnutrition. Those gradings of PEM have been successfully applied to affected individuals in third-world countries, but they may also be used for the classification of infantile malnutrition in cases of starvation as a result of deliberate withholding of food (Madea 2005; Madea et al. 1994).

The body weight should be related to the expected weight for the respective age group. Because undernutrition is not always acute but may also be chronic,

Table 24.10 Checklist of points for taking a child's medical history and conducting a physical examination

Medical history:
Usual diet before current episode of illness
Breast-feeding history
Food and fluids taken in past few days
Recent sinking of eyes
Duration and frequency of vomiting or diarrhea, appearance of vomit or diarrheal stools
Time when urine was last passed
Contact with people with measles or tuberculosis
Any deaths of siblings
Birth weight
Milestones reached (sitting up, standing, etc.)
Immunizations
Physical examination:
Weight and length or height
Edema
Enlargement or tenderness of liver, jaundice
Abdominal distension, bowel sounds, "abdominal splash" (a splashing sound in the abdomen)
Severe pallor
Signs of circulatory collapse: cold hands and feet, weak radial pulse, diminished consciousness
Temperature: hypothermia or fever
Thirst
Eyes: corneal lesions indicative of vitamin A deficiency
Ears, mouth, throat: evidence of infection
Skin: evidence of infection or purpura
Respiratory rate and type of respiration: signs of pneumonia or heart failure
Appearance of feces

WHO 1999

classification systems that were developed for chronic PEM in the third world should also be used (Table 24.14). They may be particularly helpful in distinguishing acute from chronic malnutrition. Simpler classifications such as the Wellcome classification or the Gomez classification of PEM use the expected weight for the respective age group as standards (Tables 24.14, 24.15).

With these classifications, because small infants will always be of low weight, chronic and acute undernutrition cannot be distinguished. Furthermore, infants who are tall for their age and have a reduced body weight would be classified as normal and, accordingly, a chronic state of malnutrition cannot be recognized. However, these classifications are superior to simple percentile charts insofar as grading of the degree of malnutrition can be achieved.

The Waterlow classification of PEM takes into account not only the weight but also the height and the expected weight for the actual height (Tables 24.14, 24.16). Using this classification system, it becomes evident that those infants are not only

Table 24.11 Laboratory tests for investigation of malnutrition

Test	Result and significance
Tests that may be useful	
Blood glucose	Glucose concentration <54 mg/dl (3 mmol/l) is indicative of hypoglycemia
Examination of blood smear by microscopy	Presence of malaria parasites is indicative of infection; anemia, malignancy
Hemoglobin or packed-cell volume	Hemoglobin <40 g/l or packed-cell volume <12 % is indicative of severe anemia
Examination and culture of urine specimen	Bacteria on microscopy (or >10 leukocytes per high-power field) is indicative of infection
Examination of feces by microscopy	Blood is indicative of dysentery Giardia cysts or trophozoites is indicative of infection
Chest X-ray	Pneumonia causes less shadowing of the lungs in malnourished children than in well-nourished children Vascular engorgement is indicative of heart failure Bones may show rickets or fractures of the ribs Osteopenia
Radiographs	Osteopenia, rickets, osteomyelitis
Skin test for tuberculosis	Often negative in children with tuberculosis or those previously vaccinated with BCG vaccine
Metabolic and chromosomal analysis	
Vitreous chemistry	
Fecal test for retrovirus	
Serum viral antibodies	
Tests that are of little or no value	
Serum proteins	Not useful in management, but may guide prognosis
Test for human immunodeficiency virus (HIV)	If done, should be accompanied by counseling of the child's parents and result should be confidential
Electrolytes	Rarely helpful and may lead to inappropriate therapy

WHO 1999

light for their age (loss of body weight of 50 % of the standard value of the same age group), but also, as a sequel to chronic malnutrition, are impaired in their growth.

Data from 12 starved infants (cases taken from the author's cases and the literature) with an estimation of state of nutrition according to the Waterlow classification are presented in Table 24.17. These calculations are based on measurements and weight determination at autopsy. In these cases, the actual body weight related to the expected body weight for the actual height reveals (according to the Waterlow classification) severe life-threatening malnutrition. Nearly all infants were well below the critical values for severe malnutrition that are given in the literature. In all cases shown in Table 24.17, the actual weight as a percentage of the ideal weight for height is near or below 70 %. Of course, cutoff values for fatal starvation are

Table 24.12 Potential mimickers of pediatric starvation, malnutrition and dehydration (Modified from Collins 2010)

Potential mimickers of pediatric dehydration	Potential mimickers of pediatric starvation/malnutrition
Diabetes mellitus	Oromotor abnormalities
Diabetes insipidus	Cleft palate
Chromosomal and genetic disorders/mental retardation	Pyloric stenosis
Neuromuscular incoordination	Celiac disease, short gut syndrome
Metabolic disorders	Intestinal malabsorption, enzyme deficiencies
Cystic fibrosis	Cystic fibrosis
Viral gastroenteritis	Glycogen storage diseases
Congenital adrenal hyperplasia	Carcinoma, malignancy
	Congenital heart disease
	Cerebral palsy
	Chromosomal and genetic diseases
	Congenital heart diseases
	Neurologic diseases
	Immunodeficiencies
	Side effects of therapies and prescribed medications
	Chronic exposure to toxins and drugs
	Rare metabolic diseases
	Food allergy

Table 24.13 Causes of failure to thrive (From Block and Krebs 2005)

Unintentional
Breast-feeding difficulties
Errors in formula preparation
Poor diet selection
Improper feeding technique
Organic diseases
Cystic fibrosis
Cerebral palsy
HIV infection/AIDS
Inborn errors of metabolism
Celiac disease
Renal disease
Lead poisoning
Major cardiac disease
Child neglect

Table 24.14 Classifications of protein energy malnutrition (PEM)

Wellcome classification of PEM **Body weight related to age**	**Without edema**	**With edema**
60–80 %		
<60 %	Malnourishment,	
marasmic	Kwashiorkor,	
marasmic		
GOMEZ Classification of PEM		
Body weight related to age (% of reference value)		
90–110 %	Normal	
75–89 %	Grade I: malnourishment (mild)	
60–74 %	Grade II: malnourishment (moderate)	
<60 %	Grade III: malnourishment (severe)	

Waterlow classification of PEM		
	Height (body height for age in %)	**Body weight–height relation (weight related to height in %)**
Normal	>95 %	>90 %
Mild	87.5–95 %	80–90 %
Moderate	80–87.5 %	70–80 %
Severe	<80 %	<70 %

Table 24.15 Simplified classification of protein-calorie malnutrition

	Body weight as % of standard[a]	**Edema**	**Deficit in weight for actual height**
Underweight child	80–60	0	Minimal
Nutritional dwarfing	<60	0	Minimal
Marasmus	<60	0	++
Kwashiorkor	80–60	+	++
Marasmic Kwashiorkor	<60	+	++

[a]Standard taken as 50th percentile of Harvard values (Modified according to WHO 1971).

Table 24.16 Grading of protein-energy malnutrition

Stunting (chronic malnutrition)				
Grade	0	1	2	3
Actual height in % of normal height of respective age group	>95 %	95–87.5 %	87.5–80 %	<80 %
Wasting (acute malnutrition)				
Grade	0	1	2	3
Actual weight in % of normal weight for height	>80 %	90–80 %	80–70 %	>70 %

Information based on the Waterlow classification. By using this table, a grading of both chronic malnutrition (stunting) and acute malnutrition (wasting) can be achieved.

Table 24.17 Data for 12 infants who died of starvation with estimation of the state of nutrition according to the Waterlow classification; in some cases (e.g., 10, 11) signs of dehydration were also present

	Age	Sex (M/F)	Actual height in cm	Normal height for respective age in cm	Actual height in % of normal height for respective age	Actual weight in g	Normal weight (50 % percentile for age) in g	Actual weight in % of normal weight	Ideal weight for height in g	Weight in % of ideal weight for height
Case 1	7 weeks	M	53	58	91.4	2,010	4,540	44	3,900	51.5
Case 2	3 months	F	55	59	93.2	2,570	5,600	54.8	4,500	57.1
Case 3	5 months	M	61	66	92	4,020	7,300	55	5,800	69.3
Case 4	6.5 months	F	56	68	96.5	3,400	7,500	45	4,800	70.8
Case 5	7 months	M	58	70	82.8	3,520	7,700	45	5,000	70.4
Case 6	7 months	F	59	68	86.8	2,720	7,700	35	5,600	48.6
Case 7	8.5 months	F	53	70	75.7	2,500	8,300	30	3,900	64.1
Case 8	14 months	F	68	76	89.5	4,740	10,300	46	8,000	59.25
Case 9	2.4 years	F	86	88	97.7	6,800	12,700	53.5	12,300	55.3
Cases 10 + 11 (twins)	2.5 years 2.5 years	M M	79 79.5	92.3 86.1	85.6 86.1	6,510 6,200	13,600 13,600	47.9 45.6	10,700 10,750	60.8 57.9
Case 12	2.5 years	M	78	84.5	84.5	5,450	13,600	40.1	10,900	50

Calculation based on measurements and weights determined at autopsy (own cases) or on measurements given in Adelson et al. (1963), respectively (From Madea 2005)
M male, *F* female

Table 24.18 Classification of malnutrition in adults by body mass index[a]

Body mass index	Nutritional status
≥18.5	Normal
17.0–18.49	Mild malnutrition
16.0–16.99	Moderate malnutrition
<16.0	Severe malnutrition

[a]WHO (1999)

missing in the literature; there are only occasional published case reports on starvation using the Waterlow classification, and the actual weight at the time of death depends on various other factors such as dehydration and infections. Because most cases show a weight quotient below 70 %, this may be an indication of the validity of the grading of the Waterlow classification concerning the severity of starvation. Four of the infants over 1 year of age presented "stunted" (height below 90 % of normal) for the respective age group, whereas infants younger than 1 year have mainly a quotient above 90 %. One may speculate that in older infants undernutrition may have lasted longer (weight remains constant after result of stunting), whereas in younger infants undernutrition caused death more rapidly without the possibility of compensation of body weight as a result of stunting.

Malnutrition in Adolescents and Adults

Severe malnutrition in adolescents and adults occurs in famine, situations of dependency (e.g., in the elderly), those with mental illnesses, and in prisoners. Malnutrition in adolescents and adults is often associated with other illnesses such as chronic infections, intestinal malabsorption, alcohol and drug dependence, liver disease, endocrine and auto immune diseases, cancer, and AIDS (WHO 1999). In adults over 18 years, malnutrition is classified using the body mass index (BMI). BMI is defined as the body weight (in kilograms) divided by the square of the height (in meters, Table 24.18).

For adolescents (10–18 years), a WHO expert committee has recommended BMI-for-age as the indicator of thinness, the cutoff value being <5th percentile. In that case, or when nutritional edema exists, malnutrition should be diagnosed. For stunting or low height-for-age, the cutoff value is <3rd percentile or below −2 SD of the median NCHS/WHO reference values (WHO 1999).

Comparison of Different Criteria for Defining Acute Malnutrition

Anthropometric variables such as weight, height, and length are used to define nutritional status. Worldwide, various classification systems have been developed, and cutoff points are used to define and classify malnutrition (mild, moderate, severe). These classification systems were originally established to describe syndromes of protein-energy-malnutrition in children in developing countries (Tables 24.19 and 24.20).

Table 24.19 Different criteria for defining acute malnutrition

Anthropometric criteria of failure to thrive
Weight <75 % of median weight for chronological age (Gomez criterion)
Weight <80 % of median weight for length (Waterlow criterion)
Body mass index for chronological age <5th centile
Weight for chronological age <5th centile
Length for chronological age <5th centile
Weight deceleration crossing more than two major centile lines; centile lines used: 5, 10, 25, 50, 75, 90, 95, from birth until weight within the given age group
Conditional weight gain = lowest 5 % adjusted for regression towards the mean from birth until weight within the given age group

From Olsen et al. (2007)

Table 24.20 Criteria for defining acute malnutrition

Reference	**"Mild"**	**"Moderate"**	**"Severe"**
Gomez et al.	75–90 % standard weight	60–74 % standard weight	<60 % standard weight
Tanner et al.		<5th percentile WFH	
Waterlow	80–90 % WFH	70–80 % WFH	<70 % WFH
WHO		−3 < WFH SD score < −2	WFH SD score < −3

Joosten and Hulst (2008)
WFH weight for height

Different anthropometric methods of classifying failure to thrive in order to identify children at risk and severity of malnutrition have been recommended. A comparison of these anthropometric indices revealed that the methods varied widely in categorizing children, with some identified as moderately or severely failing to thrive in one method and normal or mild in another.

The authors (Olsen et al. 2007; Raynor and Rudolf 2000) concluded that there is no simple anthropometric measure that highlights the degree of risk for a child. Weight alone, being the simplest, is still the most reasonable marker for failure to thrive (Raynor and Rudolf 2000). According to these authors, there is no simple anthropometric measure that highlights the degree of risk for a child. Olsen et al. (2007) compared seven criteria of failure to thrive. The concurrence among the criteria was generally poor, with more children identified by only one criterion. Positive predictive values for different criteria ranged from 1 % to 58 %. No single measurement on its own seems to be adequate for identifying nutritional growth delay. For cases of fatal starvation, we have had good experience with the Waterlow classification (see above) (Madea 2005; Madea and Banaschak 1999; Madea et al. 1994).

STAMP

STAMP (Screening Tool for the Assessment of Malnutrition in Pediatrics) is a validated nutrition screening tool in the United Kingdom for use in hospitalized

children aged 2–16 years. STAMP is a simple five-step tool that was developed by a team from the Royal Manchester Children's Hospital and the University of Ulster. STAMP provides a simple way of determining whether a child is at risk of malnutrition and also provides guidance in developing a care plan according to the child's overall risk of malnutrition. The five steps are listed in Table 24.21.

- Step 1: diagnosis: Does the child have a diagnosis that has any nutritional implications (see Table 24.22)?
- Step 2: nutritional intake: What is the child's nutritional intake?
- Step 3: weight and height
- Step 4: overall risk of malnutrition by adding the scores from step 1 to step 3 together
- Step 5: develop a care plan.

Information about STAMP can be found at www.stampscreeningtool.org.

Duration of Starvation

Published data concerning the duration of starvation until death involve mainly the acute withdrawal of food and liquid until death in adults, or infants with inborn malformations of the upper gastrointestinal tract. It seems possible to survive without food and drink within the time span of 8–21 days; if a person is only deprived of food, the survival time may increase to about 2 months (although this is influenced by many other factors). According to observations in 10 young, previously healthy hunger strikers (mean age 25.6 $\pm$ 0.7 years) the survival period until death varied between 53 and 73 days (means 61 $\pm$ 2.5 days) (Leiter and Marliss 1982). These data are, of course, only of limited value in cases of chronic starvation, especially in infants in whom birth was premature and failure to thrive was reported in medical records.

In inborn malformations of the upper gastrointestinal tract, for instance, atresia of the esophagus, survival from 3 to 4 days was observed; in cases of atresia of the small bowel or duodenum, survival from 3–5 days up to 10 days has occurred.

Physical Condition Prior to Death

Medical records of affected infants must be reviewed to identify evidence of the duration of malnutrition (body weight, height, Table 24.10). The medical expert witness may be asked whether some time (days to weeks) prior to death, undernutrition of the child was recognizable (e.g., by caretakers, such as the parents or health-care workers). If so, the caretakers would have been obliged to request medical advice and care. In such cases, extrapolation of the time interval prior to death may be made by taking as a basis that complete withholding of food results in a loss of body weight of about 0.7–1 % of total body weight per day. Using the Waterlow classification, the extrapolated body weight related to the ideal weight for height gives an impression of the severity of malnutrition. When withholding of

Table 24.21 STAMP screening form

Step 1 – Diagnosis				
Does the child have a diagnosis that has any nutritional implications	Score	1st screening	2nd screening	3rd screening
Definite nutritional implications	3			
Possible nutritional implications	2			
No nutritional implications	0			
Step 2 – Nutritional intake				
What is the child's nutritional intake	Score	1st screening	2nd screening	3rd screening
No nutritional intake	3			
Recently decreased or poor nutritional intake	2			
No change in eating patterns and good nutritional intake	0			
Step 3 – Weight and height				
Use a growth chart or the centile quick reference tables to determine the child's measurements	Score	1st screening	2nd screening	3rd screening
		wt:	wt:	wt:
		ht:	ht:	ht:
>3 centile spaces / ≥3 columns apart (or weight <2nd centile)	3			
>2 centile spaces / = 2 columns apart	1			
0–1 centile spaces / columns apart	0			
Step 4 – Overall risk of malnutrition				
Add up the scores from the boxes in steps 1–3 to calculate the overall risk of malnutrition	Score	1st screening	2nd screening	3rd screening
High risk	≥4			
Medium risk	2–3			
Low risk	0–1			
Step 5 – Care plan				
What is the child's overall risk of malnutrition, as calculated in step 4?	Use management guidelines and/or local nutrition policies to develop a care plan for the child			
High risk	Take action			
	Refer the child to a dietitian, nutritional support team, or consultant			
	Monitor as per care plan			
Medium risk	Monitor the child's nutritional intake for 3 days			
	Repeat the STAMP screening after 3 days			
	Amend care plan as required			
Low risk	Continue routine clinical care			
	Repeat the STAMP screening weekly while the child is an in-patient			
	Amend care plan as required			

Table 24.22 Diagnostic table to be used to assign a score for step 1 of STAMP

Definite nutritional implications	Possible nutritional implications	No nutritional implications
Bowel failure, intractable diarrhea	Behavioral eating problems	Day case surgery
Burns and major trauma	Cardiology	Investigations
Crohn's disease	Cerebral palsy	
Cystic fibrosis	Cleft lip and palate	
Dysphagia	Celiac disease	
Liver disease	Diabetes	
Major surgery	Gastroesophageal reflux	
Multiple food allergies/ intolerances	Minor surgery	
Oncology on active treatment	Neuromuscular conditions	
Renal disease/failure	Psychiatric disorders	
Inborn errors of metabolism	Respiratory syncytial virus (RSV)	
	Single food allergy/intolerance	

Source STAMP, www.stampscreeningtool.org

food was not absolute, it can be assumed that the real body weight for the extrapolated time was lower in a particular case of chronic starvation.

Calculations have been recommended to determine the duration of starvation from the estimated caloric deficit. However, these calculations are based on a number of assumptions that may not be appropriate for the case in question (Byard 2010; Meade and Brissie 1985).

Immediate Cause of Death

The final causes and mechanisms of death in cases of starvation may be infectious complications, ventricular tachyarrhythmia, or hypoglycemic coma (Rich et al. 1990). Furthermore, starvation may be accompanied by lethal dehydration.

Manifestations of Child Neglect

Physical neglect is defined as deprivation of necessary care, including sufficient nourishment and hydration. Manifestations of child neglect are (Block and Krebs 2005; Hobbs et al. 1999; Reece 2009):

- Nonadherence (noncompliance) with health-care recommendations
- Delay or failure in obtaining health care
- Refusal of medical treatment
- Failure to thrive, food insecurity (limited access to enough food), hunger
- Drug-exposed newborns and older children

– Inadequate protection from environmental hazards
– Inadequate nurture and affection
– Inadequate supervision or abandonment
– Inadequate hygiene
– Inadequate clothing
– Educational neglect

In children, failure to thrive (FTT) can often be observed due to neglect. However, inadequate nutrition causes not only poor weight gain but also delayed development and abnormal behavior as well as disturbed social interactions.

Risk factors as a cause of FTT include (Block and Krebs 2005):

– Parental depression, stress, marital strife, divorce
– Parental history of abuse as a child
– Mental retardation and psychological abnormalities in the parent(s)
– Young and single mothers without social supports
– Domestic violence
– Alcohol or other substance abuse
– Previous child abuse in the family
– Social isolation and/or poverty
– Parents with inadequate adaptive and social skills
– Parents who are overly focused on career and/or activities away from home
– Failure to adhere to medical regimens
– Lack of knowledge of normal growth and development
– Infant with low birth weight or prolonged hospitalization

Dehydration

A man of 70 kg body weight consists of 60 % water, representing altogether 42 l. The main part of the water is found in the intracellular compartment (40 % related to the body weight), while interstitial and intravascular water make up 16 % and 4 %, respectively (Fig. 24.6). Both water and electrolyte metabolism are regulated within narrow ranges to maintain homeostasis. The loss of 15 % of body water after acute and over 20 % after longer-lasting dehydration is fatal. Although the extracellular space makes up only one third of the total body water, the single water spaces are regulated mainly by the extracellular fluid compartment. Newborns and infants are extremely susceptible to dehydration. Daily fluid intake and excretion account for 10–20 % of body weight, while in adults it is just 3–4 % of body weight. For a 7-kg infant, fluid exchange accounts for half of the extracellular space, while in adults only for 1/7th. This means that in infants half of the extracellular volume has to be replaced daily, but in adults only 1/7th. The regulation of water–electrolyte metabolism may be reversibly or irreversibly disturbed in the following ways:

1. Ambient factors (hemorrhage, thirst, hot environment)
2. Diseases of the regulating organs (enteritis, renal insufficiency, burns, respiratory insufficiency)

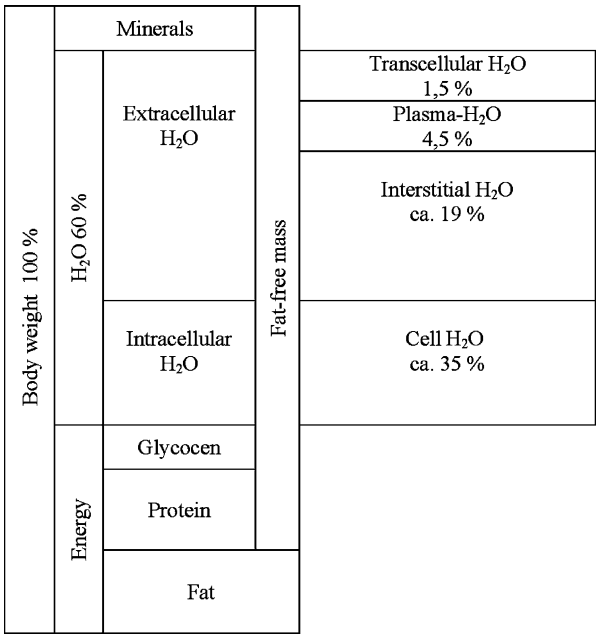

Fig. 24.6 Fluid compartments of the body

3. Diseases of regulating endocrine organs (diabetes insipidus, Addison's disease).

External factors (point 1), such as the hypertonic dehydration due to liquid deprivation, the forced feeding of salt, or water intoxication, are of the utmost forensic importance. Classical autopsy findings to substantiate the diagnosis of hypertonic dehydration are

- Poor skin turgor
- Tenting of skin
- Sunken eyes
- Dry galea and dry organ surfaces (Fig. 24.7)

During life, the loss of body water results in an elevation of sodium-, chloride-, and urea nitrogen-levels in blood; therefore, it can be readily diagnosed.

A grading of dehydration based on clinical findings can be found in Table 24.23.

Case Example

An 8-month-old girl was brought to a pediatric clinic with severe dehydration. At presentation, the girl had clinical signs of severe hypertonic dehydration (apathetic, no adequate reactions, tenting of skin, dry mucosa, sunken eyes). There was elevation of sodium (173 mmol/l), creatinine (0.94 mg/dl), and urea (100 mg/dl).

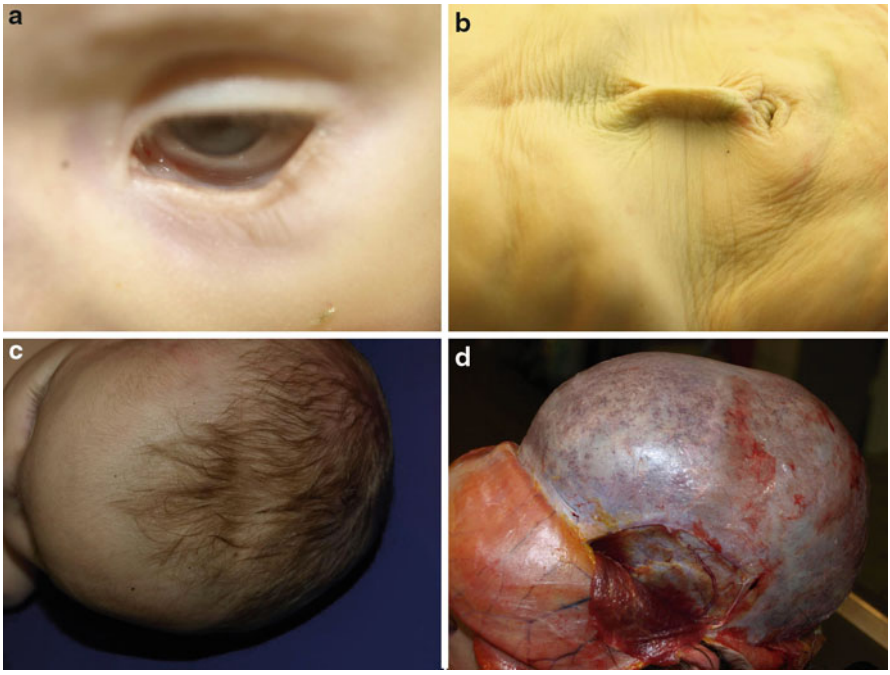

Fig. 24.7 Typical autopsy findings in hypertonic dehydration: (**a**) sunken eyes; (**b**) tenting of skin; (**c**) sunken fontanelles; (**d**) dry galea

Body weight was 6,800 g. The hypertonic dehydration was treated with intravenous fluid administration. Within a few days the laboratory tests normalized (sodium 141 mmol/l, creatinine 0.36 mg/dl, urea 6 mg/dl). Nine days after admission the girl was discharged. The background of this case was that the father of the girl murdered the mother by ligature strangulation and left the infant alone with the dead mother for 7 days without any care and nutrition. In court, it was a question whether it was possible for an 8-month-old infant to survive for 7 days without any fluid administration. From the older literature it is already known that infants with severe malformations can survive for several days, for example, in esophageal atresia for 7 days and in duodenal atresia from 3–5 to 12 days. The loss of 15 % of the water content of the body causes a life-threatening situation. This loss is achieved after 6–8 days of total fluid deprivation. A loss of more than 20 % of water content causes death. A normal daily water intake in adults is approximately 2.5 l and is comprised of water in drinks, water in food, and oxidation water from metabolism.

The mean water turnover in relation to body weight is 1–30 (2.5 l divided by 70 kg body weight) for adults and for infants 1–10 (0.7 l divided by 7 kg body weight). Therefore, babies are much more susceptible to dysregulations of water metabolism.

Table 24.23 Grading of dehydration based on clinical findings

Degree of dehydration			
Clinical symptoms	Minimal	Mild to moderate	Severe
Turgor	Normal/ slightly reduced	Reduced	Tenting of skin
Mucous membrane	Dry	Rough	Cracked
Appearance	Thirst, well, alert	Tachycardia, decreased blood pressure, sunken eyes, sunken fontanelles	Shock, rapid thready pulse, cyanosis, cold extremities, deep breathing, lethargy, unconsciousness, seizures
Urine production	Still normal	Decreased	Absent
Loss of body weight			
Suckling babe	<5 %	5–10 %	>10 %
Child	<3 %	3–6 %	>6 %
Expected fluid deficit (ml/kg body weight)			
Suckling babe	<50	50–100	>100
Child	<30	30–60	>60

Dehydration Pattern in Vitreous Humor

Due to postmortem loss of selective membrane permeability, a diagnosis of serum electrolyte disturbance at the moment of death is not possible postmortem. Serum values at the moment of death are, however, quite well reflected in the vitreous humor, and a characteristic dehydration pattern (Table 24.24) with elevation of sodium, chloride, and urea nitrogen can be diagnosed postmortem (Coe 1969, 1973). In all cases of suspected dehydration, vitreous humor should be analyzed so that these values can be used in determining the cause of death. However, conclusions must be drawn carefully and based on the complete morphological and toxicological status (Madea and Lachenmeier 2005).

Acute Dehydration

A 4-month-old boy was found dead by his mother in his bed. His last feeding had been 4 h prior to this. He had a history of hypertrophic pyloric stenosis, with an operation at the age of 1 month. The postoperative course was normal. At autopsy the boy showed signs of neglect, body weight 4,060 g (67.6 % of weight for height), body length 61 cm, sunken eyes, scaphoid abdomen, depressed fontanelles with protruding ribs, tenting of skin, nearly empty stomach and gastrointestinal tract, and hepatic microvesicular steatosis. In the vitreous humor there

Table 24.24 Vitreous humor values

Antemortem abnormality	Flame photometry or SMA 6/60	Ektachem 400	Beckmann Astra
Dehydration:			
Sodium (mmol/l)	>155	>165	>155
Chloride (mmol/l)	>135	>125	>140
Urea nitrogen (mg/dl)	40–100	40–100	40–100
Low salt condition:			
Sodium (mmol/l)	<130	<135	<130
Chloride (mmol/l)	<105	<95	<110
Potassium (mmol/l)	<15	<15	<15

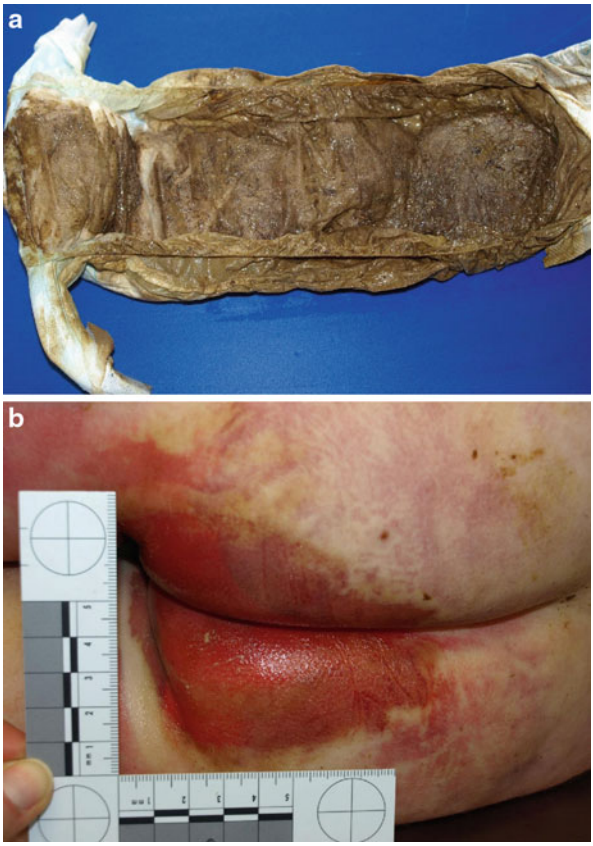

Fig. 24.8 Fatal neglect in a 9-year-old disabled boy: (**a**) soiled diaper due to poor hygiene; (**b**) maceration and erythema of the skin

were elevated levels of sodium (169 mmol/l), chloride (157 mmol/l), creatinine (3.05 mg/dl), and urea (254 mg/dl). The cause of death was malnutrition with dehydration. The body weight was below 70 % of weight for height and weight for age, respectively.

Table 24.25 Comparison of clinical signs of dehydration and septic shock in the severely malnourished child

Clinical sign	Some dehydration	Severe dehydration	Incipient septic shock	Developed septic shock
Watery diarrhea	Yes	Yes	Yes or no[a]	Yes or no[a]
Thirst	Drinks eagerly[b]	Drinks poorly	No[a]	No[a]
Hypothermia	No	No	Yes[a] or no	Yes[a] or no
Sunken eyes	Yes[b, c]	Yes[b, c]	No[a]	No[a]
Weak or absent radial pulse	No[b]	Yes	Yes	Yes
Cold hands and feet	No[b]	Yes	Yes	Yes
Urine flow	Yes	No	Yes	No
Mental state	Restless, irritable[b]	Lethargic, comatose	Apathetic[a]	Lethargic
Hypoglycemia	Sometimes	Sometimes	Sometimes	Sometimes

WHO (1999)
[a]Signs that may be useful in diagnosing septic shock
[b]Signs that may be useful in diagnosing dehydration
[c]If confirmed as recent by the mother

Dehydration in a 9-Year-Old Disabled Boy

A 9-year-old boy was found dead in his bed. He had a history of mental retardation, epilepsy, and folate deficiency, body length 118 cm, body weight 21.3 kg, both much below the 3rd percentile for age. The diaper was full of feces and urine (weight 610 g) (Fig. 24.8a). The boy presented with severe dehydration and malnutrition, with sunken eyes, tenting of skin, dry skin and dry mucosa, an empty stomach, and only a small amount of feces in small and large intestine. Signs of neglect also included maceration and erythema of the skin of the buttocks and scrotum (Fig. 24.8b). There was hepatic microvesicular steatosis, fatty degeneration of renal tubular epithelium, bronchitis, peribronchitis, and an early bronchopneumonia. In the vitreous humor, there were elevated values of sodium (150 mmol/l), chloride (147 mmol/l), urea (410 mmol/l), and osmolality (428 mosmol/kg). The cause of death was dehydration in combination with hypothermia and early bronchopneumonia. The boy had been left unattended by his mother for a week; his caretaker was an underage sister who had left him in his bed in his room with open windows, unattended for several days.

Acute Dehydration Due to Wrong Diet

A 3-month-old infant was treated in hospital for "toxicosis and prolonged gastroenteritis." The child required a special diet with Alfaré. With this diet, the weight increased in hospital from 3,900 to 4,710 g over 3 weeks. One evening the parents appeared at the hospital and took the infant home against the advice of doctors. The attending physician informed the parents that the infant required a special diet

with Alfaré. Twenty-six hours later the infant was found dead at home. At autopsy, signs of severe dehydration were present with a body weight of 3,900 g (loss of 17 % of body weight within 1 day). Using immunological methods with an Ouchterlony test it could be demonstrated that the child was fed with contraindicated food (powdered milk) instead of the special diet. In the Ouchterlony test, precipitation lines for the powdered milk and bovine protein using antibovine antibodies were observed while the special diet showed no precipitation lines.

Both parents received sentences of manslaughter.

In developing countries, clinical signs of dehydrations must be distinguished from septic shock in severely malnourished children. A helpful table was recommended by WHO in 1999 (Table 24.25).

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Pediatric Suicide

25

Kim A. Collins

Contents

Abstract

Classifying the manner of death as suicide is often difficult in the younger victim. Some investigators try to determine intent while others use an age cutoff to separate accident versus suicide or undetermined versus suicide. If variables are studied, methods examined, and the definition of suicide held consistent, the determination is not necessarily easier from a humane or emotional viewpoint but is at least epidemiologically sound. By methodically examining cases and trends, treatment and prevention can hopefully be successful.

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Introduction

Suicide among children and adolescents has recently been studied in an attempt to better classify the typical victim, method(s), and risk factors. For the purposes of this chapter, children will be defined as less than or equal to 19 years of age. The World Health Organization defines adolescents as 10–19 years of age (http://www.un.org.in/Jinit/who.pdf). Preadolescents are 0–9 years of age. Due to physiological, developmental, social, and emotional differences, child suicide victims cannot be examined as a single group. While no exact dividing line exists, it is best to divide these individuals into three distinct groups: 0–9 years of age, 10–14 years of age, and 15–19 years of age. Although some statistics may differ according to geography and demographics, common features of childhood suicide will be discussed in this chapter.

Terminology

Manner of death is the classification of how a death occurred. Five manners of death are commonly used: natural, accident, homicide, suicide, and undetermined. Sir Thomas Browne was the first to coin the term "suicide" in 1642 (Minois 1999). Suicide is death brought about by a self-inflicted act which is meant to end one's life or to do self-harm. A suicide may also be classified as the manner of death if a person dies from an intentional self-inflicted act that was meant to, or has an inherently high risk of, resulting in self-harm or death.

Suicidality is a broad term which refers to suicidal ideation and/or attempts, thoughts, or actions that if fully carried out may lead to serious self-injury or death (Pfeffer 1981). It is the attempt to cause self-injury or death regardless of the cognitive ability to understand finality, lethality, or outcomes (Pfeffer 1997, 2000; Connolly 1999).

Suicidal ideation is the thought of killing oneself, the feeling of being tired of life, a belief that life is not worth living, and a desire not to wake from sleep. Suicidal ideation is more common in females than males and has been associated with self-reported depressive symptomatology and a higher risk of suicide attempts (Kosky et al. 1986; Centers for Disease Control and Prevention 2008).

Suicide attempt is a self-injurious act that includes some degree of seriousness and/or lethality.

Deliberate self-harm refers to an act of purposefully harming oneself physically that may or may not reflect a real suicidal intent (Greydanus and Apple 2011). The most common methods are overdosing, self-poisoning, and self-cutting. The risk for suicide increases considerably in those who express a strong desire for death, use a highly lethal method, take clandestine means to prevent detection, and/or have underlying untreated psychiatric disorders.

Self-mutilation is the direct and deliberate destruction or alteration of parts of the body without conscious suicidal intention (Favazza 1999).

Risk Factors

Risk factors for pediatric suicide will vary depending on the study population and demographics, but four categories of risks predominate in studies worldwide: (1) social and environmental, (2) psychiatric, (3) biological, and (4) life events (Self-Directed Violence 2002).

1. *Social and environmental*: Social alienation, social isolation, family adversity, problems with friends, poverty, and access to lethal methods (guns, medications).
2. *Psychiatric*: Depressive disorders, dysthymic disorders, bipolar disorder, schizophrenia, anxiety, conduct disorders, impulsivity, substance abuse, and eating disorders. Comorbid psychiatric disorders comprise a significant risk.
3. *Biological*: Much research has looked at suicide in twins and biological relatives. Suicide in a family member is a risk for subsequent suicide in a child (Kuramoto et al. 2010). Monozygotic twins have a significantly higher concordance for both suicide and suicide attempts than dizygotic twins. Also, abnormal neurobiological processes that underlie certain psychiatric disorders, such as those listed above, and chronic health conditions, such as epilepsy, diabetes, cerebral palsy, obesity, and scoliosis, carry an increased risk (Barnes et al. 2010).
4. *Life events*: Personal loss/bereavement, interpersonal conflict, relationship dissolution, legal problems, sexual abuse, physical abuse and neglect, and exposure to violence (Hagland et al. 2012; Singh and Lathrop 2008).

In addition, a previous suicide attempt is one of the most powerful predictors of subsequent fatal suicidal behavior (Miranda et al. 2008). The risk is higher in the first year and especially within the first 6 months, after the attempt (Moscicki 1985). On the other hand, the majority of those who commit suicide have not previously attempted it (Graham et al. 2000). Most suicides are not impulsive acts triggered by an isolated event but are a response to a long-term difficulty or stressful situation (Singh and Lathrop 2008).

Before examining the three categories of pediatric suicide, variables, and risk factors, three topics deserve mention: peer victimization, sexual orientation, and body image.

Peer Victimization

Youths who are threatened with or experience violence or who are injured by peers report more suicidal thoughts and behaviors than non-victimized youths (Kaminski and Fang 2009; Tishler et al. 2007). Youths threatened or injured by peers are 2.4 times more likely to report suicidal thoughts and 3.3 times more likely to report suicidal behavior than non-victimized peers. The violence need not be physical, and cyberbullying has gained notoriety recently. Adolescent peer aggression is strongly linked to suicidal ideation, suicide attempts, and completed suicide (Hinduja and Patchin 2010; Cooper et al. 2012). Research has also shown that the offender is also at greater risk for suicidality (Cooper et al. 2012).

Sexual Orientation

Gay, lesbian, and bisexual (GLB) youths are significantly (four to five times) more likely to attempt suicide compared to heterosexuals (Hatzenbuehler 2011; Bagley and Tremblay 2000). The risk of attempting suicide is 20 % greater in unsupportive environments compared to supportive environments (Hatzenbuehler 2011). Factors related to GLB suicide include discrimination, unsupportive environments, stress in interpersonal relations, anxiety over secrecy, anxiety about HIV/AIDS, and limited sources of support (Bagley and Tremblay 2000; Millard 1995; Stronski Huwiler and Remafedi 1998). Among GLB youths, over 40 % have attempted suicide (Tulloch et al. 1997).

Body Image

Adolescent body dissatisfaction and poor body image are risk factors for eating disorders and suicide in adolescents (Singh and Lathrop 2008). Females are concerned over weight, physical figure management, body fat, and peer and family judgment. Males are concerned over peer judgment and being teased. Girls most often feel overweight, and boys most often feel underweight. This dissatisfaction leads to health-compromising behaviors, drug use, steroid use, extreme weight fluctuations and body fat control, and suicide. Suicide is one of the major reasons for death among those with eating disorders and is the leading cause of death for females aged 14–25 years with anorexia nervosa. The rate of suicide in females with anorexia nervosa is 23 times higher than the general population (American Association of Suicidality 2010). Risk-taking behavior and suicide are also higher in extremely obese adolescents (Greydanus and Apple 2011; Ratcliff et al. 2011).

Pediatric Categories: Preadolescents, Younger Adolescents, and Older Adolescents

Preadolescents: Age 0–9 Years

Children as young as those in preschool may display suicidal behavior and thinking (Connolly 1999; Tishler et al. 2007) (Table 25.1). Suicide in the preadolescent age group of 0–9 years of age is not common but does occur. Most studies report suicide in this group beginning at 5 years of age (O'Leary et al. 2006; Clark et al. 1993; Pelkonen and Marttunen 2003). The current estimate is approximately 0.4–0.9 per 100,000 suicides in this group, a rate that has doubled over the past three decades (O'Leary et al. 2006). More males in this group commit suicide than females (Pelkonen and Marttunen 2003; Sauvageau and Racette 2008; Pandolfo et al. 2011; Lee et al. 1999; Centers for Disease Control and Prevention 1991) (M:F = 3:1) (Tishler et al. 2007). The leading cause of death is hanging, and the second most common is gunshot wound. The location of the event is usually in

Table 25.1 Childhood suicide trends

Victim category	Preadolescents	Younger adolescents	Older adolescents
Age range	5–9 years of age	10–14 years of age	15–19 years of age
Rate	~0.4–0.9 per 100,000	1 per 100,000	7 per 100,000
Gender	M:F = 3:1	M:F = 3:1	M:F = 3–5:1
COD	Hanging	Hanging, GSW	GSW, hanging
Location	Home	Home	Home, home vicinity
Toxicology	Negative	22–33 %+	9–33 %+
Note left	Unknown	Rare to 33 %	Rare to 39%
PMH/PPH	Depression; SI and SA reported	~25–30 % (<50 %), depression #1	~25–30 % (<50 %), depression #1
Previous SA	+ risk, unknown %	~20 %, F > M	~20 %, F > M
FHP, biological	FHP is a risk	FHP is a risk	FHP is a risk
Life events and stressors	Family violence, bullying	Negative home environment, bereavement, parental argument	~30–57 % experienced a life event stressor, #1 relationship problem

COD cause of death, *PMH* past medical history, *PPH* past psychiatric history, *GSW* gunshot wound, *SI* suicidal ideation, *SA* suicide attempt, *FHP* family history of psychopathology, *F* female, *M* male

the home (Clark et al. 1993). Risk factors include depression, family violence, and a family history of psychopathology (Roche et al. 2005; Kloos et al. 2007). Major depressive disorder affects 2 % of these preadolescents (M:F = 1:1). In this age group, exposure to violence and depression is strongly linked to suicidal ideation, and suicidal ideation in this age group is strongly linked to future suicide attempts (O'Leary et al. 2006). If a preadolescent attempts suicide, he/she is six times more likely to attempt suicide as an adolescent. The role of sexual orientation and the relationship between sexuality and suicide are probably not as important in this group, as emerging sexuality and its implications may not be strong in the prepubertal child (Kloos et al. 2007).

Adolescents: Age 10–19 Years

Adolescents comprise approximately 20 % of the world's population. This group has been referred to as "the orphan group" because few clinical trials and very little retrospective research have been performed. Adolescent deaths worldwide in descending order are due to accidents, AIDS, other infections, homicides, "war," and suicide. In 2002, the adolescent death rate in the United States (USA) was 68/100,000. Across the country, the most common reason for adolescent death was an accident, followed by natural disease, homicide, or suicide depending on the age category of the adolescent. In the 10–14-year age group, the ranking was accidents,

natural disease (cancer), and homicide, and in the 15–19-year age group, accident, homicide, and suicide. Malignant neoplasms are responsible for about 10 % of adolescent deaths in the USA. Natural cardiac deaths comprise a large number of cases and, in some studies, account for the majority of natural deaths in the forensic setting.

Suicides account for approximately 12 % of all adolescent deaths. Depression affects 5–8 % of adolescents, and the female-to-male ratio is 2:1. Attention deficit hyperactivity disorder (ADHD) is also a risk factor for adolescent suicide (Roche et al. 2005). In 2007, 14.5 % of US high school students seriously considered suicide in the preceding 12 months, and 6.9 % of students attempted suicide at least once (Centers for Disease Control and Prevention 2008). Male suicide victims outnumber females in the Western world, accounting for 71–86 %; however, since 2000, the rate of female suicides has been increasing (Centers for Disease Control and Prevention 1991; Batalis and Collins 2005; Shaw et al. 2005). Male adolescents are almost five times more likely to die from suicide although female adolescents attempt suicide more often (Singh and Lathrop 2008). The rate was higher in the 1990s than in the 1980s for all races, with an increase of about 100 %. A large increase was seen in the 15–19-year age group. In the USA, firearms are the most common mode of suicide, comprising over 70 % of cases. Suicides are more common in the white population than in the black population and in certain studies, males outnumber females. Only a minority leave a note, 4–39 % (Singh and Lathrop 2008; Shaw et al. 2005; Lee et al. 1999), although social media, cell phones, and laptops are being used more often in the young.

The 10–14-Year Age Group

For both males and females, a significant rise in the suicide rate is observed as a child moves from preadolescence into the 10–14-year age group. Males outnumber females by approximately 3:1 (Batalis and Collins 2005). In the USA, the suicide rate for this age group is 1 per 100,000. Suicidal ideation reaches its peak at approximately 14 years of age (Waldvogel et al. 2008). Most suicide attempts are by females, and the most common method is drug overdose (Pandolfo et al. 2011). Accident remains the most common manner of death, but natural death now ranks below suicide, and suicide is almost as common as homicide (Sauvageau and Racette 2008; Lee et al. 1999). The most common cause of suicidal death is gunshot wound or hanging, depending on the part of the world studied and the availability of the weapon (Pfeffer 1986). These two causes of death far outrank other causes such as poisoning and jumps from a height. Since 1998, hanging has outranked gunshot wound as the most common cause of suicidal death in the USA (Centers for Disease Control and Prevention 2004). Negative home environment, depression, and bereavement are strong risk factors for suicide in this age group (Tishler et al. 2007).

The 15–19-Year Age Group

In the 15–19-year-old group, we see homicides and suicides outnumber natural deaths. In the USA, the suicide rate in this age group is 7 per 100,000. The suicide rate was higher in the 1990s than in the 1980s for all races, with an

increase of about 100 %. A large increase was seen in the 15–19-year age group. Firearms are the most common method of suicide, comprising over 70 %. The weapon is most often owned by a family member (Johnson et al. 2010). In the USA, suicides are more common in the white population than in the black population. In studies, males outnumber females by approximately 5:1. The location is usually in the home in up to 65 % of cases (Johnson et al. 2010). Depending on the population studied, a minority (39 %) leave a note. Less than 50 % of victims have a documented psychiatric or mental illness history with studies reporting that only approximately 25–30 % have a psychiatric history (Pelkonen and Marttunen 2003; Lee et al. 1999; Johnson et al. 2010). Fifty-seven percent had recently experienced a relationship problem such as a romantic relationship problem/breakup, conflict with parents, and/or disciplinary crises (Tishler et al. 2007; Johnson et al. 2010; Asarnow et al. 2008; Wienberger et al. 2001). A previous attempt(s) is reported in 17–19 % (Johnson et al. 2010).

High-Risk Behavior and Russian Roulette

"Risk-taking behavior" is defined as any behavior where there is a high probability of death as an outcome. This ranges from participation in dangerous sports to drug, tobacco and alcohol use, sexual activity, and the use of weapons. Many adolescents are at significant risk for health-compromising problems resulting from the early initiation of such health-risk behaviors. During this time in their lives, they are entering into a stage of self-sufficiency, experimenting with independence and testing limitations for risky activities. Drives underlying risk-taking behavior surge during adolescence, while the capacity to control them lags. The origin of sensation seeking in the dopaminergic brain pathways drives interest in novel and rewarding activities. Research suggests that dopaminergic activity increases during adolescence, potentially fueling an increase in this sensation and then later declines (Collins 2010).

Russian roulette is one of the riskier activities that adolescents may participate in. The action is deliberate and carries with it the knowledge of a high probability of death. Russian roulette is usually classified as suicide because the act of placing a loaded gun to one's own head and pulling the trigger is inherently dangerous. By engaging in this activity, the individual accepts the risk of serious injury or death (Collins 2010).

Cluster and Copycat Suicides

A cluster suicide is defined as an excessive number of suicides occurring in close temporal and geographic proximity (Gould et al. 1989; Austin et al. 2011). Victims are usually adolescents or young adults who know one another, are peers, or learn of a suicide through the media. The role of peer pressure and imitation is significant especially when the individuals are already at risk (see preceding sections). Cluster suicides tend to occur in small communities and are known to

be influenced by various communications such as media transmissions, word of mouth, and discussions among friends. With the growth of information dissemination and the social media, geographic proximity becomes less of a factor. A copycat suicide is the emulation of a previous suicide. These suicides occur when an individual identifies with the previous suicide victim, supports the motive behind the suicide, is inspired by the suicide, or honors the act itself. The original suicide is sensationalized and often romanticized by the copycat or the copycat feels that suicide is the only option as it was for the original victim. The copycat will imitate the method of the suicide. Also, many copycat suicide victims are of the similar age, race, and gender to the victim in the original report.

Scene Investigation

The scene investigation is very important not only to aid in determining the cause of death but also to support suicide as the manner of death. The classifications of cause and manner may be deemed obvious at the death scene resulting in conclusion of the investigation.

However, an autopsy is recommended in all cases of suicide as well as analysis of the method used, e.g., gun, ligature, poison. Other evidence supporting suicide may also be discovered. This includes cell phone records, text records, electronic mail, computer documents, Internet usage and sites visited, reading materials, video materials, correspondences with friends, and/or a suicide note. Such corroborating information is used to correlate with the initial scene investigation and the autopsy findings in order to accurately assign the manner of death.

Conclusion

Only by acknowledging that pediatric suicide exists, studying each individual case, and examining trends can forensic pathologists, pediatricians, and investigators accurately assign the cause and manner of death and work toward future prevention of such tragedies. The healthcare community and general public must be cognizant of these potential suicide victims, family and social dynamics, and scenarios. Below are common trends that we currently see with these cases.

Common Trends of Pediatric Suicide

- Male > female.
- Most are aged 5–19 years.
- Many have a history of life stressors in the home or school environment.
- Peer pressure: bullying, sexual orientation, body image.
- Location is most often home.

- Method based on availability; gunshot wound and hanging.
- Minority leave a note.
- Minority (<50 %) have a documented past psychiatric history.
- Minority (~20 %) have attempted suicide in the past.
- Minority (~33 %) of adolescents have positive toxicology.
- Family psychopathology is a risk factor but its weight is unclear.

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Sports-Related Injuries and Deaths

26

Stephen J. Cina and Darin Trelka

Contents

Abstract

Physical activity in children and adolescents should be strongly encouraged. While there is a very low risk of death associated with participation in athletics within this age group, the epidemic of childhood obesity and sedentary lifestyle

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must be combated to ensure the long-term health and quality of life of today's youth. Sports-related deaths due to trauma are usually readily identified; others require careful examination, adjunctive testing, and/or the expertise of consultants. A thorough investigation of circumstances surrounding the death, review of the medical records, and autopsy is mandated in these cases.

Introduction

The loss of a child is always tragic. When death comes to a young person in peak physical condition engaged in athletics, the fatality strikes a blow to an entire community and often attracts the attention of the national media. In some cases, screening studies or training modifications could have prevented the end result. In many others, however, these sudden, unexpected deaths are the result of conditions that cannot reasonably be anticipated or avoided.

The benefits of physical activity in young people are incontrovertible. In fact, a presidential initiative has focused on the necessity for solid nutrition and exercise among American youth. Physical activity is essential to well-being, and it must be encouraged in children. Childhood obesity has dire health consequences and creates a pattern that can result in significant morbidity and mortality in later life (see ▶ Chap. 33, "Childhood Obesity"). That being said, engagement in athletics can result in serious injury or death, albeit very infrequently.

Deaths secondary to trauma are fairly self-explanatory so only a brief overview is in order. Much of this chapter will focus on natural disease processes and pathologic conditions that can present as sudden death while a child or adolescent is involved in physical activity.

Definitions

A sports-related fatality is one in which death occurs while the participant is engaged in athletics. Within this broad category, death can be directly attributed to an injury received during the activity in which case the manner of death is best certified as an "accident" provided that the trauma was received in accordance with the rules of the sport. In the case of death due to trauma inflicted flagrantly outside of the rules of the sport or if the lethal injury was intentionally inflicted, a manner certification of "homicide" may be more appropriate. In many cases, sudden death may be the result of physical stress superimposed upon a natural disease process or pathologic condition, often involving the heart. In this setting, the manner of death should be certified "natural," analogous to myocardial infarction occurring in an older person engaged in physical exertion (Froede 2003).

Traumatic Death

Head and Neck Injuries

The sequelae of repetitive blows to the head have attracted much attention in recent years (Omalu et al. 2005, 2010). While the manifestation of repeated concussions usually appears in middle age or later, it is probable that the damage begins when the brain is first jarred with resultant alteration in mental status that is characteristic of a concussion. What is certain is that concussions must be treated as a serious medical condition, and vigilance is necessary to ensure the safety of participants who are in a post-concussive state. The clinical entity known as the "second impact syndrome" (SIS) can cause morbidity and mortality following head injury (Bey and Ostick 2009). SIS is comprised of two events: (1) a concussive head injury and (2) a second head injury within several weeks followed by cerebral edema, herniation, and death. Although the incidence is arguable and is yet to be firmly established, it is thought to be a rare outcome of head injury (Bey and Ostick 2009). In any event, any athlete who manifests concussive symptoms following a head injury (e.g., fatigue, confusion, headache, nausea, vomiting) should be closely observed and not be permitted to return to play for 7–14 days (Bey and Ostick 2009) (Table 26.1).

Most serious head injuries occur in the traditional contact sports. They run a spectrum that includes superficial lacerations, contusions, and abrasions to skull fractures, cerebral contusions, deep axonal injury (in the delicate white matter of the brain), and intracranial bleeding.

When a human head collides with another object, skull fractures may occur. Protective gear, such as helmets, minimizes this risk in many sports. In an unprotected head, skull fractures may be associated with tearing of arteries within the bones of the calvarium, including the middle meningeal artery, resulting in epidural hematomas (EDH) that may evolve rapidly and compress the underlying brain. Cerebral contusions may also occur at the fracture site. These types of injuries are surgical emergencies. With a more significant direct impact to the head, an open fracture may occur with resultant direct injury and extrusion of the brain. Impacts to the face can result in fractures with resultant compromise of the upper airways.

Deceleration injuries to the head can also be devastating. When a moving or falling head makes contact with a firm surface, injuries to the brain and intracranial bleeding may occur. In contradistinction to the cerebral contusions and/or fractures directly subjacent to the site of impact of a moving object with a stationary head, deceleration injuries may be associated with contrecoup cerebral contusions. These lesions are located opposite to the site of impact of a moving head with a stationary surface. Common locations for contrecoup cerebral contusions are the inferior aspects of the frontal lobes and the anterior temporal lobes. Contrecoup contusions may or may not be accompanied by basilar skull fractures. Rapid deceleration of the cranial contents can also result in diffuse axonal injury (DAI) in the white matter and intracranial hemorrhage. Subdural hematomas (SDH) secondary to venous

Table 26.1 Guidelines for the management of sports-related concussion (Adapted from Bey and Ostick 2009)

Symptoms	First concussion	Second concussion
Grade 1: no loss of consciousness, transient confusion, resolution of symptoms, and mental abnormalities in <15 min	Remove from play. Examine at 5-min intervals. May return to play if symptoms disappear and results of mental function exam return to normal within 15 min	Allow return to play after 1 week if there are no symptoms at rest or with exertion
Grade 2: as above, but with mental symptoms for >15 min	Remove from play for rest of day. Examine for signs of intracranial lesion at sidelines and obtain further examination by a trained person the same day. Allow return to play after 1 week if neurological examination is normal	Allow return to play after 2 weeks of no symptoms at rest or with exertion. Remove from play for season if imaging shows abnormality
Grade 3: any loss of consciousness	Perform thorough neurological exam in hospital and obtain imaging studies when indicated. Assess neurological status daily until post-concussive symptoms resolve or stabilize. Remove from play for 1 week if loss of consciousness lasts seconds and for 2 weeks if it lasts minutes; must be asymptomatic at rest and with exertion to return to play	Withhold from play until symptoms have been absent for at least 1 month

bleeding following rapid deceleration of the head can result in a potentially lethal increase in intracranial pressure that must be aggressively managed.

With a whiplash type of motion or significant hyperextension of the neck, severe injuries to the cervical spine and underlying spinal cord can occur (Watanabe et al. 2010) resulting in paralysis, respiratory arrest, hemodynamic instability, or death. This type of injury can be seen in violent collisions between bodies, after being ejected from a moving vehicle or animal, or upon impact with the ground while the body is tumbling or rolling. Violent impacts to the face, as seen in boxing, can also cause the head to snap back or rapidly rotated with laceration or dissection of the vertebral arteries and subsequent subarachnoid hemorrhage (Nedeltchev and Baumgartner 2005).

Special Techniques: Head and Neck Injuries

At autopsy, the pathologist should remove the brain, cerebellum, pons, and medulla and may choose to preserve the block in formalin to permit careful sectioning after 2 weeks. If cervical injuries are anticipated, the pathologist should employ anterior and posterior neck dissections and/or vertebral artery dissection for accurate evaluation.

Thoracoabdominal and Pelvic Injuries

Injuries to the ribs and internal organs with subsequent internal bleeding can occur with significant impact to the chest, back, or abdomen. While rib fractures can be debilitating and painful, they are not usually lethal unless there are associated vascular or visceral lacerations or collapse of the lung and pneumothorax.

Internal bleeding is most often associated with lacerations of the spleen or liver following an impact. The bleeding may occur over a matter of hours or days, so a careful history may be required to establish that the injury occurred during participation in a sport. The spleen is particularly prone to injury if enlarged due to infectious mononucleosis, so infection with Epstein-Barr virus should be considered if rupture occurs after relatively trivial impact. Direct impacts to the abdomen can also injure the mesentery, pancreas, or gastrointestinal tract. The kidneys, being relatively protected by their retroperitoneal position and the presence of a thick fat pad, are injured less frequently.

A well-established cause of death in athletes receiving a precordial impact is commotio cordis (Westrol et al. 2010; Geddes and Roeder 2005). Death is the result of a lethal dysrhythmia related to a blunt force impact to the chest occurring at a vulnerable phase in the cardiac cycle. Classically, the athlete is struck in the mid-chest by a projectile (e.g., a baseball) and collapses within a matter of seconds. Reconstruction of the events leading up to death is required to establish this diagnosis as there may be minimal or no anatomic signs to establish chest trauma and the mechanism of death is transient disruption of impulses within the cardiac conduction system.

Injuries to the pelvis are unusual in contact sports. However, a significant impact to the perineum, a situation that may occur during riding events (e.g., riding cycles, motorbikes, horses), may cause pelvic fractures, injuries to the genitourinary tract, and internal bleeding. Impacts to the scrotum and penis can also result in significant pain and morbidity, but they are rarely life threatening.

Injuries to Extremities

Fractures, sprains, strains, and dislocations are commonly encountered in sports, but these injuries are also rarely life threatening. While in a prolonged debilitated state during rehabilitation, however, thrombi may develop in the deep veins of the lower extremities which may embolize to the lungs resulting in sudden death. If a preexisting coagulation disorder is present, the risk for deep venous thrombosis is increased. Smokers and female athletes on birth control pills may be at greater risk for this complication.

Fractures can lead to embolization of marrow elements, predominantly fat, throughout the body (Fig. 26.1). In addition to the problems associated with physical obstruction of vessels by large emboli, disseminated intravascular coagulation (DIC) and activation of chemical mediators can result in death (Hofmann et al. 1995). The fat embolism syndrome typically occurs 24–72 h following a long bone fracture or

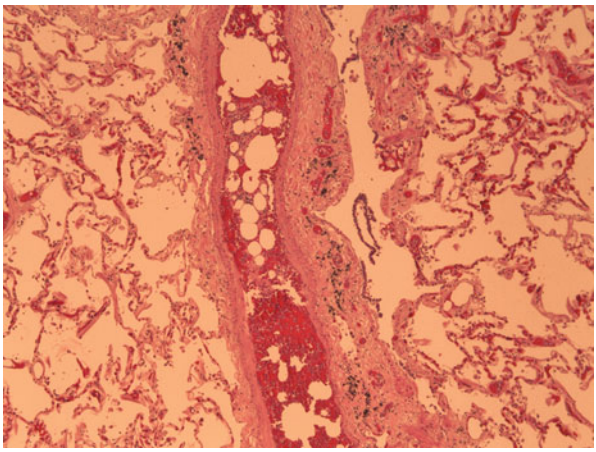

Fig. 26.1 Fat and bone marrow elements may embolize from fracture sites to the lungs. This may be a cause of death, an artifact of trauma, or secondary to cardiopulmonary resuscitation (Hematoxylin and Eosin, H&E × 10)

crush injury presenting as Adult Respiratory Distress Syndrome (ARDS). Deep trauma to adipose tissues can also cause fat embolization. Of note, fat and marrow emboli are often the result of cardiopulmonary resuscitation with associated rib and/or sternal fractures, so clinical correlation is required. Soft tissue injuries have also been associated with the development of "flesh eating" (Group A Streptococcus) bacterial infections, even with no breach of the integument (Chang et al. 2009). It should be remembered that even if death is due to a natural disease process, such as sepsis or pneumonia, the manner of death should be certified as "accident" if trauma initiated the chain of events that culminated in death.

Diet, Nutrition, and Drugs

Sport participants are often under intense pressure to perform at a high level, and they may be encouraged to maximize performance through the use of supplements and dietary modification. This is not only true of professionals but also of amateurs and individuals as young as preadolescents. When investigating the death of an athlete, a complete dietary history, including inquiry into the use of chemicals, vitamins, herbal supplements, and performance-enhancing drugs, should be obtained and any such substances procured.

Anabolic steroids have been historically used to facilitate strength and speed increases, muscle hypertrophy, and decreased recovery time and to generally improve athletic performance (Hartgens and Kuipers 2004). Pathologic changes manifested following anabolic steroid use may be appreciated on external examination and can include testicular atrophy, male pattern alopecia, male gynecomastia, masculinization, breast size and body fat decreases, clitoral enlargement, acne, and hirsutism in females (US Department of Health and Human Services National Institute on Drug Abuse 2001). Anabolic steroid use can result in peliosis of the liver, psychiatric instability, cardiomyopathy, and death

(Hartgens and Kuipers 2004). Recently, anabolic steroid use has been implicated in suicides and homicides (so-called "roid rage"). The long-term effects of other performance-enhancing substances, such as Human Growth Hormone (hGH) and creatine, have not been well established and are not recommended for children and adolescents. Testing for these "performance-enhancing substances" are commonly performed on urine and hair samples through the use of reference laboratories.

Stimulants and diet aids can also cause or contribute to sports-related deaths. Substances containing ephedrine and ephedra alkaloids have been linked to sudden death (Haller and Benowitz 2000). "Energy drinks" often contain agents that can contribute to cardiac deaths and hyperthermia as can certain antihistamines (Clauson et al. 2003; López-Barbeito et al. 2005). It goes without saying that illicit drugs, including cocaine and methamphetamine, can contribute to or directly cause the death of athletes.

Participants in sports requiring lean body mass are at risk for death related to dehydration or metabolic abnormalities associated with anorexia nervosa and bulimia (Warren 2011; Misra and Klibanski 2011). It should be stressed that these disorders afflict adolescents who are concerned about their body image as well as those participating in competitive sports. Investigative history consistent with these disorders are drastic weight loss, a history of using either prescription or over-the-counter medications to facilitate urination and defecation, use of appetite suppressants, a history of vomiting after eating, and exercising incessantly. Physical manifestations appreciable on external examination may include cachexia; calluses, scars, or abrasions on the hands if fingers are used to induce vomiting; dental caries or loss of tooth enamel from chronic exposure to gastric acid; and periorbital, conjunctival, or scleral petechiae from induced vomiting (Department of Health and Human Services Office on Women's Health 2009). Vitreous electrolyte analysis may shed light on deaths due to dehydration or self-imposed starvation or malnutrition, but it may not establish the cause of death in all such cases. Once again, a careful investigation may be required to establish this risk factor for sudden death (see ► Chap. 24, "Starvation, Malnutrition, Dehydration, and Fatal Neglect").

Natural Deaths in Sports

Cardiovascular

Cardiac disease is the leading cause of sudden death in athletes engaged in sports and strenuous activities. Until proven otherwise, a cardiovascular source of death should be sought when an athlete unexpectedly collapses and dies. This category of death can be broadly divided into infection, congenital conditions (molecular and structural), coronary artery anomalies, neoplasms, and progressive organic diseases.

Myocarditis is an inflammatory process involving the heart characterized microscopically by an inflammatory infiltrate in the myocardial interstitium accompanied by myocyte necrosis (Fig. 26.2). In the majority of cases, the inflammation is due to

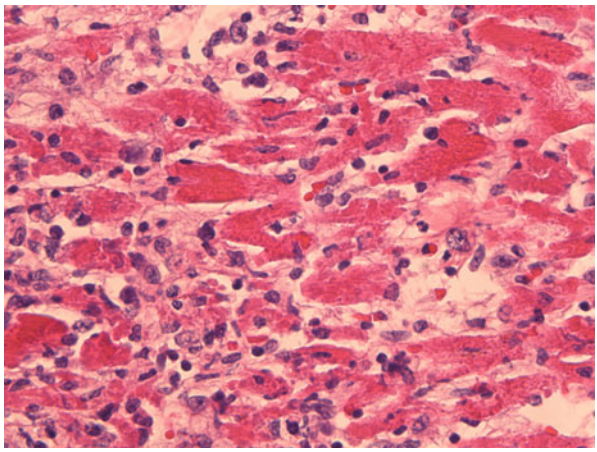

Fig. 26.2 Viral myocarditis is characterized by an inflammatory infiltrate, usually lymphocyte rich, accompanied by myocyte necrosis (Hematoxylin and Eosin, H&E × 40)

a viral infection (e.g., Coxsackie virus and Adenovirus), and a lymphocytic infiltrate will predominate. Clues to the diagnosis include a recent viral illness and a "floppy" heart upon gross examination. Although a viral etiology can be demonstrated in some cases through laboratory studies, in other cases the infectious agent will not be isolated. Other myocarditides are caused by bacteria, fungi, parasites, or autoimmune processes. Depending on the etiology of the process, the inflammatory infiltrate may consist of giant cells, eosinophils, histiocytes, or neutrophils. Histologic sections may require special stains (e.g., Brown and Hopps, silver, or Periodic Acid-Schiff stains) in order to better delineate microorganisms. Sarcoidosis, a granulomatous inflammation of the heart, may be the result of a postinfectious inflammatory response or of an autoimmune process, the etiology of which remains unclear. Special stains to rule out tuberculosis and fungi should be employed to support this diagnosis.

Congenital conditions may manifest themselves at a structural, cellular, or molecular level. There are a litany of metabolic diseases that may infect the heart, including Pompe disease and other storage disorders. These are beyond the scope of this chapter and will not be discussed in further detail, other than to say that they may be a cause of sudden death in childhood. Many of these diseases are symptomatic early in life (see ▶ Chap. 31, "Cardiac Channelopathies and the Molecular Autopsy," ▶ Chap. 32, "Other Pediatric Cardiac Conditions," and ▶ Chap. 34, "Pediatric Metabolic Diseases").

At the molecular level, two major considerations are Long QT Syndrome and Brugada Syndrome (Goldenberg et al. 2008; Escárcega et al. 2009). These cardiac ion channelopathies may result in sudden, unexpected death in apparently healthy individuals. There is an association with death during swimming with Long QT syndrome (Choi et al. 2004), which may be diagnosed by evaluation at reference laboratories if it is suspected and appropriate samples are obtained. These diagnoses can be made by retrospective analysis of electrocardiograms in some cases; however, in many young people, this antemortem study has never been performed.

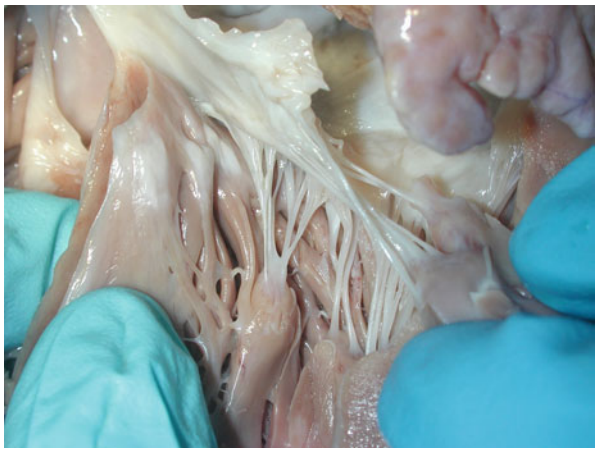

Fig. 26.3 In hypertrophic cardiomyopathy, a fibroelastotic "jet lesion" is often found on the endocardium subjacent to the aortic valve

These conditions cannot be diagnosed at the gross or microscopic level as they are rhythm disturbances.

Hypertrophic cardiomyopathy (formerly asymmetric septal hypertrophy, idiopathic hypertrophic subaortic stenosis) can be diagnosed grossly and microscopically. In classic cases, the interventricular septum will be markedly thickened when compared to the left ventricular free wall. In other cases, the left ventricle may show concentric hypertrophy; the right ventricle may also be thickened. Often, fibroelastosis of the endocardium below the aortic valve is seen as a "jet lesion" (Fig. 26.3). Microscopically, myocyte disarray with intervening fibrosis is the characteristic histologic finding (Fig. 26.4). This finding may be focal, and multiple microscopic sections of the heart with trichrome staining may assist in the diagnosis. This disease is caused by a protein abnormality in the heart resulting from a mutation in the genes encoding for the sarcomeric proteins (e.g., myosin heavy and light chains, myosin-binding protein C, troponins I and T, and tropomyosin) (Harris et al. 2011). As hypertrophic cardiomyopathy is an autosomal-dominant inheritable condition in approximately half of the victims, this diagnosis has implications for surviving family members (Cirino and Ho 2008).

Marfan Syndrome affects multiple sites in the body. The cardiovascular manifestation of this condition is cystic medial necrosis of the aorta. This may result in aortic dissection with rupture into the pleural spaces or pericardial sac with cardiac tamponade or dissection of the coronary arteries. Marfan syndrome should be suspected in the sudden collapse and death of tall athletes with long hands and feet (arachnodactyly), a desirable physique for basketball and volleyball players. This disease is caused by a mutation in the fibrillin-1 gene, the product of which is an extracellular matrix glycoprotein that maintains the structural integrity of connective tissues (Robinson et al. 2006).

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) may be inherited in an autosomal-dominant pattern (Azaouagh et al. 2011). It is characterized by progressive replacement of the myocardium of the right ventricle by adipose tissue

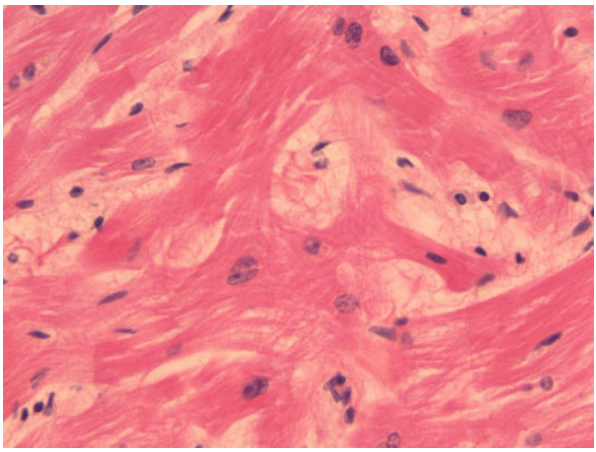

Fig. 26.4 Myocyte disarray with intervening fibrosis is characteristic of hypertrophic cardiomyopathy. It may be focal, and multiple heart sections should be examined if there is no apparent cause of death in an athlete following autopsy (Hematoxylin and Eosin, H&E × 100)

and fibrosis. Occasionally, there are a few scattered inflammatory cells. In advanced cases, the left ventricle may also be involved. This condition may be undiagnosed as the findings are subtle in the early stages, and the right ventricle is often undersampled for histologic analysis. This diagnosis can, at times, be difficult to make, and cardiovascular pathology consultation may prove beneficial.

Structural defects resulting in sudden death may or may not be grossly apparent. Valvular anomalies, septal defects, and transposition of the great vessels can be readily identified at autopsy. Deaths due to structural anomalies of the coronary arteries may be more subtle. Consultation with a cardiovascular pathologist may be helpful in identifying coronary arterial atresia, intramyocardial tunneling, or acute origin from the Sinus of Valsalva. These experts may also assist in identifying problems with the cardiac conduction system. These may be either aberrant neural pathways or stenoses of the arteries supplying the atrioventricular (AV) or sinoatrial (SA) nodes. A microscopic tumor of the AV node can also result in sudden death (Fig. 26.5).

Structural anomalies of other blood vessels may also lead to sudden death. Arteriovenous malformations, particularly within the central nervous system, may rupture with catastrophic results. “Berry” aneurysms of the cerebral vasculature may enlarge over time, and intense physical exertion with associated elevation of blood pressure (e.g., weightlifting) may precipitate bleeding. Aneurysms and pseudoaneurysms of large arteries cause massive internal hemorrhage.

Primary cardiac neoplasms are rare but they can lead to death. Tumors that affect the heart include atrial myxoma, fibroma, and rhabdomyoma, the latter associated with tuberous sclerosis. The heart may also be affected by lymphomas, angiosarcomas, and metastatic disease. The most common cancers metastatic to the heart are lung, breast, melanoma, and leukemia/lymphoma.

Adolescents are not immune to cardiovascular diseases that kill older individuals. Especially in the setting of familial hypercholesterolemia, atherosclerotic coronary artery disease may develop in the mid-teen years. Hypertension may also result in myocardial hypertrophy and lethal dysrhythmia; however, this must

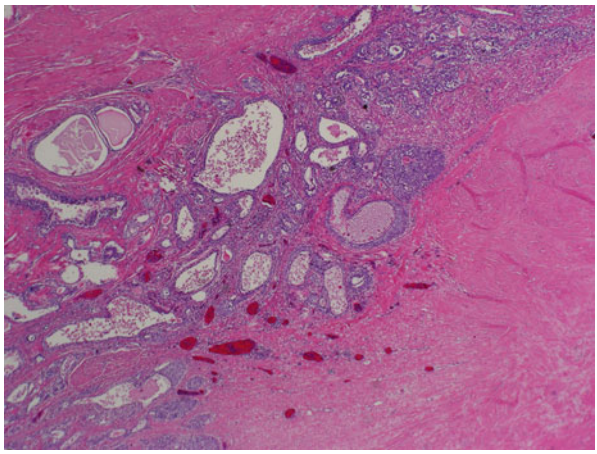

Fig. 26.5 Cystic tumor of the atrioventricular node (Hematoxylin and Eosin, H&E × 10)

be distinguished from hypertrophic cardiomyopathy, discussed above. Whereas hypertrophic cardiomyopathy commonly affects the septum on gross inspection and is associated with myocyte disarray, hypertension generally results in concentric thickening of the left ventricular chamber and enlarged, hypertrophic myocytes with hyperchromatic "box car" nuclei at the microscopic level. Lastly, morbid obesity has been associated with sudden death (see ▶ Chap. 33, "Childhood Obesity").

Special Techniques: Cerebrovascular Aneurysms

When faced with an unanticipated subarachnoid hemorrhage, the pathologist should remove the brain themselves with frequent photographic documentation of the process in order to capture occult lesions prior to onset of any removal artifact(s). Once removed, the brain, cerebellum, pons, and medulla should be copiously rinsed with water to remove adherent blood and clot. In lieu of water, hydrogen peroxide may be used to facilitate the lysis of adherent blood from the delicate vasculature so that it can be better examined. Care must be taken to avoid destruction of subtle vascular malformations and aneurysmal sacs.

Chronic Diseases

Sickle-cell disease may be diagnosed in childhood, and it can afflict participants in athletics and other strenuous activities. If the diagnosis of sickle-cell disease is known, recognition and treatment of an impending crisis can avert death. Many people with sickle-cell trait, however, are unaware of their condition. When subjected to intense physical exertion, high temperatures, and a component of dehydration, a crisis may ensue and death may rapidly follow

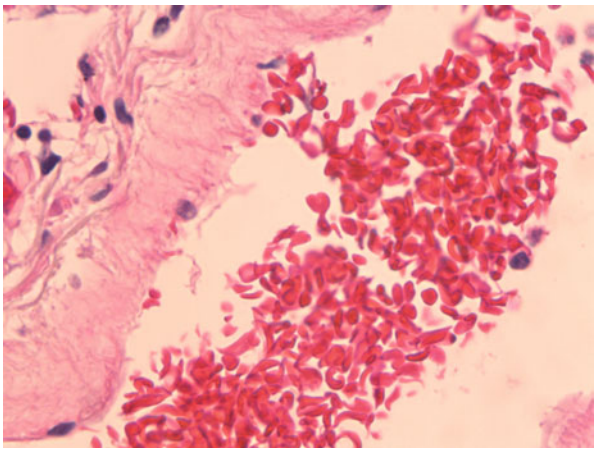

Fig. 26.6 Sickled erythrocytes in the pulmonary vessels in a case of sudden collapse and death in a person with sickle-cell trait (Hematoxylin and Eosin, H&E × 100)

(Scheinin and Wetli 2009; Manci et al. 2003). A recent viral illness could also be an exacerbating factor. This condition should be considered when an athlete of African or Mediterranean descent complains of joint pain, chest pain, fatigue, and weakness prior to collapse. It is often misdiagnosed as a heat-related illness. The diagnosis is made at the microscopic level wherein virtually all organs will be congested by sickled erythrocytes (Figs. 26.6 and 26.7). At the gross level, persons with sickle-cell disease may have fibrotic, atrophic spleens, whereas those with sickle-cell trait may have enlarged spleens, congested with sickled erythrocytes. The diagnosis can be confirmed with hemoglobin electrophoresis (blood best procured in a tube with anticoagulant/EDTA) and correlated with information obtained regarding prevalence and distribution of this disease within the family.

Asthma is a common disease among children and teens, and acute attacks may be precipitated by physical activity. In order to certify death due to asthma, the circumstances of death need to reflect a respiratory crisis. In many cases, an inhaler and/or a nebulizer will be found near the victim or with their personal belongings. Grossly, the lungs will be hyperinflated, often touching over the heart in the midline, with prominent mucus plugging of the airways. The microscopic findings of chronic asthma in the bronchioles (thickening of the basement membranes, smooth muscle hypertrophy, and mucus gland hyperplasia) will be accompanied by an eosinophil-rich inflammatory infiltrate that extends into the luminal mucus plugs (Figs. 26.8 and 26.9). A history of asthma should not be a default cause of death in these cases without the circumstances and scene findings supporting a respiratory catastrophe.

Epilepsy, like asthma, may be a cause of death, however, the circumstances should support the diagnosis. In the absence of a witnessed seizure, other causes of death must be excluded prior to attributing death to epilepsy. Further, intracranial trauma must be excluded as a cause of the seizure. Some epileptics will die suddenly and unexpectedly in the absence of a seizure (sudden unexpected death in an epileptic person or SUDEP), but this does not typically occur while the victim

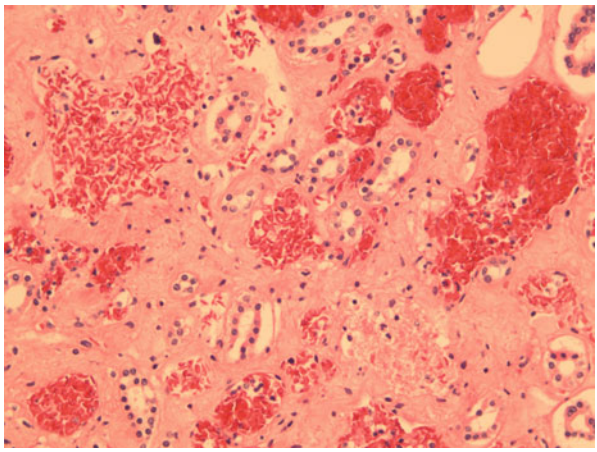

Fig. 26.7 Sickled erythrocytes are often readily identified in the renal vasculature in deaths due to sickle-cell disease or exacerbation of sickle-cell trait (Hematoxylin and Eosin, H&E × 20)

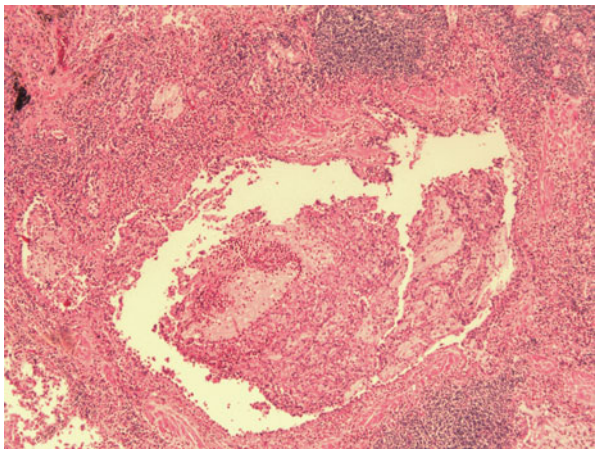

Fig. 26.8 Mucus plugs with admixed inflammatory cells in a person who died of status asthmaticus (Hematoxylin and Eosin, H&E × 10)

is engaged in sports. The autopsy may or, more commonly, may not identify the anatomic correlate of the seizure focus in the brain.

Spontaneous pneumothorax may occur during sports presumably due to increased shear forces at the apex of the lung (Abolnik et al. 1993). It may cause death if it progresses to a tension pneumothorax, a condition that results in both hypoxia and mechanical alterations of the cardiovascular system. This is a diagnosis that may be missed if it is not suspected.

Diabetes mellitus can kill children and adolescents engaged in sports. Activities which entail dietary restrictions may predispose those with the disease to ketoacidosis. Young people more often have type I diabetes and may be insulin dependent. As teens have a tendency toward denial and risk-taking behavior, they may not be fully compliant with their treatment regimens and therefore be prone to significant blood glucose fluxes. The gross findings at autopsy will be minimal in

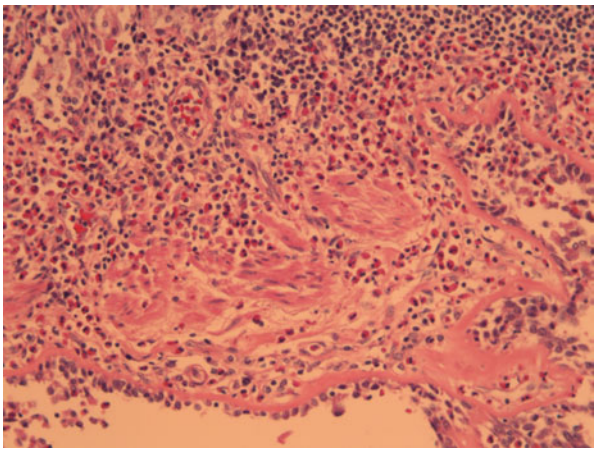

Fig. 26.9 The findings of chronic asthma (basement membrane thickening, smooth muscle hypertrophy, mucus gland hyperplasia) with an intense eosinophilic inflammatory response in a person who died during an asthma attack during exercise (Hematoxylin and Eosin, H&E × 20)

these cases. Microscopically, the islets of Langerhans in the pancreas may be infiltrated by lymphocytes ("insulitis"), or they may be diminished in number. Urine screens for glucose and ketones may be useful, but postmortem blood analysis is unreliable. The best sample for diagnosing diabetes mellitus and ketoacidosis postmortem is vitreous humor. The presence of ketones and significantly elevated glucose (> 500 mg/dL) in the vitreous humor is diagnostic of this condition (Chansky et al. 2009). Vitreous glucose levels drop significantly after death, however, so a lower ocular glucose level does not exclude hyperglycemia. Further, hypoglycemia cannot be diagnosed postmortem due to the aforementioned postmortem change. In the evaluation of a nontraumatic death occurring during sports, analysis of vitreous glucose, ketones, and electrolyte levels is recommended in all cases.

Special Techniques: Pneumothoraces

Prior to the examination, chest radiographs including lateral and seated views may illustrate free pleural air and displacement of the heart. At autopsy, care should be taken to reflect the skin and soft tissues of the chest without breaching the intercostal tissues or entering the chest cavities. A pocket which should be filled with water can be created using the reflecting chest tissues. The intercostal tissues can then be pierced below the water level to examine whether air bubbles emerge.

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Other Pediatric Accidental Deaths

27

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Abstract

Injury, both intentional and accidental, is the most common cause of death in children throughout the world. Many injury patterns that are seen in children are similar to those in adult populations; however, others differ, reflecting the age, stature, and development of children. This chapter focuses on differences in injury patterns of children across the spectrum of childhood development and growth, including injuries and fatalities that primarily occur in infancy and early childhood. Risk factors for injury and death are identified within the context of childhood development. Topics covered include deaths associated with motorized and nonmotorized vehicles including pedestrian, occupant, and operator fatalities; farming and ranching deaths; drowning, boating, and diving deaths; fires and burns, including electrical deaths; animal-related deaths; falls; and airway-associated deaths. There are significant disparities in childhood injury and death among racial, ethnic, geographic, and socio-economic groups. A brief consideration of these differences is provided to assist in forensic case examination.

Introduction

Accidental injuries cause a high proportion of deaths in children. In some age groups, injury is the leading cause of childhood death. Injuries and death differ across the spectrum of childhood development and growth (Agran et al. 2001, 2003). An understanding of these differences is critical to the performance of a forensic investigation and autopsy in children and adolescents; conversely,

well-performed forensic investigations and autopsies will identify risk factors and opportunities to reduce childhood morbidity and mortality from injuries.

Vehicle-Related Deaths

Pediatric vehicle-related injuries and deaths are commonly seen in forensic pathology. Infants and children may be occupants in motor vehicles or may be pedestrians struck by motor vehicles. Children may be operators of recreational vehicles, including bicycles, and in adolescence, drivers of motorized vehicles. Worldwide, over 260,000 children die annually in road-related crashes, and children accounted for 21 % of all road fatalities (World Health Organization 2012b). Childhood deaths from vehicle-related events are highest in Africa and are consistently increased in low- and middle-income countries as compared to higher-income countries throughout the world (World Health Organization 2004).

Passenger Injuries

Each year in the United States (USA), about 1,400 children under the age of 14 years are fatally injured while passengers in motor vehicles, and another 200,000 sustain injuries, many of which significantly impair the child's quality of life (Department of Transportation (US), National Highway Traffic Safety Administration (NHTSA) 2009). The Centers for Disease Control and Prevention (CDC) in the USA estimates that restraint systems for children (positioning, age, and weight-appropriate car or booster seats, lap and shoulder harnesses, etc.) prevent 400–500 fatalities each year (Centers for Disease Control and Prevention 2012e). These same initiatives also reduce childhood fatalities in other regions of the world. However, restraint systems may also cause injury and death, particularly when improperly used for the age, size, and development of the child, or when a child is seated in the front seat of a vehicle. The American Academy of Pediatrics and the CDC have each produced guidelines and best practices for child passenger safety (Centers for Disease Control and Prevention 2012e; American Academy of Pediatrics Committee on Injury, Violence and Poison Prevention 2011). Children under the age of 13 years should always ride in the rear seats of vehicles. As a general guideline, rear-facing car seats should be used until the age of 2 years. After 2 years of age, forward-facing child seats should be used until the child is over 4 years of age or 40 lb (18 kg). Belt-positioning booster seats should be used after that point until adult lap-shoulder seat belts fit appropriately at upper thighs and chest when a child is over 8 years of age and 4′9″ (1.4 m) tall. Disabled children have a similar incidence and distribution of injuries related to safety restraint use as compared to children without disabilities (Huang et al. 2009).

Head Injuries

A review of forensic findings from passenger airbag injuries demonstrates that face, upper extremity, and chest injuries are more common in children than adults,

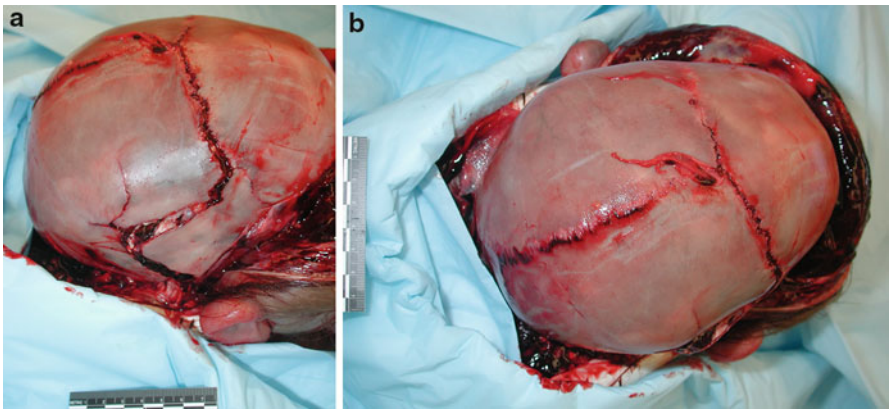

Fig. 27.1 Airbag head injury in an infant riding in the front seat of a car. (**a**) Skull fracture from a deployed airbag in a 6-month-old infant. The infant was in an unsecured infant seat located in the front seat of a car. (**b**) Separation of sutures and extensive galeal hemorrhage are present

and isolated head injuries are more common in infants as compared to older children (Sato et al. 2002). In the majority of airbag injuries, a child was unrestrained or improperly restrained in the front seat, and all injured infants were in the front seat in rear-facing child restraint seats (Fig. 27.1a, b). The smaller stature of children and infants and the position of the head closer to the upward deploying airbag may account for the mechanism of these injuries. The relatively flat and horizontal character of the atlanto-occipital (AO) articulation in children also places them at greater risk of AO dislocation or separation (Saveika and Thorogood 2006). Other large studies have confirmed passenger airbag injuries when children under 14 years of age occupy the front passenger seat (Newgard and Lewis 2005).

Head injuries occur in children restrained with adult seat belts (Fig. 27.2a, b). An adult-designed shoulder harness may cross the child's face and/or neck. Children may slip the belt under an arm or behind the back, compromising the restraint of the upper torso making these areas susceptible to injury in a collision with rapid deceleration. In a crash, the unrestrained forward motion of the child's upper body may cause the head to collide with knees or parts of the vehicle. Small children may also "submarine" completely out of an adult restraint system on impact, become airborne, collide with the interior of the vehicle and/or other occupants, or may be ejected from the vehicle (Tibbs et al. 1998).

Abdominal Injuries

Children are more vulnerable to blunt abdominal injury from vehicular seat-belt restraints as compared to adults, particularly when child booster seats are not used or the child is inappropriately restrained by the lap-shoulder harness system designed for adults (Lapner et al. 2001). Current recommendations call for use of special child restraint systems until the child is over 4′9″ (1.4 M) tall, and the lap restraint can be positioned on the upper thighs (not the abdomen) and the

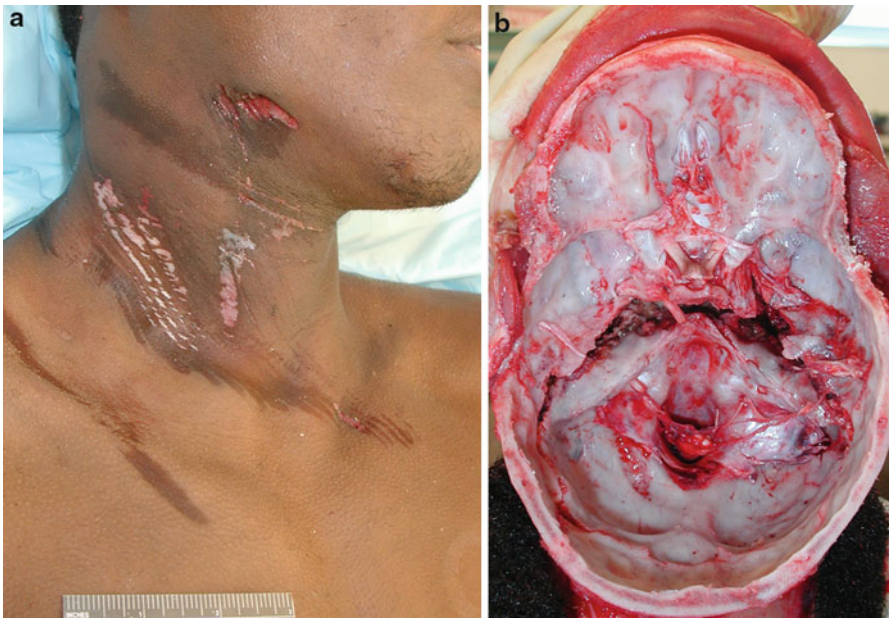

Fig. 27.2 Injury caused by an adult shoulder harness restraint in a child. (**a**) The 12-year-old boy was slight in stature at 55 in. (1.4 M), below the recommended height for adult seat belt use. Injury pattern demonstrates the restraint position was across the neck and face instead of the intended design of across the chest. (**b**) A basilar skull fracture was present and the head injury caused the death of this child

shoulder harness crosses the chest while not crossing directly over the neck (American Academy of Pediatrics Committee on Injury, Violence and Poison Prevention 2011). The immature pelvis of a child under the 4′9″ (1.4 M) height requirement cannot be appropriately restrained with the lap-shoulder harness until the child is tall enough to position the harness in the correct areas (across the thighs and not the abdomen). Abdominal-wall contusions are infrequent in both optimally and suboptimally seat belt-restrained children, but when abdominal contusions are present, they often herald intra-abdominal injury (Lutz et al. 2004). Intestinal injury, perforation, and shearing of the fixed ligaments and mesenteric structures are the most common abdominal manifestations of pediatric seat belt-related injuries (Davies 2004). Because the small anterior pelvis of a child is not appropriately stabilized by the lap restraint system designed for adults, deceleration allows the seat belt to override the child's pelvis, producing hyperflexion of the child over the lap belt. This forces the abdominal organs against the vertebral column and momentarily increases the intraluminal pressure of the hollow organs, resulting in sudden compression. In addition to the abdominal injuries, the deceleration-induced compression and hyperflexion of the abdomen may also cause lumbar spine and sacral injuries (Hart et al. 2004; Papavasiliou et al. 2007). Intestinal compromise may be immediate or may occur days to weeks after the injury (Hardacre et al. 1990; Lynch et al. 1996).

Posttraumatic small-intestinal obstruction and delayed perforation may comprise an important finding in a forensic evaluation of a delayed vehicular death.

Pedestrian Injuries

Pedestrian deaths in children demonstrate age differences in the types and patterns of injury. In children under the age of 4 years, deaths from "backover" accidents in driveways peak in incidence, likely due to the small stature of children, their tendency to "hide" or play behind parked vehicles, and their lack of awareness of the dangers of moving vehicles. Crush injuries of young children, usually occurring from low-velocity impacts resulting from vehicles backing out of home driveways, are often fatal due to blunt-force injuries of the head (including closed-head injuries), skeleton, and torso (Partrick et al. 1998). The most common vehicles involved in these accidents are sport utility vehicles (SUV), trucks, and minivans, as opposed to passenger cars (sedans, compact cars, etc.), perhaps due to the increased frequency of larger vehicle ownership by families with small children and the increased "blind spot" of vehicles with higher ground clearance behind the vehicle. In contrast to most other vehicular head injuries, these "backover" injuries are generally static; that is, they do not have significant rotational and acceleration–deceleration components.

Pedestrian injuries of older children tend to be on roadways rather than home driveways. This reflects cognitive awareness of the age groups: younger children are more at risk of mid-road impacts, associated with impulsive behaviors, such as darting into traffic in areas other than crosswalks; older children and adolescents are more likely to be involved in pedestrian accidents at crosswalks and intersections. As compared to head injuries sustained in "backover" collisions, head injuries in pedestrian roadway accidents in older children and adolescents tend to be complicated by rotational and acceleration-deceleration components as opposed to isolated static forces.

The site and character of pediatric pedestrian injuries also reflects the child's age and development (Chakravarthy et al. 2007). The point of vehicular impact (bumper) in a small child is at the head or chest level, both sites that are above the child's center of gravity. Because of this injury location, the initial impact usually results in a second impact, with the initial impact projecting the child away from the vehicle and against another fixed object, usually the ground. Consequently, the child may be run over by a subsequent vehicle. In contrast, the impact point in older children is below the child's center of gravity, resulting in impact patterns similar to that of adults. In older children, the impact point is at the legs with the body projected over or onto the hood of the car. Rotational motion is seen in these impacts with the legs rotating over the head on impact and with increasing speed, and the entire body may somersault over the vehicle following hood/windshield impact. The injury patterns seen in children reflect these different impact patterns, with head, neck, and chest injuries more common in pediatric pedestrian injury populations than in the adult population (Chakravarthy et al. 2007).

Pedestrian accidental deaths are more common in males and in children from minority groups, particularly in lower socioeconomic areas (American Academy of Pediatrics Committee Injury, Violence, and Poison Prevention 2009). This may relate to socioeconomic considerations including denser traffic patterns, increased vehicular speed, on-street parking, fewer guard-monitored crosswalks near schools or playgrounds, poor sidewalk maintenance, increased need for pedestrian transportation within lower socioeconomic communities, and reduced safety awareness (Hotz et al. 2009). Gender differences, as well as the potential influence on parental supervision, have been examined in the context of improving pedestrian safety (Barton and Schwebel 2007). Geographic information system (GIS) studies have assisted in targeting high-risk areas and led to a reduction in both injuries and fatalities (Weiner and Tepas 2009; Statter et al. 2011).

Operator Injuries

Children may be drivers/operators of a variety of nonmotorized vehicles (wagons, bicycles, gravity go-carts) or "off-road" non licensed motorized vehicles (golf carts, all-terrain vehicles, snowmobiles, motorized go-carts). Accidents from these vehicles cause a disproportionate incidence of injury in children when compared to adult populations (Siman-Tov et al. 2012; Lord et al. 2010; Hamming and Henry 2009; Curran and O'Leary 2008; Kelleher et al. 2005; DeCou et al. 2003; Rice et al. 2000).

Bicycles

Children operating bicycles may be injured from falls, collisions with objects, or collisions with other vehicles, including motorized vehicles. Head injuries, including traumatic brain injury, are the most common cause of fatalities involving bicycles; however, blunt-traumatic injury to abdominal organs, abdominal-wall injury, and genital injuries may occur, usually from impact with handlebars or bicycle frame (De Jong et al. 2011; Klin et al. 2011; Rowell and Chin 2011; Widni et al. 2011; Nellensteijn et al. 2009). Helmet use reduces the occurrence and severity of head injuries in bicycles and other motorized and nonmotorized vehicle accidents. (Barnes et al. 2012; Juang et al. 2010; Pardi et al. 2007). Some trauma centers report an increase in severe thoracic and abdominal injuries from bicycle accidents in children as helmet use increases, reducing the incidence of severe head injuries. (Klin et al. 2009). A 1995 review of 2,333 bicycle-related injuries in the National Pediatric Trauma Registry (USA) further identified children with mental disorders as a high-risk group for bicycle injury and suggested targeted prevention programs (Li et al. 1995).

Off-Road and All-Terrain Vehicles

Training and licensing prior to the operation of off-road and all-terrain vehicles is not as regulated, or as common, as licensed road vehicles (Upperman et al. 2003). The vehicles are often operated off-road and on irregular terrains, which contribute to vehicle instability and subsequent vehicle rollovers (Finn and MacDonald 2010).

Crush injuries and asphyxia may result from rollovers of heavy off-road vehicles onto individuals. Blunt trauma, fractures, and amputations may occur from impacts with trees, fences, or other obstacles. "Clothesline" injuries, including deep lacerations or cervical fracture, may occur to the face and neck when vehicles pass under horizontally strung fence lines. In some instances, multiple children are involved in an accident when an off-road vehicle is being driven with children riding on sleds or skateboards tied behind the vehicle (similar to waterskiing). If the vehicle makes a sudden turn, the increased rotational velocity may throw the child who is on the skateboard/sled away from the vehicle, resulting in blunt-force injuries due to the primary impact and/or a secondary impact with a subsequent structure (tree, vehicle, etc.). The majority of these accidents occur at lower velocities than traditional motor vehicle accidents, although some motorized off-road vehicles can reach speeds of 30 mph (50 km/h) or more, increasing the likelihood of fatal injuries and approaching patterns seen in traditional motor vehicle collisions.

Licensed Motor Vehicles

Adolescent drivers of licensed motor vehicles have higher accident and death rates as compared to adults. Injury patterns are similar, since adult size and stature are generally reached by the age of legal vehicular licensing. Many provinces, states, and countries have limited the adolescent (14–18 years of age) motor vehicle licensing in several manners, including increasing the minimum driving age, mandating driving courses, restricting hours of driving, limiting the number of adolescents in a vehicle, or requiring a licensed adult driver in the car (Russell et al. 2011). These and other regulations reflect efforts to reduce accidents and fatalities among adolescents until driving skills become more accomplished. Some jurisdictions may also limit or have additional requirements before licensing adolescents to operate motorcycles or may restrict operators less than 18 years of age to a smaller-sized motorcycle. On private property and some Indian reservations, state or provincial driving laws may not be applicable or enforceable, and children may drive motorized vehicles at a younger age.

Other Vehicular Injuries

There are some unusual vehicle injury mechanisms that forensic pathologists need to consider in pediatric death investigations. Infants are more susceptible to carbon monoxide toxicity due to the greater affinity of fetal hemoglobin. Individuals with hemoglobinopathies, such as sickle-cell anemia or thalassemia, may also have increased susceptibility to carbon monoxide toxicity (Blumenthal 2001). Rarely, defective motor vehicle exhaust systems may produce high levels of carbon monoxide within the interiors of moving or idling vehicles. "Open-air" carbon monoxide poisoning is a well-known hazard around combustion engine exhaust, even from vehicles in outdoor spaces. Asphyxia and positional asphyxia may occur with vehicle rollovers, entrapment within vehicle restraint systems, or in automatic window or door closure systems. Findings at autopsy are similar to other asphyxia

deaths, with petechial hemorrhages often seen in eyes and intrathoracic cavity and hemorrhage within sinuses and sphenoid processes. Cyanosis, often intense, is present above the restraint area. Often the lividity patterns reflect the entrapment, clothing, and/or vehicular restraints (Fig. 27.3a–e).

Delayed Vehicular Injury

Delayed sequelae of motor vehicle injuries may cause death days or weeks after the motor vehicle accident, following a period of apparent recovery in the intervening time. In these instances, investigative skill is required to correctly ascertain the initiating cause of injury. Chest impacts may produce cardiac contusions, including injury to ventricular free walls, papillary muscles, or the ventricular septum. These injured areas may rupture acutely, causing death (Fig. 27.4). Alternatively, the contusion may result in an aneurysm, infarction, or ventricular rupture days or weeks after the initial injury. Cardiac contusion results from blunt-traumatic impact to the chest with compression of the heart against the sternum and/or spine. The momentarily high intrathoracic pressure with deceleration may also contribute to this type of injury. Abdominal trauma may produce ileus or injury to hollow organs, particularly the small intestine, resulting in rupture and/or peritonitis several days following the injury. Vascular trauma does occur in children, but less commonly than in the adult population (Eddy et al. 1990; Riches et al. 2002; Choit et al. 2006). These vascular injuries usually present acutely with hemorrhage or infarction, but may be delayed in discovery or presentation. Although uncommon, children may also develop pulmonary thromboemboli as a result of local trauma to the leg (Fig. 27.5) or prolonged immobilization and present as sudden death days or weeks later.

Hyperthermia in Vehicles

Death from hyperthermia of infants and children left in cars is well known and increasing in incidence since the recommendation of placing infants in carriers in the back seat. Usually these tragic deaths result from a caregiver forgetting that the infant is in the vehicle. The temperature in closed vehicles may rapidly rise well over the ambient temperature, and car interiors may reach 140° F (60° C) or more within 15 minutes (McLaren et al. 2005). Infants are most at risk for this event since older children may be able to independently leave vehicles and/or alert adults to their presence. Autopsy findings are generally nonspecific in car hyperthermia deaths, although intrathoracic petechiae are often seen (Fig. 27.6). Body temperature at time of discovery is important to confirm hyperthermia; however, this is often not available to the forensic investigator. Interior vehicle temperature is often not recorded and, if available, may not be reliable, as opening the car door will rapidly disperse heat, resulting in an erroneously low measurement. Due to the rapidity of heat exposure in a vehicle, vitreous electrolytes may not demonstrate a dehydration pattern, as is seen in slower exposure to high temperatures. If a victim survives,

complications of disseminated intravascular coagulation (DIC) and multisystem organ failure may be fatal hours-to-days after the hyperthermic event. There is considerable variation in the certification of the manner of death in these tragic events, with some practitioners certifying as accidents and others as homicides.

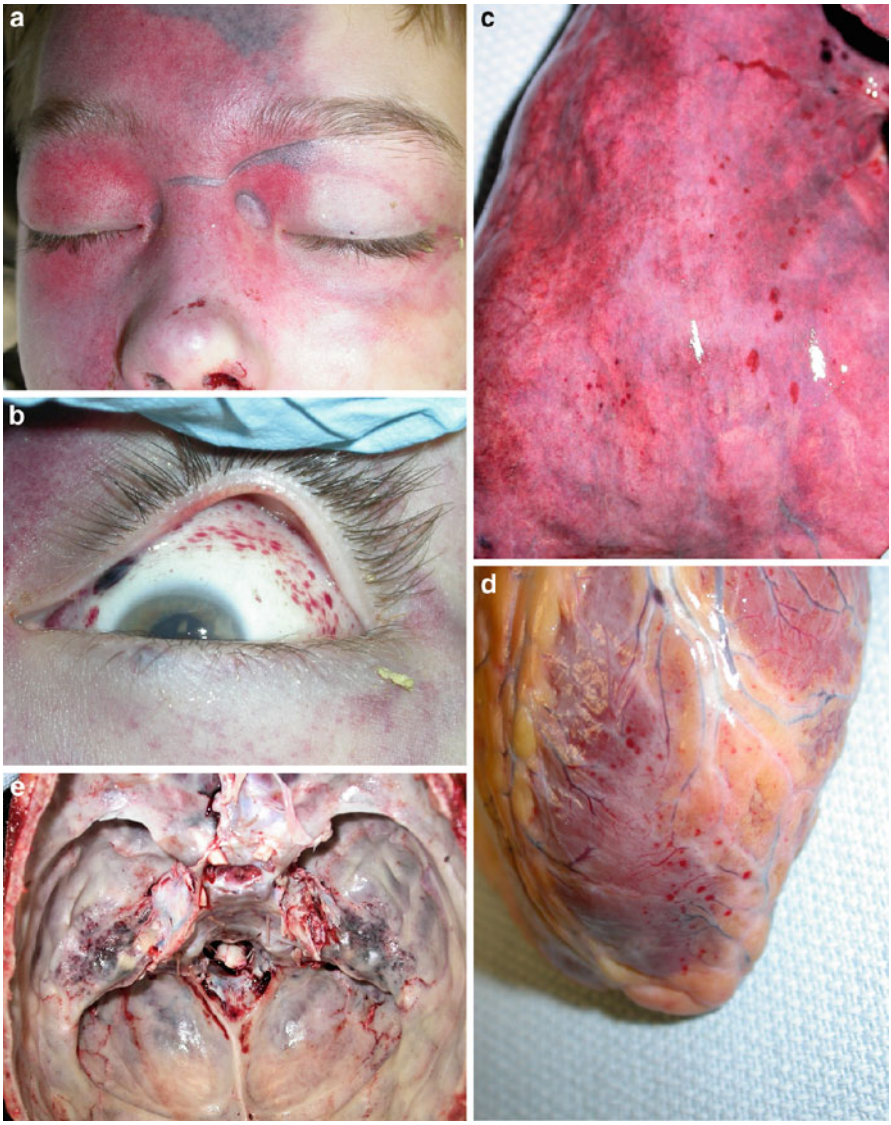

Fig. 27.3 Compression (mechanical) asphyxia and positional asphyxia from an overturned vehicle. This child was compressed in an overturned car with a second vehicle on top. Elements of both mechanical compression and positional compromise were present. There was no anatomically apparent CNS lesion or other traumatic injuries. (**a**) Florid petechiae, periorbital edema, and

Trains as Vehicles

Collisions with trains, either as an occupant in a vehicle or as a pedestrian, have high fatality rates. In contrast with adult pedestrians who are usually intoxicated and trespassers on rail yards, railroad employees, or individuals committing suicide, child pedestrians may be playing on or crossing rail tracks, riding bicycles or walking next to a moving train, or attempting to board, exit, or ride on top of a train. Traumatic amputations and head injuries are the most common features of these accidents (Thompson et al. 1983; Blazar et al. 1997).

Farm- and Ranch-Related Deaths in Children

Farm- and ranch-related injuries and deaths in children are slowly decreasing in many parts of the world; however, farm and ranch operations remain among the most dangerous occupations, second only to mining, in terms of injuries and deaths (Solomon 2002; Lachowski 2009; CDC 2012b). Unlike mining, children are often involved in farming and ranching activities, exposing them to dangers, both by working and living within farming and ranching environments (Pickett et al. 2005). Most childhood injuries occur in a nonworking capacity rather than being actively engaged in agricultural work at the time of the injury (Hendricks and Goldcamp 2010). Estimates of the cost of injuries and deaths of children on US farms alone exceed 1.3 billion USD annually (Zaloshnja et al. 2012).

Types of Ranch and Farming Injury

There are several dangers in the farm and ranching environment. Heavy equipment is used daily, creating risks for children by operating equipment, riding with others on the equipment, or simply being in the vicinity of operation. Farm machinery is consistently the most common cause of injury and death in both the North American and the UK farm-related incidents (Angoules et al. 2007). Drowning in natural lakes, irrigation

Fig. 27.3 (continued) lividity patterns contrast with blanched areas of compression. Note the imprint from eye glasses. (**b**) Scleral petechiae from the same child. Numerous petechial hemorrhages, some confluent, are present in the sclera, conjunctiva, and the periorbital skin. Retraction of the eyelid may be necessary to fully appreciate the presence and extent of petechial hemorrhages. Petechial hemorrhages are caused by rupture of small vascular channels, usually venules, and are often present in cases of asphyxia, classically above the point of compression where venous return is compromised. (**c**) Petechiae on the visceral surface of the lungs in the same child. (**d**) Epicardial petechiae from the same child. Visceral pleural and epicardial petechiae were first described as "Tardieu spots" and initially described as pathognomonic of asphyxial deaths. They are commonly seen in asphyxia, but may be present in a variety of non-asphyxial mechanisms of death. (**e**) Congestion and hemorrhage within the inner ear of the same child. Pressure changes from compression may cause sphenoid and inner ear hemorrhages similar to those seen in barotrauma or drowning deaths

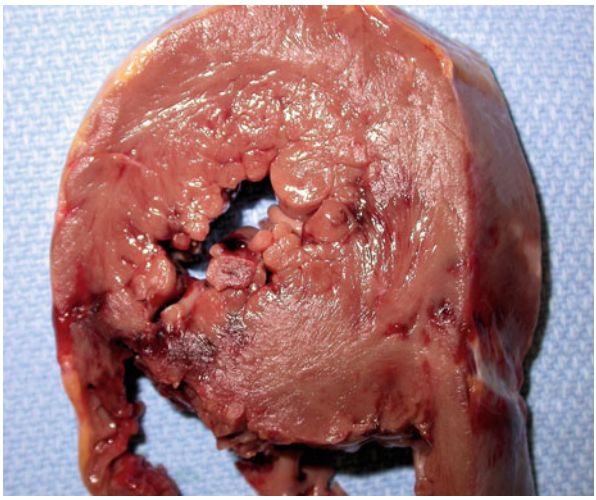

Fig. 27.4 Rupture of the cardiac interventricular septum. The injury occurred in a 15-year-old driver involved in a head-on collision with airbag deployment. The driver had no external signs of injury and exited the car, collapsing a few minutes after the accident. The other occupants of the car had minor injuries not requiring medical intervention

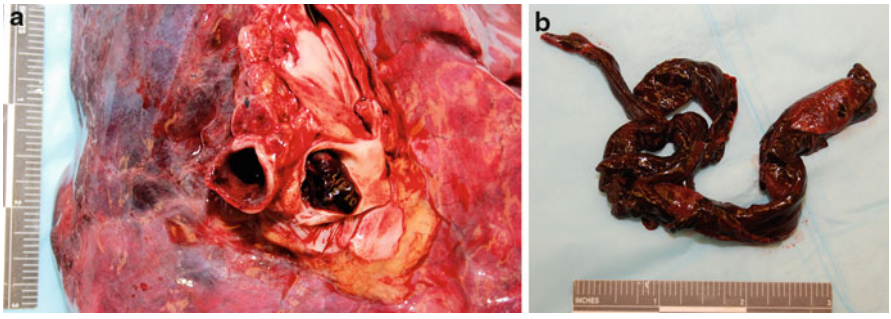

Fig. 27.5 Pulmonary thromboemboli from leg trauma. (**a**) This 12-year-old boy suffered minor injury to the knee in a bicycle accident, requiring arthroscopic surgery. Five days later, he complained of shortness of breath which improved with rest. He was found deceased one day after complaining of shortness of breath. A saddle pulmonary thromboembolus was found at autopsy. (**b**) Pulmonary thromboembolus from right-sided circulation. A leg dissection identified the site of thrombus formation at the site of the injury and subsequent surgical procedure

dams, or streams within farms is another common cause of death in farm children. Asphyxial deaths can occur from hypoxic closed spaces or slipping into grain storage bins. Lacerations, skeletal fractures, amputations, and blunt-traumatic injuries result from falls occurring in farming activities or entrapment in farm equipment. Complex tools, firearms, and sharp implements are necessary for farming and ranching and pose a danger of injury and death in children. Falls from, or kicks by, large animals and a wide variety of animal bites also occur more commonly within rural settings. Off-road vehicles, such as ATVs and snowmobiles, are more common in rural settings, increasing the risk of injury and death from the use of these vehicles by children (Lim et al. 2004).

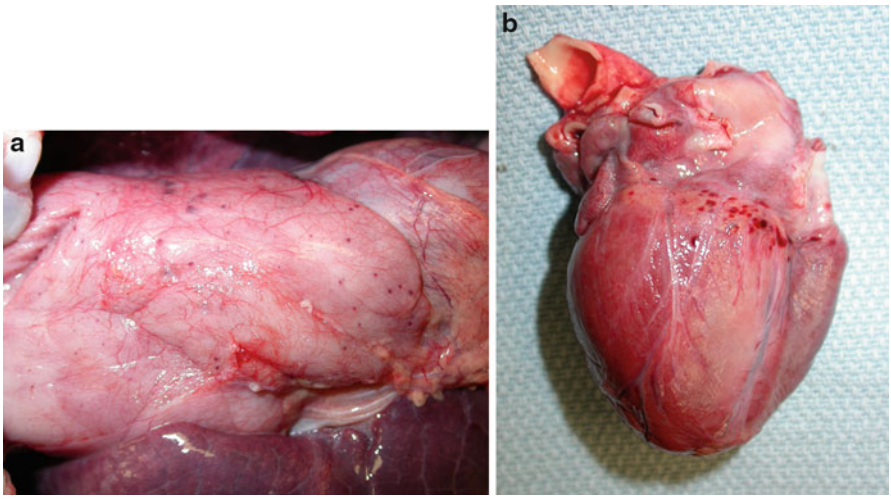

Fig. 27.6 Hyperthermia death in an infant left in a car. (**a**) This 6-week-old infant was left in the back seat of car for 6 h on a warm day (sunny, 79 °F, 26 °C). Thymic petechiae were seen at autopsy. (**b**) Epicardial petechiae and hemorrhages were present. Petechiae were also present on the visceral pleural surface. Intrathoracic petechiae are consistently seen in hyperthermic deaths and are attributed to terminal gasping in an auto-resuscitation attempt

Demographics of Farming Injuries

There are minimal gender differences in injury and death in children under the age of 5 years in farm and ranching activities; however, over the age of 5 years, boys have a higher rate of injury than girls (Hendricks and Hendricks 2010). Boys are more involved in hazardous tasks involving heavy equipment and tractors, whereas girls more commonly are involved in animal care and agriculture. Disparities exist for minority populations with higher incidence of injury and death in farms owned by Hispanics, African-Americans, or Native Americans (Goldcamp et al. 2006a, b; Layne et al. 2009). Finally, the remote location and low population density of many farming communities lead to slower emergency response and increased travel time to trauma centers. All of these factors tend to increase the mortality of injuries.

Farming Equipment

Tractors are the leading cause of farm fatalities and injuries in all age groups, but pose several particular hazards to children (Schwebel and Pickett 2012). Inspection of the safety status of tractors in rural Kentucky (USA) revealed significant safety issues in the majority of examined vehicles (Cole et al. 2009). Similar conditions of tractors are likely present in most rural communities and explain the high incidence of injuries and fatalities related to children operating, or present around, this type of

farm vehicle and the diverse forensic findings that may occur in tractor deaths. Nearly half of the tractors examined in the study lacked rollover protection structures (ROPS). Most tractors did not have seat-belt and harness systems, or these systems were difficult to use, putting all operators, particularly young operators or youngsters riding with adults, at risk. Many tractors had a narrow front-wheel stance, creating stability issues and increasing the risk of rollover accidents. Many tractors had loose or damaged seats. Protective shields for starting were present on just over half the trailers examined, and nearly a third had the starting mechanism fully exposed. Rear-wheel fenders exposed operators to moving tires in nearly 40 % of the tractors. Fully functional mounting and dismounting access steps and handrails were present in less than half of the operating tractors and, when present, were designed for an adult body. Many tractors had no functional lights, and nearly 70 % had no rear-view mirrors. Complicating these design and safety issues is the fact that all of these devices are designed for adult operators, not children. Ergonomic studies have demonstrated that even optimally functioning devices may have significant limitations for young operators who have not reached adult stature (Chang et al. 2010). Operation of tractors, equipment, and vehicles is common on family farms well before the age of normal driving licensing. In the USA and Canada, children from farms and ranches have an average of 6 years' experience in driving tractors and other farm equipment on family farms prior to formal licensing for motor vehicles (Marlenga et al. 2001), indicating that many farm and ranch children routinely begin driving farm equipment at the age of 10 years or younger.

Other Farm Injuries

Children on farms and ranches also have higher incidence of falls, lacerations, animal bites, and large-animal blunt-trauma injury. When these are fatal, the trauma is similar to that seen in adults. With any perforating injury, secondary microbial infection may occur. Secondary infections may be more common with injuries sustained on farms and ranches, reflecting contamination with dirt, animal excrement, and other foreign substances present in these environments. Farm and ranch residents may also be exposed to pesticides, herbicides, and a variety of hazardous inorganic chemicals, many of which are not common in urban settings and may cause severe injury and death (Neidich 1993). The use of alternative or supplemental heating, such as woodstoves, contributes to the higher incidence of rural fires and fire-related deaths. Even exposure to hazardous crops, such as tobacco, may be a cause of morbidity in farm children (McKnight and Spiller 2005).

Drowning and Diving Accidents

Drowning is the second leading cause of childhood death by unintentional injury in the USA, the first leading cause in Australia, and the third most common cause in the world (World Health Organization 2012c). Actual deaths may be

higher, since world figures do not account for flooding, tsunamis, boating, and water-transport deaths. Drowning is more common in children under the age of 5 years, a fact likely associated with minimal swimming skills, lapses in supervision, impulsive child behavior, and attraction to water. Drowning is more common in males and often increased in lower socioeconomic classes and minority groups with children of African-American heritage at 1.3 times the rate of Caucasian age-matched children and Native American/Alaskan Native children 1.7 times the rate of Caucasian age-matched children (Centers for Disease Control and Prevention 2012c). Infants and nonmobile children are at highest risk of death in home bathing situations or immersion in buckets containing water. Older children more commonly drown at swimming locations such as pools and natural water sites. Most of the drowning fatalities are related to the child's inability to swim; however, even children with proficient swimming skills acquired in pools or still water may drown with unexpected tidal and current flows present in some natural bodies of water. The contribution of trauma, natural disease, carbon monoxide, drugs, alcohol, hypothermia, or other risks must be investigated in drowning deaths. Many drownings occur when individuals have no intention of entering the water, that is, falling off docks or boats, water-transport accidents, or breaking through ice in a snowmobile or car. According to statistics of the International Life Saving Federation (ILSF), approximately 25 % of drownings occurs in individuals with swimming skills, or in water less than a meter deep, and 40 % within 2 m of the pool edge or shore (International Life Saving Federation 2012).

Pathophysiology of Drowning

Drowning is an asphyxial death resulting from immersion in a liquid, usually water, with resulting anoxic changes. "Near drowning" is defined as a recovery or resuscitation following submersion/immersion. Following a "near-drowning incident," individuals may recover completely or succumb at a later time from complications of anoxic injury and secondary medical complications. Rarer occurrences of drowning deaths include "hyperventilation drowning," seen in swimmers, usually youths, who hyperventilate to increase underwater swimming distance. The resultant hypocarbia may decrease the physiological stimulus for air, resulting in anoxia, unconsciousness, and subsequent drowning. "Secondary drowning" and "delayed drowning" are terms used when an individual, often a young child, aspirates water and appears to recover but develops a sudden deterioration of pulmonary function several hours after the event. Some use the term "immersion syndrome" when an individual has a catastrophic event, usually cardiovascular, while in the water and dies from the precipitating event or loses consciousness, resulting in drowning. Certification of these immersion-syndrome deaths may be problematic and is often classified as accidental drowning when the precipitating event cannot be recognized or proven.

A consideration of potential components of drowning assists in the forensic interpretation of findings (Burford et al. 2005). The pathophysiology of drownings involves lung and airway effects with resulting cerebral anoxia. In most drownings,

the initial insult results from water within the airways and lungs causing inadequate oxygenation. Aspiration of mud, debris, sand, or vomit into the bronchial tree and alveoli may also occur and complicates the physiological response. This also increases the risk of acute respiratory distress syndrome (ARDS), chemical pneumonitis, and pneumonia if the individual is successfully resuscitated. Freshwater inactivates pulmonary surfactant on contact, resulting in atelectasis, further complicating oxygenation and increasing the pulmonary blood shunting physiological response. Osmotic forces may draw more fluid into alveoli from pulmonary intravascular spaces. The resulting anoxia and acidosis have the most immediate and consequential impact on central-nervous-system (CNS) function, although other organ systems may be involved in pathophysiological changes. These changes include cardiac dysrhythmias, blood-pressure changes from catecholamine release, carbon dioxide retention, and hypothermia. Metabolic acidosis is significant in "near-drowning" victims. Although initial experiments suggested that fluid and electrolyte imbalance and hemoglobin/hematocrit changes from osmolality differences played a major role in drowning, these changes may not be as common or as important as first thought. Deaths are reported in "secondary" or "delayed drowning" scenarios where acute lung injury and rapid pulmonary failure from inhaled water, debris, or chemicals within water produce death several hours after the event.

Autopsy Findings

Forensic findings in all drowning deaths are nonspecific; thus, drowning is a diagnosis of exclusion. Numerous tests have been proposed for establishing the diagnosis of drowning, including diatom presence and electrolytes or other substance differences in right versus left cardiac blood; however, none have proven sufficiently valid for forensic use. Tenacious froth, often with slight blood tingeing, may be present in the mouth and nares and is thought to result from an admixture of water, pulmonary surfactant, mucus, and blood plasma protein (Fig. 27.7). This finding is supportive of drowning but is not present in all cases, and the absence should not be used as criteria for excluding drowning. Internally, froth and water are often present in the airway; the lungs are often heavy and edematous. During the process of drowning, individuals may swallow large quantities of water, distending the stomach. This constellation of heavy, waterlogged lungs often with water in the stomach is termed "wet drowning" and is present in the vast majority of drowning deaths; however, in a minority (about 10 %) of drownings, there is no water in lungs, airways, or stomach. Laryngospasm is postulated to occur in these cases closing the airway and resulting in "dry drowning." In all drowning cases, the struggle to breathe or submersion below 2 m of water may also result in pressure changes reflected in hemorrhage in the inner ear and sinuses that may occasionally be seen at autopsy (Fig. 27.8). Hemolysis of red blood cells may be present if copious quantities of freshwater are present. Often lividity patterns have a bright red tone when drowning has occurred in cold water (Fig. 27.9). All of these findings however are nonspecific and may occur in other deaths. Conversely, drowning may occur with none of these signs. Finally, in deaths from "near drowning" or

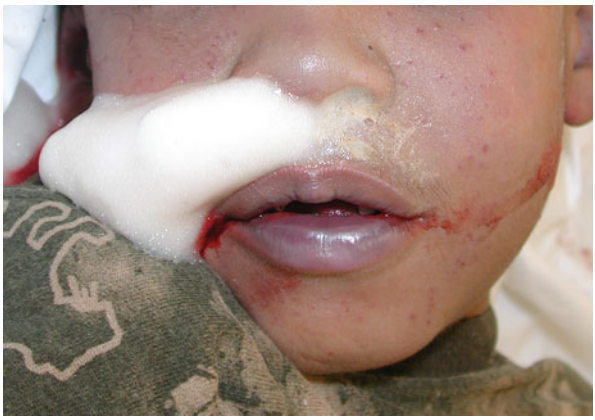

Fig. 27.7 Foam cone in drowning. This 6-year-old child drowned in freshwater. A tenacious froth, often blood tinged, exudes from the nares and/or mouth in many drowning deaths. It is caused by agonal breathing and the mixing of air, water, and respiratory mucous. It may extend to the trachea and more distal bronchi. Although commonly seen in drowning, it is not specific; drownings may occur without this finding, and similar froth may be seen in other non-drowning deaths, such as acute drug overdoses/toxicities

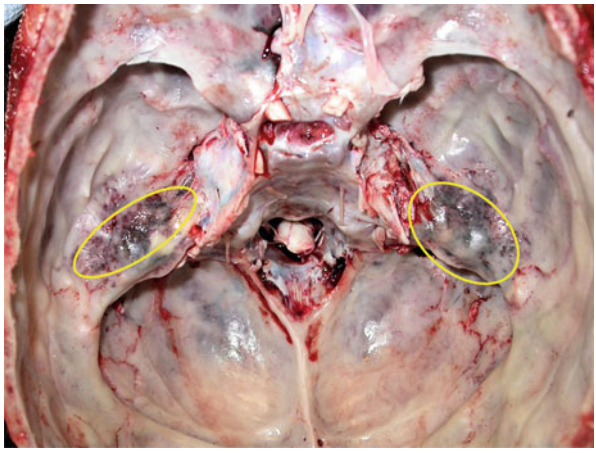

Fig. 27.8 Hemorrhage in the mastoid sinuses in drowning. This is a common, but nonspecific, finding in drowning and is thought to be related to pressure changes

"secondary drowning," the findings at autopsy will more closely reflect the anoxic and secondary complications rather than the original drowning event.

Forensic investigations of all drowning deaths should rule out the presence of trauma or other incapacitating events eg. (insect/aquatic stings, traumatic falls, entanglement in docks/ropes/flora, fatigue) as a component to the drowning. The presence of natural disease, including cardiac arrhythmias, epilepsy, metabolic derangements (eg. diabetes), and other potentially incapacitating conditions, should also be investigated in drowning fatalities. Carbon monoxide is present, often in

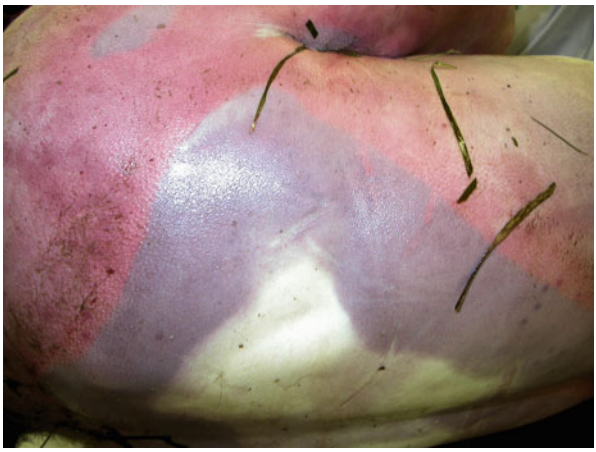

Fig. 27.9 Skin coloration in cold-water drowning. Lividity patterns may have brighter red tones in cold-water drowning, hypothermia, or refrigeration. Carbon monoxide can also produce a cherry red coloration and should be investigated in any drowning where the potential exists for exposure to internal combustion engine exhaust

lethal levels, in boats and around other internal combustion engines, and carbon monoxide quantitation should be performed in any water- or near-water-related death in which gas-powered engines were possibly present in the vicinity at the time of the incident (Jumbelic 1998). Routine drug and alcohol screening should be performed to rule out incapacitating toxicities such as alcohol or opiate intoxication. Depending on potential medical and other case findings, additional toxicology or clinical testing, including vitreous electrolyte, ketone, and glucose levels, may be helpful (Byard and Summersides 2011). Forensic investigations of drowning deaths should document water temperature to assess the potential role of hypothermia in the context of the case. If there is a possibility of diving contributing to the death, careful neck examination, including a posterior neck dissection and cervical spinal cord examination, should be performed to rule out contributions to neck and cervical injury.

Fire Deaths and Burns

House Fires

Fires and burns are a common cause of injury and death in children throughout the world (International Association for the Study of Insurance Economics 2009). Burns are usually unintentional, but may be intentionally inflicted. In house fires, children under 4 years are at the highest risk of death, followed by the elderly (Centers for Disease Control and Prevention 2010). Fire deaths have striking disparities in occurrence, with victims more likely to be from a lower socioeconomic group and of Native American or African descent as compared to Caucasians (Istre et al. 2001; Flynn 2010). The incidences of both fires and fatalities are higher in rural areas contrasted with urban populations.

Most fire deaths occur in the home, particularly in homes without working smoke detectors. Infants and very young children are at greater risk of succumbing

to fire- and combustion-related injury due to the presence of fetal hemoglobin-related carbon monoxide toxicity and the inability to recognize and appropriately react to the fire. Children may tend to hide within the house or seek out sentimental items, such as personal belongings or pets, delaying their escape from the burning house. Young children may be the cause of the fire, resulting from inappropriate use of matches, lighters, and candles, and are thus at the fire's origin and are therefore exposed to the first effects of the fire.

Fire Components Relevant to Forensic Findings

A brief analysis of the components of fires is helpful in understanding the forensic findings (Peck 2011). Smoke is readily produced in fires, particularly home fires, and comprises the airborne solid and liquid particulates of combustion. Smoke is a direct eye and pulmonary irritant and is invariably accompanied by the toxic gas carbon monoxide (CO) with environmental levels of 5 % or more. The carboxyhemoglobin (COHb) saturation level in a human exposed to this level of CO gas will rise to 40 % or more within 30 seconds (Peck 2011). Other toxic gases such as hydrogen cyanide (from synthetic fibers or materials) or the highly irritating acrolein (from wood and natural products) may also be present (Einhorn 1975). Concomitantly, environmental oxygen levels in the fire environment diminish from the consumption of oxygen by combustion. Humans become significantly physically impaired with oxygen levels below 17 %, and mental judgment is compromised at 14 % (Peck 2011). House fires may smolder with oxygen levels at 12 %, and all fires have an oxygen-deficient environment. The hypoxic environment likely contributes to fatalities in fires, but this impact cannot be directly measured by current technology used at autopsy.

Thermal conditions of a fire are also important to some forensic findings (Peck 2011). Temperatures in most house fires reach 300 °F (150 °C) within 5 minutes. In some structures, such as an aircraft, much higher temperatures (approximately 1,100 °C) may be present within 2 minutes. A fire often reaches a "flashover" point, where the thermal radiation causes surfaces to reach their ignition temperature. At this point, near-simultaneous ignition of materials occurs, and the fire spreads to involve the complete room or structure within seconds. Temperatures may soar at this point to over 2,000 °F (1,000 °C) within the structure. Similar rapid acceleration in combustion and temperature may occur when partial collapse of a structure or opening a door creates a rush of oxygen causing rapid fire growth.

Autopsy Findings in Fire Deaths

All fire deaths must be autopsied to confirm the identity of the victim, establish the cause of death, and eliminate non-fire causes of death. The autopsy should include

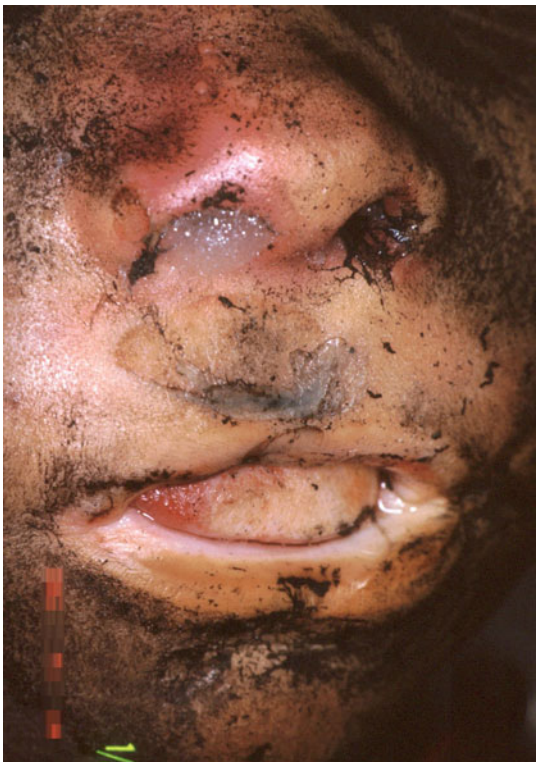

Fig. 27.10 Soot and froth of pulmonary edema in fire deaths. Soot is often present in the nares of fire victims. A slight froth of pulmonary edema may also be present. The presence of soot in the nares and mouth is nonspecific and may occur postmortem

full-body radiographic studies to detect debris, projectiles, or skeletal fractures especially if the external examination is compromised by extensive fire damage. In many children, particularly infants and small children, dental identification is precluded due to the immature developmental stage of dentition and the lack of dental records. This may require investigators to seek DNA confirmation of identity when visual identification is not straightforward. Although rare, temperatures and duration of house fires may reach cremation thresholds, resulting in limited remains of small individuals, including children, necessitating thorough scene examination. In these instances, assistance from a forensic anthropologist may be helpful in increasing the percentage of remains recovered.

The abundant smoke of most house fires is demonstrated at autopsy by readily apparent soot present in nares (Fig. 27.10) and airways (Figs. 27.11 and 27.12). The presence of soot below the true vocal cords is indicative of breathing soot-filled air and is not a fire artifact. In conjunction with the thermal injury, carbon monoxide saturation may be within the lethal range and may play a more significant role in causing the death as compared to the thermal injuries. Pulmonary edema and froth in the nares (Fig. 27.10) and upper airway are often present. Skin blistering may be present (Fig. 27.13), and geographic desquamation of the hands, also

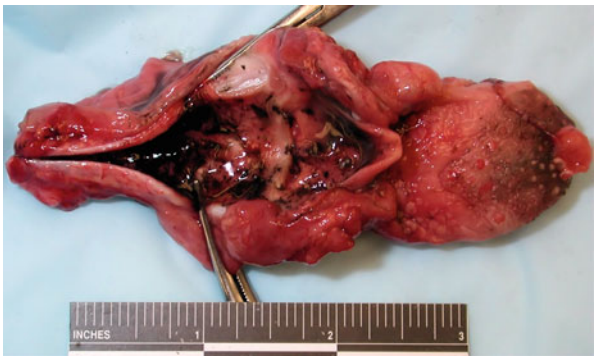

Fig. 27.11 Soot in the airways in fire deaths. Soot deposits in the trachea below the true vocal cords are indicative of breathing while in a smoke-filled environment. The soot often extends to deeper bronchioles. Hyperemia and edema are commonly present in the mucosal airway surfaces

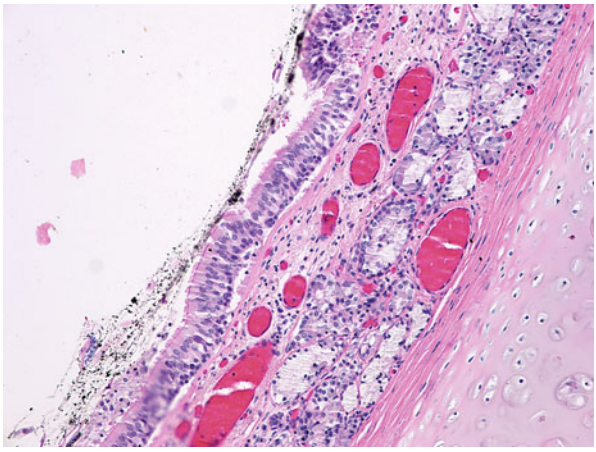

Fig. 27.12 Microscopic soot deposits in fire deaths. A thin layer of carbonaceous soot is appreciated within the mucus and sloughed epithelial cells in this section of trachea from a fire victim (Hematoxylin and Eosin, H&E × 200)

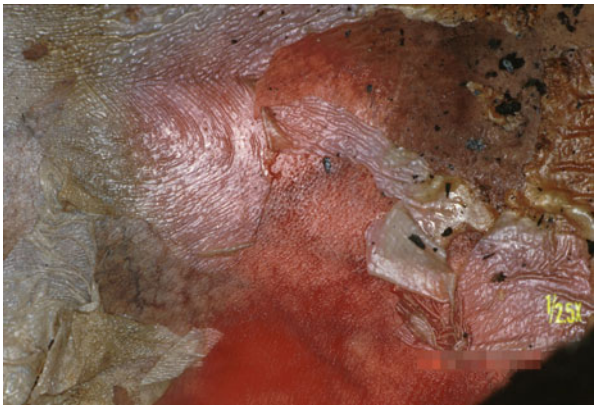

Fig. 27.13 Skin blistering in thermal injury. Skin blistering is common in fire victims. This may be from direct thermal injury or may occur postmortem as an artifact of the fire/heat

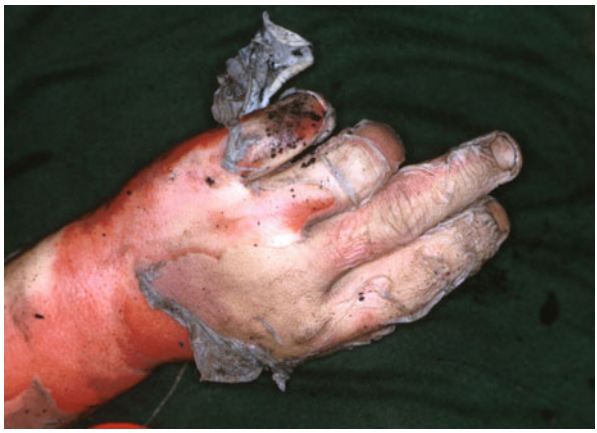

Fig. 27.14 "Degloving" in thermal injury. The epidermal layer may blister and "deglove" in fire deaths. This is usually a postmortem artifact. Fingerprint impressions may be made from the "glove" to aid in identification if suitable pre-injury prints are available for comparison

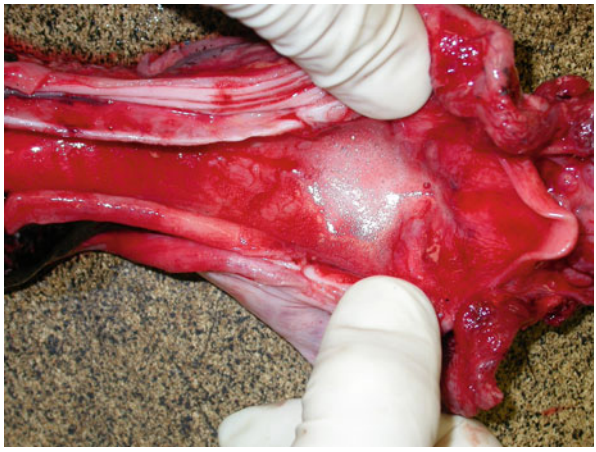

Fig. 27.15 Tracheal hyperemia in thermal injury. In flash fires or steam burns, there may be minimal soot deposition within the airway. The trachea may be intensely hyperemic from burns of superheated air. Edema is often present

referred to as degloving, may occur (Fig. 27.14). More severe heat injury results in extensive charring and reduction in body mass, sometimes with marked reduction in the size and bulk of the extremities and head. Bodies may assume the so-called pugilistic posture, a postmortem artifact of heat-related, differential muscle contraction.

Victims of "flashover" fires or explosions, such as from natural gas leaks or incendiary devices, often have minimally elevated or normal carbon monoxide saturation levels and an absence of soot in the airways, which may be intensely hyperemic (Fig. 27.15). In this scenario, death is usually related to heat-induced laryngospasm or vagal-reflex cardiac arrhythmia. Pulmonary contusion or hemorrhage may be present from blast injuries if an explosion has occurred; debris or bomb material may be embedded in the victims. Hemorrhage in the inner ears and sphenoid processes may be apparent at autopsy in such explosions and subsequent fires.

Fig. 27.16 Skin splitting artifact in thermal injury. Skin splitting in fires is a known postmortem artifact and should not be mistaken for sharp force injury. Note the yellow base of the surface and lack of vital reaction. The slight reddish appearance is from drying

Traumatic Injury in Fires and Fire Artifacts

Traumatic injuries, falls, and blunt trauma from structural collapse may be present in fire fatalities. These injuries may be the primary cause of death, contribute to the cause of death by restricting egress from the fire, or occur postmortem. Heat-related fractures of bones, including the skull, occur in fires and should not be mistaken for premortem injury. A common fire-related artifact is an epidural accumulation of blood and marrow; however, this is readily distinguished from a premortem epidural hematoma by the granular, foamy, or flaky texture and brownish coloration. The victim's skin may be dry with large splitting defects exposing the underlying fascia or abdominal cavities (Fig. 27.16). Clothing or objects near the victim may burn or melt and be deposited on the skin. Care must be taken to distinguish these postmortem artifacts from actual premortem injury.

Additional Procedures and Testing in Fire Deaths

Assistance from anthropologists is helpful in many fires to accurately recover and identify bone fragments which may be difficult to recognize among fire debris at the scene (Figs. 27.17 and 27.18). Radiological examination is extremely helpful, but suspicious findings must be confirmed by direct examination (Fig. 27.19).

Toxicology testing for alcohol and drugs is important in fire fatalities, since the use of these substances may contribute to the start of the fire or failure to successfully leave the burning structure. Testing for carbon monoxide is needed in all fire deaths, and testing for additional toxicants (such as cyanide) may be necessary for a complete forensic investigation. Select cases may benefit from CO saturation levels at different anatomic sites; for example, CO saturation of a fresh subdural hematoma or an area of trauma may reveal different levels compared with to cardiac blood, indicative of prefire trauma contributing to death. In cases where there are no/minimal airway-soot

Fig. 27.17 Bone fragment in fire death. Portion of long bone retrieved from a fire. The irregular fragmentation and splitting is a postmortem artifact and does not indicate traumatic premortem injury to bone

Fig. 27.18 Bone fragment in a fire death. Microfissures within a long-bone fragment. Small-bone fragments such as this may not be recognized by responders. Consultation with forensic anthropologists is extremely helpful in the recovery of human material in a fire scene

and nonlethal-CO saturation levels, death prior to fire must be seriously considered in the investigation. If an incendiary device is suspected, consultation with experts at the time of the initial investigation and autopsy will assist in the specialized collection of evidence from victims which is required for case investigation.

Scalding

Contact with or immersion in hot liquids or gases is more common in infants and small children than adults. Scalding is the most common burn injury in the pediatric age group (Shah et al. 2011); however, most accidental scalding injury is not fatal, so this is less commonly encountered at autopsy. The skin in a scalding injury is markedly erythematous, blistered, or, with severe injury, completely denuded with intense underlying erythema. Sharp borders are invariably present between injured and uninjured areas. A characteristic of scalding injury is the distinctive injured/uninjured pattern created by different modalities of injury, including pouring, splattering, or immersion. In an accidental scalding injury, irregular patterns of splattering are often present on the face, hands, or upper body often from children pulling or tipping pans of hot liquids from stoves. In immersion injury, larger, more confluent areas of burning are seen which correspond to the child being dipped or held in hot water. The buttocks, back, and feet are

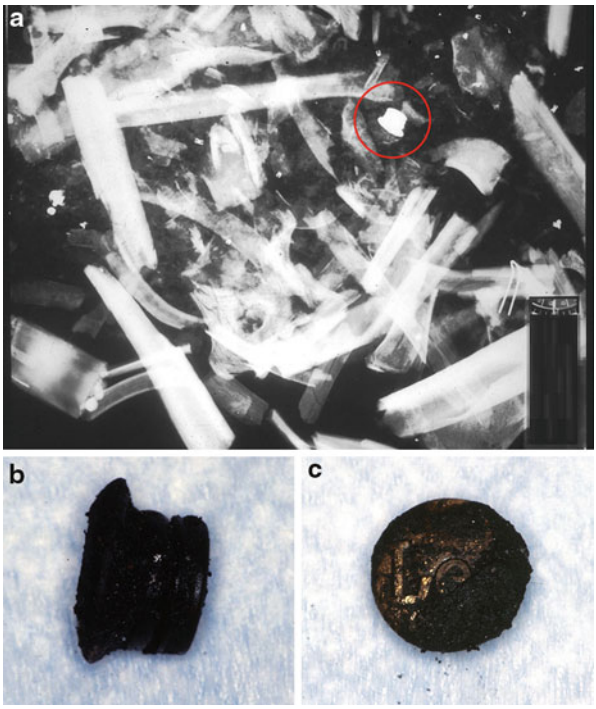

Fig. 27.19 Misleading radiologic image in a fire death. These fragments were recovered from a house fire. Routine radiologic imaging showed a radio-opaque object suggestive of a projectile (**a**: circled). Retrieval and subsequent cleaning of this object (**b**, **c**) demonstrated it was a metal button from jeans

the most commonly burned areas. Characteristic of the immersion burn is the sparing of injury in skin folds, such as inguinal regions or behind the knees, resulting from the child withdrawing the lower extremities to avoid the immersion. Large-immersion pattern scalding injury is indicative of inflicted trauma. Children under 4 years of age are most at risk of immersion injury, and this form of inflicted trauma is often precipitated by adult frustration with toilet training of the young. Deaths from scalding injuries result from direct thermal injury or complications of these injuries. Vitreous chemistry and microbiological studies may be of value in investigating these deaths.

Water is the most common medium for scalding injuries, likely due to its universal availability. Infants' and young children's skin is more susceptible to thermal and scalding injury (Diller 2006), and burns can occur within 3 seconds with water temperatures 140 °F (60 °C) or higher (Feldman et al. 1978, 1998). Many residential water heaters are set to this temperature or higher, increasing the risk and ease of injury to children.

Chemical Burns

Fatal chemical burns are uncommon in pediatrics but may occur in young children from exposure to caustic household chemicals, such as lye (Elshabrawi and A-Kader 2011). Most of the fatal injuries involve ingestion, and deaths may occur following prolonged medical intervention.

Surface Burns

Contact with hot objects is a cause of childhood burns and is often seen in child abuse (Toon et al. 2011). In the forensic setting, these are usually a component of an inflicted-injury pattern and not the primary cause of death. In many instances, patterned impression of the causative object, such as a hot plate, cigarette, poker, or other object, is present. It is critical to document these pattern injuries with extensive photography and detailed measurements. As with other patterned injuries, body curvature and positioning may cause interrupted patterns or may assist in interpretation of body posture or defensive positioning when inflicted.

Fireworks

Deaths from fireworks are rare, but a large percentage of these fatalities are in children. Deaths usually result from blunt-traumatic injury and/or flash fire resulting from fireworks (Smith et al. 1996). Rarely blast and explosive injuries are a component of these deaths.

Delayed Fire and Burn Deaths

In many burn injuries, death occurs after considerable time has passed from the time of the injury with numerous intervening medical and surgical procedures. The original pattern of burn injury may not be present, and there are usually a number of medical complications leading to the demise. Burn victims are susceptible to a wide variety of infections, electrolyte and metabolic derangements, and medical complications including ARDS, DIC, and multisystem organ failure. Careful documentation of medical interventions and events is part of the forensic autopsy of these patients. Death certification must accurately relate medical complications back to the initiating injury.

Electrocution

Most childhood electrical fatalities result from low-voltage electrocution in the home (Rabban et al. 1997). Household appliance cords or extension cords are the most common causes of electrocution in children, followed by wall outlets. Younger children may contact cords orally or via a conductive foreign object such as a key or pin. Less commonly, contact with poorly grounded and electrified appliances or heaters may cause electrocution. High-voltage electrocution is rare in young children but may be seen in adolescents, particularly among males. An even rarer event is death due to lightning injury in the pediatric population; however, fetal death due to maternal electrocution may be seen even when the mother survives the lightning strike.

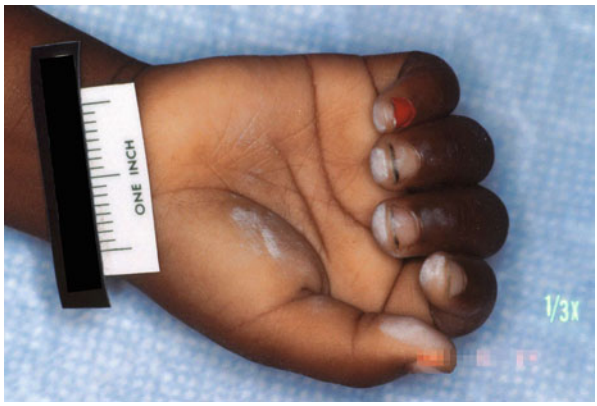

Fig. 27.20 Electrical injury: Joule burn. The point of electrical contact may be subtle. These cutaneous injuries are from a 2-year-old child who touched a poorly grounded electric space heater while sitting in a water-filled bathtub

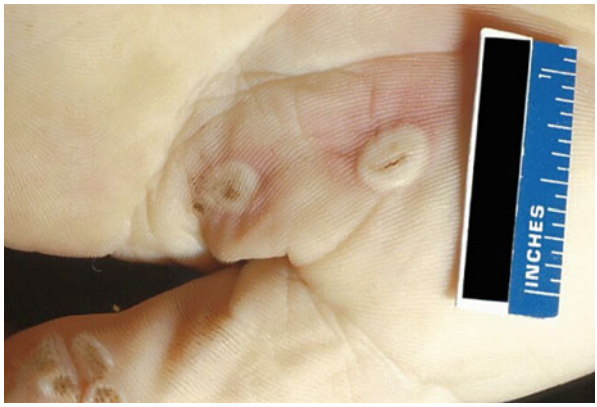

Fig. 27.21 Electrical injury: contact site. The epithelium is often raised and pale white with a central point of contact and mild hyperemia at the base

Low-Voltage Electrocution

The findings of electrical injury in children are similar to those seen in adults, and the elements of forensic investigation and autopsy are identical. Electrical injury is challenging since often there are no distinguishing features. A high index of suspicion, through scene investigation and consultation with electricians, is critical to identifying and appropriately categorizing these deaths. Low-voltage (<1,000 V) electrocution is the most common type of electrocution in both children and adults. The classic "Joule burn" or electrical mark is present in approximately half of the cases. When present, it identifies the point of electrical current entering or exiting the body. The skin may be whitish (Fig. 27.20) surrounding a raised, oval, or round crater with hyperemic borders and a pale center (Fig. 27.21). The shape of the burn may relate to the conductor shape in contact with the skin. Charring or edema is often present, and prolonged contact may result in deep burning of tissue. Microscopically, a "streaming" appearance of cells and nuclei is often present accompanied by thermal homogenization of the dermis, deep fascia, and underlying tissue

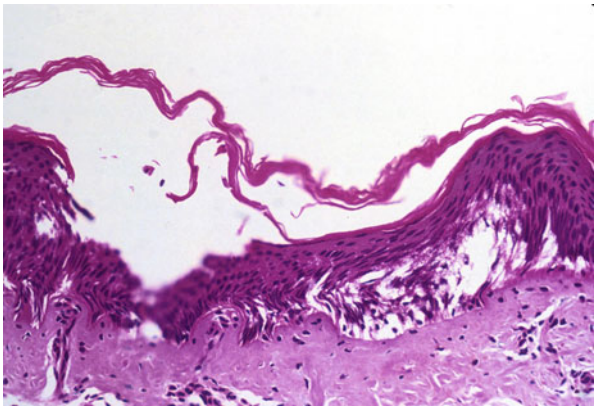

Fig. 27.22 Electrical injury: histology of a contact site. On microscopic examination, there is a "streaming" appearance of the cells and nuclei, often with thermal homogenization of the dermis, deep fascia, and underlying tissue (Hematoxylin and Eosin, H&E × 400)

(Fig. 27.22). The epithelial basal layer of the skin is often detached. These changes are supportive, but not diagnostic of electrical injury. Occasionally, trace evidence of metal deposition from wires may be present at the site of electrical contact. The point where electric current exits the body is usually more difficult to identify and may be entirely absent. When present, it may have many of the characteristics of the site of current entry. Deaths from low-voltage electrocution are caused from electrical disturbances, primarily ventricular fibrillation of the cardiac conduction system or respiratory paralysis from interference with brainstem function, both autonomic disturbances that leave no physical trace to be identified at autopsy.

High-Voltage Electrocution

High-voltage electrocution (over 1,000 V) is uncommon in the pediatric population and, when present, has the same characteristics of blast injuries and flash burns as with adult deaths due to high-voltage electrocution. Death is usually related to blast effects, thermal injury, and secondary trauma rather than to an electrical interruption of cardiac or brainstem function. With extremely high voltage, charring and bone fusion may be present, and the muscles will appear gray-white from the effects of temperature. Skin may be denuded, and the hair is often scorched or a lighter color following high-voltage electrocution.

Lightning

Lightning strikes are uncommon events, and, because of the extremely short time interval of electrical exposure, over two-thirds of victims survive a lightning strike. In the event of a death, the majority of findings may be nonspecific. A faint, erythematous, arborizing pattern on the skin, the so-called Lichtenberg figure, may be present initially, but will subsequently fade in a relatively short time frame. Rupture of eardrums and opacification of corneas may occur in lightning injury.

Falls

Falls are a part of normal childhood, an expected result of the need for exploration, as the young push their limits in developing coordination and locomotion skills while navigating their environment. Most falls are inconsequential; however, each year in the USA, 2.8 million children seek emergency department care for falls (Centers for Disease Control and Prevention 2012d). Analysis of fall data in children can identify intervention strategies to reduce this common cause of injury (Khambalia et al. 2006). Falls are responsible for death in over 46,000 children annually (World Health Organization 2012a) and may be a component of inflicted injury of children. Delineation of these injuries is one of the most challenging tasks in forensic pathology.

Types of Fatal Injury in Falls

Fatal injury from falls usually involves trauma to the head, although extremity fractures and internal injuries can occur and may cause death. The assessment of the degree of injury relative to the presenting story is a key component in distinguishing accidental and inflicted injury in the evaluation of a fall. In general, short-distance falls (less than 10 ft or 3 m) and falls down stairs rarely produce fatal injury to children (Chadwick and Salerno 1993; Chadwick et al. 1991; Chiaviello et al. 1994a). The presence of an adult may complicate injury to the child as falls occurring with children being carried down stairs by an adult have a higher injury index and more frequent skull fractures than falls down stairs by children themselves (Joffe and Ludwig 1988). The added mass of an adult and secondary impact(s) may be responsible for the increased severity of injury. Numerous studies of falls in specific situations exist in the literature including falls from buildings (Vish et al. 2005), playgrounds (Centers for Disease Control and Prevention 2012a; Petridou et al. 2002), beds/couches (Belechri et al. 2002), high chairs (Schalamon et al. 2006), infant walkers (Shields and Smith 2006; Chiaviello et al. 1994b), child-restraint seats (Desapriya et al. 2008), infant slings/carriers worn on adult bodies (Frisbee and Hennes 2000), heights (Thompson et al. 2011; Murray et al. 2000), and in hospital settings (Jamerson et al. 2009). Case reports of severe injury from accidental stairway and short-distance falls exist (Lantz and Couture 2011), although the presence of severe head injury is more indicative of inflicted trauma.

Disparities

Disparities exist in pediatric falls. Falls with injuries are more common in children of nondominant populations and lower socioeconomic classes (Faelker et al. 2000; Shenassa et al. 2004) in most but not all countries (Engström et al. 2002). This is correlated to older and poorer conditions of environmental factors, such as reduced

repair of playground equipment, older model cribs and beds, and poor maintenance of stairwells, balconies, and windows in lower socioeconomic populations.

Investigation and Autopsy

Forensic investigation and autopsy in childhood deaths from falls is challenging since inflicted versus accidental trauma is often the question. Careful and extensive photography of injuries, full radiological examination, fixation of the brain, and extensive histology are considered a baseline in the performance of the autopsy. Specialized dissections, such as removal of optic nerves, eyes, and posterior neck dissections including examination of cervical spinal roots (Matshes et al. 2011) may assist in interpretation. When there is a question of inflicted skeletal trauma, removal of the affected bone and the contralateral control bone may be important for evaluation. Careful review of all clinical records and police investigation is required for optimal interpretation. Correlation or identifying points of discordance with the given clinical history of how the event occurred is critical for case assessment. It may be helpful to have at least one meeting with all interested professionals, including clinicians providing care, radiologists (if appropriate), police and investigating agencies, child-protective services, and legal prosecutorial representation if jurisdictionally allowed. The adage "We speak for the deceased as discoverers of truth, not makers of cases" rings true in evaluation of the difficult area of pediatric deaths due to falls.

The rapid advances in imaging and pediatric head-trauma interpretation will likely assist in defining appropriate studies and interpretations as more evidence-based practices in forensic medicine evolve.

Animal-Related Deaths

Most children have many positive exposures to animals – from appreciation of wild animals, visits to zoos, and caring for animals as pets, companions, or livestock. Care and responsibility for animals is a major step in normal childhood development; abuse of animals is a critical warning sign of behavioral problems. With this overarching exposure to animals, childhood injuries and fatalities occur in a variety of animal-related scenarios (Bury et al. 2012a, b). The majority of these fatalities occur either with large animals or with commonly encountered animals such as dogs.

Horses and Other Large Animals

Injuries and deaths associated with large animals are increasingly seen both in and outside rural environments. The non rural increase is primarily due to the popularity

of horseback riding among urban and suburban youth. A horse can weigh over 1,000 lb (450 kg) and reach speeds approaching 40 mph (65 km/h), both accounting for the inherent dangers of this sport. This danger is amplified for young children where the injury rate for children in horseback riding is nearly twice that of adults from both falls and kicks from horses (Jagodzinski and DeMuri 2005). A Mexican proverb states "It is not enough for a man to learn to ride; he also must learn how to fall," alluding to the danger admixed with the joy of this sport.

Most injury in horseback riding occurs when the rider falls off the horse; occasionally, this is complicated by a secondary kick from the horse, being stepped on by the horse, or through entrapment in a stirrup and subsequent dragging. The use of "break-free" stirrups can decrease the risk of entrapment and dragging following a dismounting fall. In nearly a third of horse-related injuries, the child is not riding the horse, but is kicked while in the vicinity of the horse. Head injuries are the most common and the most serious type of injury, accounting for most fatalities in horse-related accidents (Ghosh et al. 2000). In children, upper-extremity injury is more common than lower-extremity injury. Injuries to the back, pelvis, chest, and abdomen do occur, but with much less frequency in children as compared to adult horse enthusiasts. Horse-related injury is second in severity only to pedestrian versus motor vehicle injury, and horse-related injury has greater severity than injury from ATVs, bicycles, and passenger-related motor vehicle crashes (Bond et al. 1995). Helmet use reduces the severity of injury and the likelihood of death.

Dog Bites

Nearly five million dog bites occur every year in the USA, with over 40 % occurring in children under 14 years of age (Centers for Disease Control and Prevention (CDC) 2001). Children, particularly those under the age of 5 years, are more likely to have provoked dogs, often unintentionally through play, and are often incapable of escape or defending themselves from a dog attack.

Most dog bites are generally single bites to the extremities and are usually not fatal; however, most dog attacks and fatalities involve multiple bites to the head and neck region where extensive mutilating and defleshing injuries may occur. Exsanguination and air embolism via neck veins are common causes of death in dog attacks. Most dog-attack fatalities have multiple puncture wounds from the teeth and extensive defleshing from the tearing and hunting behavior of the dog(s). Severity of injury and increase in fatal attacks may be increased when more than one dog is involved due to "pack" behavior (Tsokos et al. 2007). Abrasions and shallow incised wounds from paws or friction contact abrasions from surfaces may also be present. Large breed dogs may cause crushing injuries to the very young, including infants and toddlers, resulting in severe skull fractures and cerebral injuries. Several studies have examined the incidence and breed characteristics of fatal dog attacks, but may be confounded by the lack of accurate data into breed

type actually present in a community as well as the effects of legislation restricting ownership of certain breeds (Raghavan 2008; Sacks et al. 2000). Bite-prevention programs show initial promise in educating young children about safe behavior with dogs (Meints and De Keuster 2009).

Special considerations at autopsy of a fatality involving a dog bite include documentation of any canine odontological trauma for comparison (De Munnynck and Van de Voorde 2002). When an animal is captured, examination of material between the teeth or within the gastrointestinal tract at necropsy may confirm human tissue. Consultation with veterinarians is very useful for testing of an animal for rabies, tumors, or other conditions that may have led to the attack, including examination for prior animal maltreatment, starvation, or training for fighting activity. Investigation of the events leading to the attack, including a history of dog behavior, breed characteristics, and any precipitation or provocation by the victim, is helpful in reconstructing the events and interpreting injury patterns.

Bites and other trauma from animals may also be a cause of delayed death from microbial infections contracted from oral animal flora, human skin flora, or subsequent contamination of the original bite (Dendle and Looke 2008).

Other Animal-Related Deaths

A wide variety of wild animals, on both land and sea, may cause injury and death in both provoked and unprovoked attacks. Children are often more susceptible due to their decreased ability to flee or defend themselves, lower cognitive awareness of danger, and provoking animal attack behavior either intentionally or through play. The smaller mass and stature of young children also increases risk of fatal outcome of a wild-animal attack. Many animals may attack causing injury and death including bears, feral dogs, coyotes, cougars, and wolves on land and sharks or other predatory fish in the sea. Predatory land animals usually maul and bite victims, and if hunger precipitated the attack, the predators may devour most of the victim. Large non predatory animals, such as cattle or moose, may cause injury and death from a stampede or trampling of victims.

In water, sharks are the most common human predator. Sharks may swim very near land and docks and attack surfers and swimmers. Shark attacks are characterized by large bites and tearing of limbs and viscera. Examination of the body for bite marks or fragments of teeth may assist in species identification. Crocodiles and alligators are territorial animals and may attack individuals within their home wetlands. Alligators are generally timid but may lose their fear of humans when fed or with repeated contact. In contrast, large crocodiles are more predatory by nature. Both species can move very fast on both land and in water, increasing the danger of attacks to small children. These species will occasionally drag victims underwater, preserving a portion of the body for later consumption. Their jaws exert the most pressure of any predator (Erickson et al. 2012), with up to 3,700 lb per

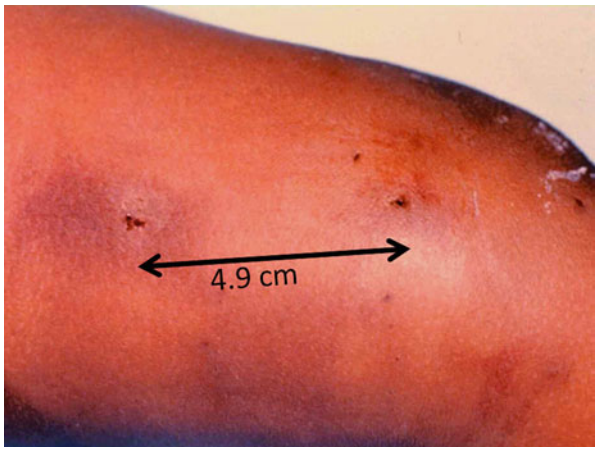

Fig. 27.23 Cutaneous site of a snake bite. This 3-year-old child collapsed suddenly while playing in the tall grass at a campsite. Her family reported a single scream before the collapse. She was unresponsive and could not be resuscitated. Later, this site of likely envenomation was found on her thigh

square inch pressure (25.5 MPa, 255 bar, 251 ATM), causing instantaneous massive trauma to victims. All these predators produce findings in child victims similar to those seen in adults, although children may be more susceptible due to their small size and inability to defend or flee from an attack. Rarely, smaller sea life may sting or envenomate victims, causing injury or death, by either venom or secondary drowning. In all these animal attacks, the findings at autopsy are similar to those in adults. With the wide variety of animals and predators throughout the world, forensic pathologists should be aware of regional species that may cause injury and death.

Venomous Creatures

Fatal envenomation may occur from several land-based (snakes, scorpions, spiders) or marine-based creatures (jellyfish, stonefish, octopus, Portuguese man-o'-war, cone snails). Autopsy findings vary with specific venomous species and may be subtle, requiring detailed historical investigation and/or careful cutaneous evaluation for envenomation site (Williams and Milroy 2012). Venomous-snake fatalities are uncommon, but young children may be particularly susceptible due to their small body mass (Figs. 27.23–27.25).

Insects

Insect bites and stings may also produce death from anaphylaxis, zoonotic transmission of disease, or rarely overwhelming envenomation. Worldwide, the deadliest "animal" is the mosquito, causing malaria across wide areas of the tropics as

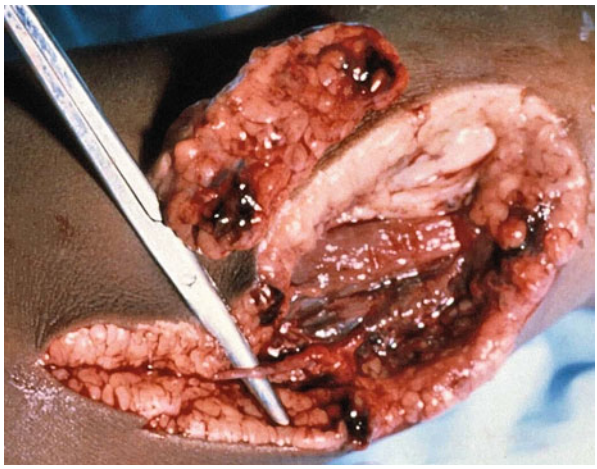

Fig. 27.24 Dissection at site of snake envenomation. Hemorrhage is clearly present in the subcutaneous tissue tracts, and direct envenomation of an artery is identified

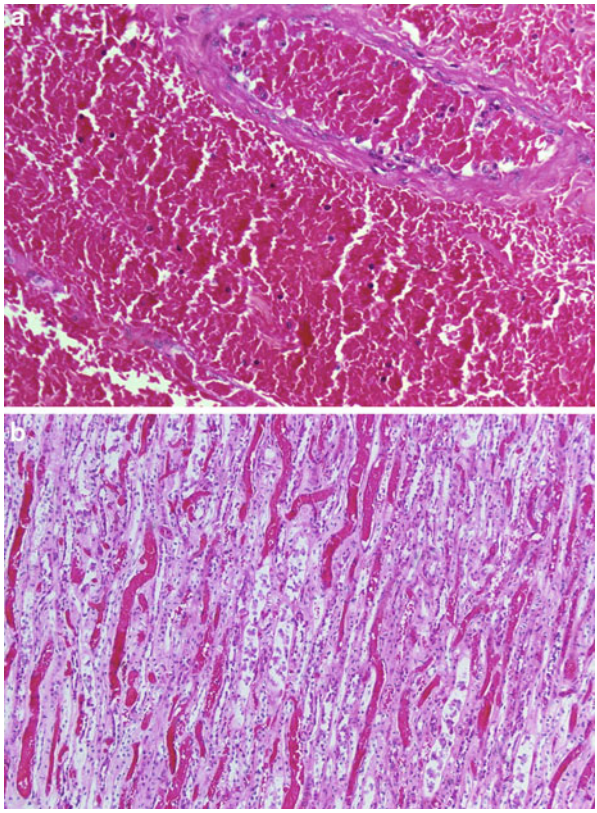

Fig. 27.25 Microscopic findings in envenomation (Hematoxylin and Eosin, H&E ×100). (**a**) Massive hemorrhage in the soft tissue surrounding the envenomation site. (**b**) Renal tubules with massive DIC and myohemoglobin within renal tubules

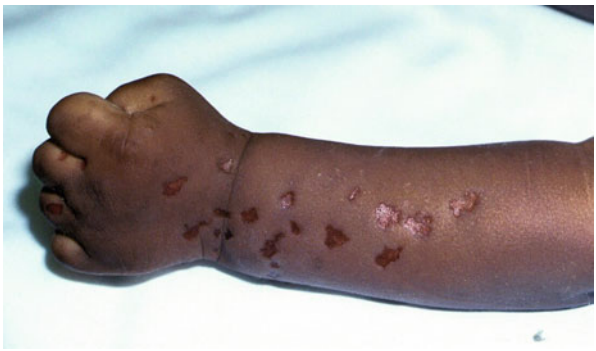

Fig. 27.26 Postmortem ant bites. This 3-month-old infant was found deceased after a sleep period. Scene investigators were concerned with the lesions identified on her arm, raising the possibility of child abuse. The irregular and shallow erosions are typical of postmortem ant bites. These normally have a yellow base, but drying artifact can darken the lesions, suggesting a vital reaction. It is critical to correctly assess postmortem artifact from abuse and traumatic injury in any forensic investigation

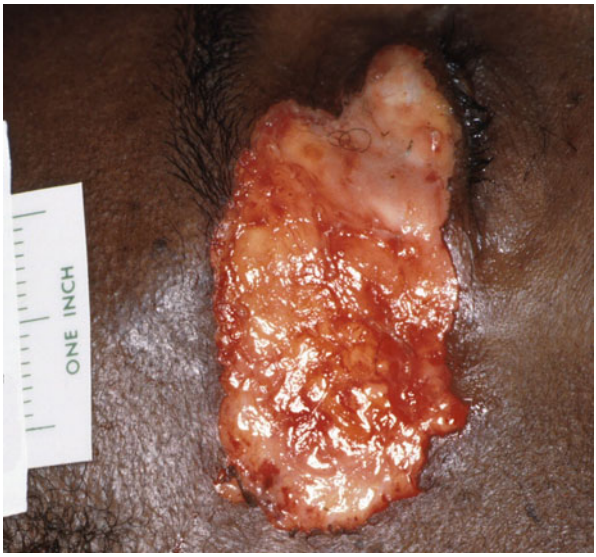

Fig. 27.27 Postmortem rodent activity. Lesions from rodent postmortem predation have shallow and irregular contours and are often centered on natural orifices, such as eyes or sites of premortem injury. Note the uniform shallow contours and yellow base of this lesion, both indicative of postmortem rodent predation. Similar patterns may be seen with some aquatic predators, such as crabs in cases of drowning in crab-infested waters

well as yellow fever, West Nile virus disease, dengue fever, Rift Valley fever, and a variety of encephalitis-related diseases on every inhabited continent.

Artifacts and Postmortem Changes

A variety of animals and insects are natural scavengers in the postmortem period (Byard 2011). The disfigurement caused by postmortem predation is considerable, and care must therefore be taken to avoid confusion with premortem injury

(Figs. 27.26 and 27.27). There are striking regional differences in postmortem scavenging activity, and forensic pathologists should be aware of local scavenging patterns. Forensic pathologists and investigators should also be aware that household pets often are involved in postmortem predation (Buschmann et al. 2011).

Airway-Associated Deaths

Choking hazards are greatest in very young children due to the proclivity of infants and toddlers to place objects in their mouths, the lack of cognitive awareness of dangers in this age group, the smaller upper airway, and poorer cough reflex in very young children. In contrast with adults, where alcohol, drugs, and/or neurological impairment may be predisposing factors in airway-associated deaths, these factors are usually not a component of pediatric airway-associated fatalities. Food, coins, and balloons are the most common objects causing obstruction in children (Altkorn et al. 2008; Rimell et al. 1995). Total obstruction of the upper airway produces rapid loss of consciousness and death. Occasionally, a child is found dead without a history or suspicion of airway compromise, even in a supervised environment. Physical findings in airway-associated ("choking") deaths may or may not include external petechiae or head and neck cyanosis; however, internal intrathoracic petechiae are usually present. The object is usually readily found within the larynx or trachea (Figs. 27.28, 27.29, and 27.30), or at the carina (Fig. 27.31). Occasionally resuscitative efforts may force the object into the proximal major bronchi. Objects smaller than the expected caliber of a child's airway may cause death either through laryngospasm or direct obstruction of a scarred and narrowed airway. Children most at risk for airway scarring are those who had been previously intubated, particularly as a preterm neonate.

Game-Playing Asphyxia

Game-playing asphyxial deaths occur primarily in older children and young adolescents (Le and Macnab 2001; Andrew et al. 2009). Widely termed the "choking

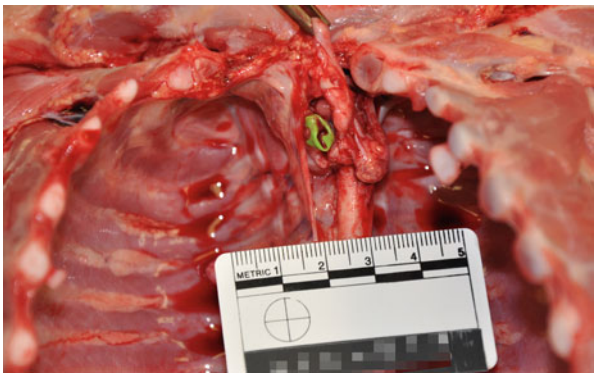

Fig. 27.28 Airway obstruction by a balloon. This was the autopsy finding in a 5-month-old infant who was found deceased by his caregiver. The father had lain down with the infant on a quilt and both fell asleep. On awakening, the father found the infant unresponsive a few feet off the quilt. Autopsy revealed an object in the upper trachea

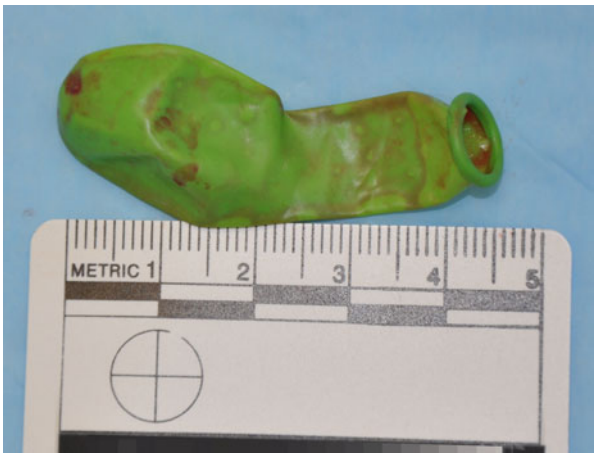

Fig. 27.29 The object recovered from the trachea was a small balloon

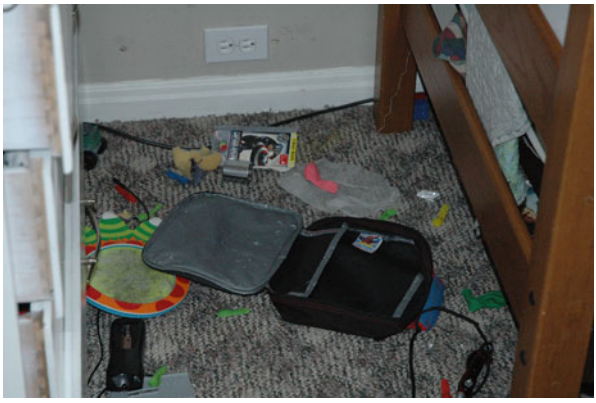

Fig. 27.30 Scene investigation in this airway death revealed multiple balloons and other small choking hazards on the floor where the infant was found

game" within the literature and community, this activity usually involves a form of strangulation to achieve a brief period of euphoria. Strangulation may be achieved by use of hands, ligature, or noose and may be self-administered or done by others. Rarely, a variant of chest compression produces the asphyxial state. The resulting cerebral hypoxia is reported as a "high" with light-headedness or a few seconds of unconsciousness. With release of external neck compression, a "rush" or "tingling" is described among children experiencing this activity. This activity is commonly known among preadolescents and goes by over 75 local variations in both name and activity (Centers for Disease Control and Prevention (CDC) 2010; Macnab et al. 2009) and is seen throughout the world (Noirhomme-Renard and Gosset 2011). The cases presenting to a forensic service usually involve solo-game playing and are often initially thought to be suicidal hanging deaths (Andrew and Fallon 2007). The physical findings at autopsy are similar to other strangulation or hanging deaths (Figs. 27.32 and 27.33), and the key to recognition is within the scene and death

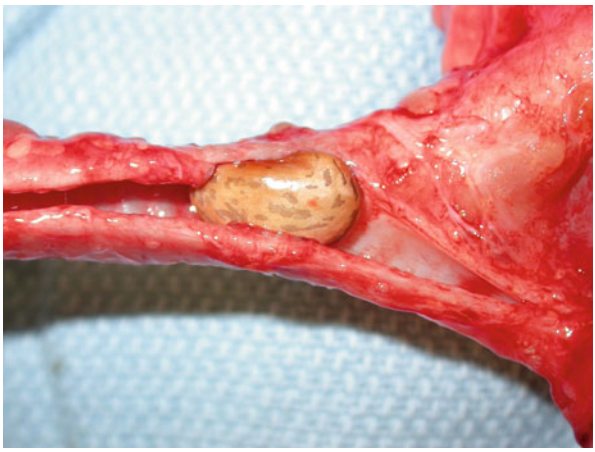

Fig. 27.31 Bean obstruction at the carina. This 8-month-old child was visiting his grandparents, crawling on the kitchen floor during a family gathering. He stopped moving and adults thought he was napping. A few minutes later, they noticed a darkening blue tone to his lips and tried to arouse him. He was unresponsive and EMS was called. He presented to the medical examiner's office as a sudden death in infancy during sleep. A sack of pinto beans had spilled in the kitchen the day before; adults thought all were cleaned up. The child had found a single bean in a floor crevice

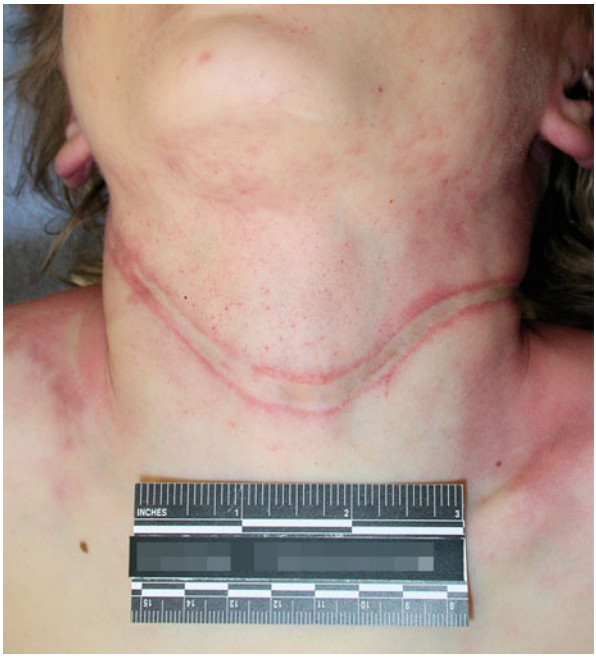

Fig. 27.32 Neck findings in game-playing asphyxia. The pattern of ligature compression is seen at the neck. The hyperemic borders and pale center suggest the diameter or width of the constricting object. Often, a pattern may be present that corresponds to the ligature material

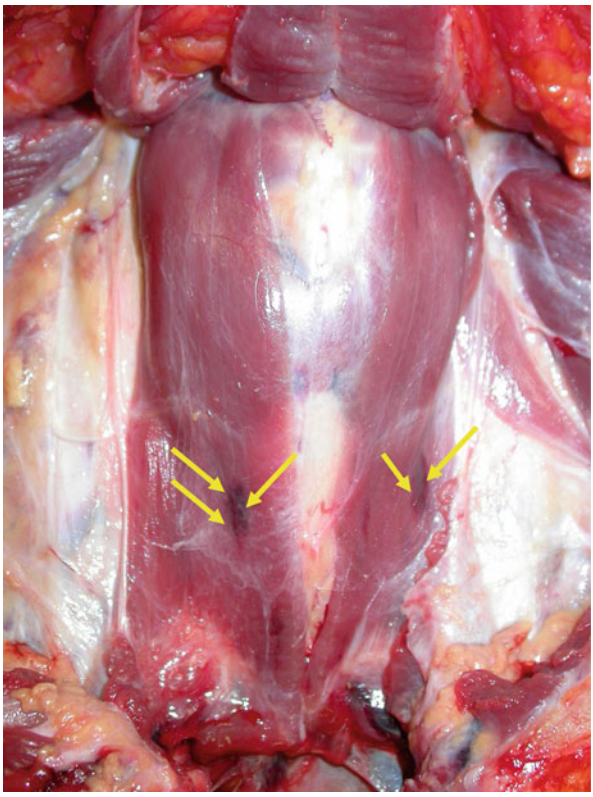

Fig. 27.33 Layered neck dissection in ligature hanging. Careful neck dissection after removal of the CNS and body organs may reveal hemorrhage within strap muscles of the neck, corresponding to the site of constriction

investigation (Fig. 27.34). The activity is usually hidden from adults, but is widely acknowledged among peers, who usually regard the activity as a safe, drug-free "high," a part of thrill-seeking activity and risk-taking behavior of early adolescence. There are no indications of suicide at the scene or by history, and there is no evidence of autoerotic activity. The incident usually occurs in a private location that the child regards as safe, often within a home or school. The children are often "good kids," without behavioral, mental health, school, or drug/alcohol use problems. There are minimal gender differences in most studies, although some studies show a male predominance. In the USA, it is more common in Hispanic and Native American/Alaskan Native populations as compared to Caucasian populations (Toblin et al. 2008). Key to recognition at the scene is the "private yet safe" location, the simplicity of the noose, absence of suspension, and facile ability to self-extricate from the compressing object (Fig. 27.34), which usually is a simple loop against which youngsters lean. There are often wear marks on hooks or furniture from previous episodes or historical incidences of syncopal episodes, voice changes, new onset headaches, abrasions on the neck, disorientation after time alone, or accessing various electronic activities (websites, blogs, chat rooms)

Fig. 27.34 Scene findings in game-playing asphyxia. This simple loop was present suspended from slats of an upper bunk. The child would lean against the loop as part of game playing; however, in this instance, unconsciousness prevented the simple action of lifting the head to remove neck constriction

for asphyxial games. The absence of suicidal ideation, depression, or farewell messages is also important to ascertain. Invariably, peers will either acknowledge similar past group or individual "game playing" or confirm that the victim sought information about game-playing asphyxia. Although some describe this as a new risk, it may be a continuum of asphyxial games of past preadolescent generations, such as "breath holding" or hyperventilation to achieve momentary alterations of consciousness. The recent deadly inclusion of ligatures and nooses greatly increases the potential for death, especially when children engage in this activity alone.

Autoerotic or sexual asphyxia deaths in children are rare and when they occur tend to be in older adolescent males (Sauvageau and Racette 2006). Key findings of autoerotic deaths are generally scene-related with sexually explicate material and/or sexual devices present, privacy of the scene, evidence of masturbatory activity, sexual fetishes, bondage or masochistic activity, and often elaborate asphyxial producing and escape mechanisms (Shields et al. 2005a, b). A review of cases from Australia and Sweden revealed no autoerotic deaths below the age of 20 and confirmed the male predominance seen in previous studies (Byard and Winskog 2012).

Disparities in Childhood Injury and Death

Accidental deaths and injuries occur in all socioeconomic, ethnic, and racial groups. However, disparities exist in the occurrence, severity, and numbers of fatalities from pediatric injuries caused by both accidental and non accidental modalities. In the USA, African-American (Brown 2010), Hispanic (Mallonee 2003), and Native American children (Goldcamp et al. 2006a; Berger et al. 2009) all have higher rates and severity of injury and death over Caucasian children, even when adjusted for socioeconomic class. Rural and frontier children are also at higher risk of injury and death during childhood as compared to their urban and suburban counterparts (Cherry et al. 2007). Forensic pathologists play an important role in correctly identifying traumatic injury and risk factors within larger communities, as well as in groups within the population they serve through a complete medical legal death investigation.

Conclusions

Accidental injury in infancy and childhood is a common, and often preventable, cause of childhood morbidity and mortality. Many of the types of injury are similar to adults; however, others have differences in incidence and character of injury that are unique to the stature and development of a child. It is imperative that forensic investigations of these deaths include information salient both to the preventability of future deaths and addressing the disparities that exist within gender, socioeconomic, and other class characteristics. Injury remains the most common cause of childhood death in most parts of the world. Prevention strategies rely in no small part on accurate assessment of the causes of death and injury in children. Forensic pathology and forensic medicine can contribute significantly in efforts to improve child safety, health, and life.

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Pediatric Iatrogenic Deaths

28

Robyn C. Reed and John J. Buchino

Contents

Abstract

Investigating an unexpected death during hospitalization poses a unique set of challenges to the pathologist. Complex medical history and hospital course are the norm rather than the exception. The autopsy examination must distinguish between expected changes arising from disease and therapy and unexpected findings that suggest a cause of death. Reviewing the medical record, including surgical, radiologic, and laboratory findings, is crucial in guiding the autopsy and the interpretation of autopsy findings. Many causes of unexpected death in the hospital may be difficult to detect at autopsy in the absence of a clinical suspicion. Some situations may require collection and/or preservation of pre- or postmortem

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fluids or tissues, such as serum or liver to detect drug levels, or vitreous humor or urine to determine electrolyte, glucose, and ketone levels. In some cases, special dissection techniques may be required. Common causes of unexpected death and injury in the hospital include medication errors and adverse reactions, surgical and anesthesia complications, nosocomial infections, and transfusion reactions. Clinical suspicion is important in guiding autopsy technique, ancillary testing, and interpretation of findings. The autopsy also plays a unique role in hospital quality control and in detecting complications arising from new therapies and techniques.

Introduction

Following an unexpected hospital death, careful review of the clinical history and hospital course must be combined with postmortem anatomic and laboratory investigations to arrive at a cause and manner of death. Details of the patient's underlying medical condition(s) and medical and surgical therapy may conspire to form a very complex history. The possibility of a medical misadventure should always be considered in these cases.

Recent years have seen a surge of interest in quantifying and characterizing medical error and iatrogenic injury. A report by the Institute of Medicine in 2000 estimated that 44,000–98,000 deaths per year in the United States (USA) were attributable to medical error (Kohn et al. 2000). Population-based estimates of the impact of medical error and iatrogenesis on pediatric patients suggest that infants and children may be especially vulnerable to life-threatening complications during hospitalization. A recent study estimated that preventable complications accounted for at least 4,400 deaths per year among hospitalized children in the USA. Infants, especially those younger than 30 days, were at particular risk of complications arising from infection, sepsis, and hemorrhage (Miller and Zhan 2004). A prospective multicenter study of intensive care nurseries in Israel estimated the incidence of iatrogenic events (including "near miss" events, in which there was no harm to the patient) at 3.2 per 100 hospital days; again, younger and smaller infants were at greater risk of therapeutic error and were more likely to be harmed by an event (Kugelman et al. 2008).

Infants and children are uniquely susceptible to iatrogenic complications for several reasons. Great variation in body size (a preterm infant can weigh 500 g, an adolescent 100 kg or more) can lead to errors of drug dosage calculation and mode of delivery. Many drugs have not been rigorously studied in children. Information concerning absorption, transport, metabolism, and excretion of drugs in this population is overall incomplete (Sullivan and Buchino 2004). Small body size, delicate tissues, and proximity of structures in a small body also raise the likelihood of error in surgery and placement of catheters and lines. Most organ systems continue to develop well into childhood, leading to other unique vulnerabilities, such as the susceptibility of neonates to infection due to immaturity of the immune system. Many congenital diseases, syndromes, and malformations have their initial

presentation in infancy or childhood and are undiagnosed on hospital admission. Finally, infants and young children cannot provide a firsthand history or describe changes of evolving disease or iatrogenic complications but are dependent upon adult caregivers. Children also depend upon adult caregivers to administer therapy (Sullivan and Buchino 2004). These considerations should be kept in mind when called upon to investigate an unexpected pediatric hospital death.

Autopsy Technique

Depending on the clinical circumstances, autopsy findings in hospital deaths range from nearly normal to extremely complex. In a surgical patient or one with a complex hospital course, it can be difficult to distinguish expected changes secondary to disease and therapy from unexpected findings that suggest a cause of death. In all cases, a review of the medical record is a critical first step, and a preliminary review should be performed prior to beginning the autopsy. It is important to discuss the case with the clinicians involved in caring for the patient in order to understand the clinical history and what they suspect led to the death. As is true of all medical devices, if malposition of a line, tube, or other device is a possibility, the device must be left in situ for autopsy examination. Review of radiographic studies and surgical reports may be helpful in understanding what anatomic changes to expect at autopsy. Depending on the circumstances, it is advisable to request that the laboratory retain antemortem blood and fluid samples for potential future testing. The blood bank and serology laboratory often keep specimens longer than other clinical laboratories. Autopsy guidelines for hospital deaths following surgery have been reviewed in detail with specific considerations and suggestions for different surgical sites (Start and Cross 1999).

The external examination should include written and photographic documentation of all incisions, lines, and devices, as well as any skin rashes, bruises/ecchymoses, or ulcers. The location, condition, and patency of devices should be examined in situ and also after removal. Lines and catheters can be evaluated by injection of colored dye, such as eosin. If clinical history raises the possibility of a pneumothorax, ordering a computed tomography (CT)/chest radiograph prior to the autopsy and making the initial chest cavity incision under water to detect escaping air are advisable. Air embolism is also best detected upon opening, so remove the chest plate very carefully to avoid introducing artifactual air into the vasculature (Start and Cross 1999).

Any desired microbiological specimens should be collected immediately after opening the body to avoid contamination. Samples may include blood, tissue, wounds/wound exudate, fluid collections, urine, and cerebrospinal fluid (CSF). Routine sterile collection of lung tissue for culture is advisable. The posterior lower pulmonary lobes and areas of consolidation are the most likely to yield positive cultures without upper airway contamination. Lung and spleen cultures may yield positive results even when blood cultures are negative.

Detecting and distinguishing between pre- and postmortem thrombi is important. Since it may be difficult based on the gross appearance of the apparent thrombus,

it is helpful to fix and examine it grossly and microscopically within its blood vessel. This technique is also useful to estimate the duration of thrombosis based on the degree of organization and recanalization. The presence, appearance, and volume of any effusions or hemorrhages should be documented. All surgical sites should be examined and photographed, demonstrating pertinent positive and negative findings. If surgery occurred more than a few days prior to death, dissection may be hindered by adhesions. In a critical specimen, such as a postoperative congenitally malformed heart, examination may require great patience and meticulous dissection, sometimes with dissection being continued after partial fixation of the excised organ. All anastomoses need to be examined for integrity and patency with sampling for histology if there is evidence of necrosis, infection, or dehiscence.

Findings at autopsy may prompt additional queries of the medical record, discussion with clinicians, or postmortem ancillary testing. In some cases, a synthesis of anatomic and clinical findings will suggest a cause of death. At other times, even a diligent search yields no conclusive result, although one or more possibilities may be suggested. Unless there is evidence of gross incompetence or negligence by a provider, it is best to present and discuss results with the involved clinicians in a neutral setting, with a focus on understanding any errors and correcting processes to prevent their recurrence.

Medication Errors and Adverse Reactions

The incidence of medication errors in hospitals is necessarily an estimate, as most errors are undetected but, fortunately, cause no harm. However, a prospective study found that 5.7 % of orders for medication in a pediatric hospital contained one or more errors (Kaushal et al. 2001). The same group found that 31 % of patients experienced a medication error and 12 % experienced two or more (Fortescue et al. 2003). The drug errors most likely to cause life-threatening injury or death include concentrated potassium chloride, insulin, 50 % dextrose, and digoxin (Argo et al. 2000).

Children are particularly prone to errors of dosage: in a small infant, a tenfold overdose may appear deceptively correct (Koren et al. 1986; Lesar 2002). Such overdoses can cause significant complications (such as requirement for mechanical ventilation in a case of pancuronium tenfold overdose and acute renal failure in a case of gentamicin tenfold overdose) or death (e.g., after a tenfold digoxin overdose (Koren et al. 1986)). Incorrect dosage is the most common drug administration error in infants and occurs most commonly in the intensive care nursery (Chedoe et al. 2007). Another cause of tenfold dosing errors is erroneous drug dilution, a particular problem when more concentrated adult formulations of intravenous drugs are used (Chappell and Newman 2004). In intravenous drug dosing, confusion of milligrams and milliliters can lead to over- and underdose errors, occasionally with fatal results as when a neonate died after receiving two nine-fold overdoses of epinephrine in the operating room (Hicks et al. 2006). Drugs that are administered using relatively imprecise measurements, such

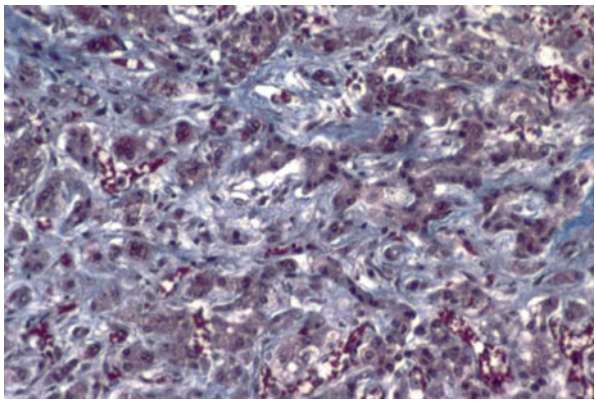

Fig. 28.1 Hepatic sinusoidal venoocclusive disease in a very low birth weight infant who received intravenous vitamin E (E-Ferol) for 27 days. In this trichrome stain, blue-staining collagen fibers fill and occlude the sinusoids between cords of hepatocytes (Trichrome stain ×160) (Image courtesy of K.E. Bove, MD)

as drops, can also lead to overdose and injury in a small patient. For example, depending on the angle at which the dropper is held, a 10-drop dose of antitussive could deliver up to twice the expected quantity of codeine (Hermanns-Clausen et al. 2009).

For up to 75 % of drugs prescribed to infants and children, there is incomplete information about drug safety, correct dosing, and pharmacokinetics (Sullivan and Buchino 2004; Chedoe et al. 2007). In some cases, drug metabolism differs greatly between infants and adults; when not recognized, these differences can lead to catastrophic outcomes. For example, the antibiotic chloramphenicol is metabolized by glucuronidation, but this process is less predictable and less efficient in neonates and young infants, leading to decreased excretion and toxicity. The resulting circulatory collapse is known as gray baby syndrome and was a cause of death for many neonates in the 1950s, with case reports extending into the 1980s (Krasinski et al. 1982). Even drug carriers and diluents may have unintended and toxic effects. For example, at least 38 infants died in late 1983 and early 1984 after a new formulation of intravenous vitamin E, known as E-Ferol, was introduced in intensive care nurseries to mitigate the effects of oxygen toxicity such as retinopathy of prematurity. Unlike previous formulations, the drug was solubilized with polysorbate 80 (9 %) and polysorbate 20 (1 %) in water. Within 5–16 days of receiving E-Ferol, affected infants developed thrombocytopenia followed by renal dysfunction, cholestasis, and, later, ascites. Autopsy examination disclosed a distinctive vasculopathy in the liver (Fig. 28.1) and renal oxalosis (Bove et al. 1985). The toxicity appears to have been mediated by the polysorbates rather than the vitamin E or any contaminant (Bove et al. 1985; Brown et al. 1986).

As with adults, children are prone to errors arising from illegible handwriting or similarly named drugs and drug formulations. This is particularly dangerous when the drugs in question have a narrow therapeutic index or two drugs with very different therapeutic dosing or purpose are confused. For instance, in the 1990s, confusion of two similarly named cardiac drugs, the antiarrhythmic amiodarone, and the inotrope amrinone, resulted in at least 11 drug errors and a patient death before the latter drug's name was changed to inamrinone (Mitka 1999). Similarly,

at least three deaths, one in a 3-month-old infant, have occurred following an overdose of the antifungal drug amphotericin B. In each case, the patient erroneously received amphotericin B deoxycholate, instead of the intended liposomal amphotericin B, which has a six- to tenfold greater therapeutic dose (Burke et al. 2006; Groeneveld et al. 2008; Mohr et al. 2005).

When multiple lines and catheters are present, wrong-route medication errors can ensue, some with life-threatening consequences. A well-known example is the injection of vincristine, a chemotherapy drug given intravenously into an intrathecal catheter, frequently leading to death or permanent neurological injury. At least 58 cases of inadvertent intrathecal vincristine administration have been reported during the 40 years the drug has been in use (Noble and Donaldson 2011), most in children with acute leukemia. Despite many efforts to analyze and eliminate this catastrophic medication error, new cases continue to be described (D'Addario et al. 2010), although systems changes can greatly reduce the incidence (Hennipman et al. 2009). Other wrong-route medication errors include enteral drugs or nutrition given intravenously such as GoLYTELY (Rivera et al. 2004), barium sulfate contrast (Soghoian et al. 2010), and breast milk (Ryan et al. 2006). Topical drugs have also been given intravenously, including epinephrine (Alberta Association of Registered Nurses 2010) and thrombin (Gershon et al. 1999), both with fatal results.

Rapid correction of electrolyte or other osmotic abnormalities can lead to a characteristic neurological injury known as osmotic myelinolysis, including both central pontine and extrapontine myelinolysis. While this phenomenon is more common in adults, there are numerous case reports of osmotic myelinolysis in children. In a typical case, a patient develops focal neurological abnormalities, including pseudobulbar palsy and spastic paralysis, during correction of an electrolyte imbalance. Hyponatremia is the most common presenting imbalance (Carpenter et al. 2007; Haspolat et al. 2004; Singh et al. 2010), but osmotic myelinolysis can also occur in children following hypernatremia (Brown and Caruso 1999; Mastrangelo et al. 2009; Shah and Tobias 2006), diabetic ketoacidosis (Bonkowsky and Filloux 2003; Sivaswamy and Karia 2007), and hyperammonemia secondary to ornithine transcarbamylase deficiency (Cardenas and Bodensteiner 2009). Central pontine myelinolysis can lead to altered mental status, pseudobulbar palsy, and spastic quadriplegia, while involvement of extrapontine sites leads to corresponding neurological deficits (e.g., ataxia with cerebellar involvement). Brain magnetic resonance imaging (MRI) shows symmetrical white matter lesions that are T1 hypointense and T2 hyperintense with restricted diffusion. With careful management of electrolytes, some patients, especially children, show partial or complete recovery. However, in some cases, the syndrome can be fatal. Autopsy findings include noninflammatory, symmetrical demyelination of affected areas of the brain although these can also be seen in clinically asymptomatic patients. There may also be evidence of cerebral edema or herniation. Common sites of demyelination include the pons, midbrain, thalamus, basal nuclei, and cerebellum (Brown 2000).

Even when medications are prescribed appropriately and administered correctly, adverse drug reactions can be a cause of morbidity and mortality in hospitalized patients. Pediatric patients are particularly susceptible to some adverse drug

reactions, and it is becoming increasingly clear that genetics plays an important role in some cases. A well-known example is malignant hyperthermia which occurs when individuals with predisposing mutations in the calcium channel proteins RYR1 and CACN1AS receive inhaled anesthetics or depolarizing muscle relaxants (Larach et al. 2008). Nearly half the cases of malignant hyperthermia occur in patients 19 years of age and younger (Larach et al. 2010). Despite heightened awareness of this complication and treatment with dantrolene, complications including coma, disseminated intravascular coagulation, and organ failure are common (Larach et al. 2010), and death due to cardiac arrest can occur (Larach et al. 2008). In another example, the antiseizure drug valproic acid can cause catastrophic liver failure in some pediatric patients (Scheffner et al. 1988; Suchy et al. 1979). Recent evidence suggests that a polymorphism in the mitochondrial deoxyribonucleic acid (DNA) polymerase gamma gene (POLG) greatly increases the risk of such hepatotoxicity (Stewart et al. 2010). Another rare mutation in POLG results in Alpers-Huttenlocher syndrome, a fatal neurometabolic syndrome with onset in early childhood which also confers marked susceptibility to valproic acid hepatotoxicity (Davidzon et al. 2005).

Other drug reactions appear to be idiosyncratic. Anaphylaxis and other allergic reactions can be triggered by a wide variety of agents. The most common drug causes include beta-lactam and other antibiotics, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), intravenous radiocontrast media, and monoclonal antibodies used as biological agents (Simons 2009). Propofol infusion syndrome most often affects children, particularly those receiving high-dose or prolonged propofol for sedation and those with neurological injury. It is characterized by bradycardia or asystole accompanied by evidence of metabolic acidosis, lipemia, fatty liver, and/or rhabdomyolysis and has a reported mortality rate of 30 % (Fudickar and Bein 2009). Organ-specific toxicities are described for many drugs affecting the kidneys (e.g., aminoglycoside antibiotics, amphotericin, cyclosporine (Jennette et al. 2006)), liver (e.g., phenytoin, carbamazepine (Roberts 2008)), heart (anthracyclines such as doxorubicin (Fulbright et al. 2010)), and lungs (e.g., methotrexate, cyclophosphamide, bleomycin (Travis et al. 2002)). Some methods of drug delivery can also cause idiosyncratic reactions. For example, Nicolau syndrome is an unusual reaction to intramuscular drug injection that mostly affects children. The syndrome is characterized by livedoid dermatitis and cutaneous and soft tissue necrosis around the injection site, thought to be due to ischemic injury. It can cause widespread soft tissue injury and compartment syndrome and is occasionally fatal (De Sousa et al. 2008; Ocak et al. 2006).

Autopsy findings in cases of medication error or adverse reaction may be very subtle or absent altogether. Detecting these cases requires a high index of suspicion which may be corroborated by examining the history, chart, orders, medication administration record, and pharmacy records. Interviewing physicians, nurses, and others involved in the ordering and delivery of medications is also helpful. In some cases, laboratory testing of antemortem or postmortem fluids, including serum, urine, and vitreous humor, is very helpful. An antemortem chemistry panel can reveal hypo- or hyperglycemia resulting from inappropriate insulin administration

or 50 % dextrose administration, and electrolyte imbalances such as hyperkalemia caused by intravenous potassium overdose. Urine (antemortem or postmortem) and vitreous humor can also reveal elevated glucose and ketones in cases of diabetic ketoacidosis. Because vitreous and serum glucose levels decline after death, postmortem fluid analysis may not be useful in determining hypoglycemia (Benjamin 2008). However, insulin levels can be measured in postmortem urine and serum in cases of suspected insulin overdose (Musshoff et al. 2011).

Toxicological testing of serum and/or urine can bring to light overdoses or wrong-route doses of some drugs including digoxin, theophylline, and narcotic analgesics. Urine should be collected in a sterile container, vitreous humor should be collected in a small sterile vacutainer, and blood in a gray top vacutainer with preservative. At times, it is advantageous to ask the laboratory for guidance on procurement and testing for possible prescription drug overdose. If there is suspicion of a medication dilution or mixing error or of an incorrect drug being given, save all syringes, intravenous fluid bags, and bottles present in the patient's room for testing.

Blood Bank

Children and infants are more vulnerable than adults to complications of blood product transfusion, with recent data estimating the incidence of adverse outcomes at 18/100,000 for children and 37/100,000 for infants under 12 months. These rates are compared to 13/100,000 for adults (Stainsby et al. 2008). Transfusion complications include hyperkalemia, acute and delayed hemolytic transfusion reactions (HTR), anaphylaxis, transfusion-related acute lung injury (TRALI), transfusion-associated graft-versus-host disease (TA-GVHD), and transfusion-transmitted infections. Transfusion complications are likely underdiagnosed, as many present with nonspecific symptoms that may be confused with other clinical conditions, particularly in very ill patients. Autopsy findings are usually subtle, and the diagnosis will only be made if there is a high index of suspicion based on clinical history.

When packed red blood cells are stored, intracellular potassium leaks into the supernatant at a constant rate; this process is accelerated with irradiation. Transfusing a large volume of red blood cells or infusing at a rapid rate can result in significant hyperkalemia and fatal cardiac arrhythmias, especially in small infants or children with underlying renal disease (Smith et al. 2008; Vraets et al. 2011). For this reason, when treating infants and children, some clinicians and hospitals transfuse only fresher red blood cells or washed red blood cells. Clinical symptoms of transfusion-related hyperkalemia include characteristic electrocardiographic changes, including peaking of T waves progressing to widened QRS complexes, a sinusoidal wave, and cardiac arrest (Parham et al. 2006). Autopsy diagnosis requires a high level of clinical suspicion and may be supported by analysis of antemortem blood samples, review of transfusion records, and assessment of electrocardiograms obtained before the cardiac arrest. Postmortem tissue and fluid samples (including vitreous humor) are not very reliable for diagnosing hyperkalemia, as potassium levels rise rapidly and steadily after death (Benjamin 2008).

Acute and delayed HTR are caused by a reaction between preformed antibodies and red blood cells. Acute HTR cause intravascular hemolysis leading to shock, acute renal failure and hemoglobinuria, fever, rigors, and back pain. The most common cause is erroneous transfusion of ABO-incompatible red blood cells leading to lysis of the donor red blood cells (e.g., when type A cells are given to a type O recipient) (Stainsby et al. 2008). However, the converse can occur, when high-titer antibodies in fresh frozen plasma or in the plasma associated with platelets cause lysis of the recipient's red blood cells (Harris et al. 2007; Sapatnekar et al. 2005). Transfusion errors are usually detectable by checking the patient and the blood bag; immunohematologic testing confirms the presence of incompatible antibodies (Leo and Pedal 2010) and may be effective several days after death (Padosch et al. 2007). Analysis is performed on blood collected in an ethylenediaminetetraacetic acid (EDTA) vacutainer (pink or lavender top) and/or antemortem blood and serum samples. In fatalities, immunohistochemical stains can detect ABO-incompatible red blood cells in the circulation, confirming the transfusion error (Pfeiffer et al. 2002). Delayed HTR results in the destruction of red blood cells and anemia days to weeks after transfusion. Hyperhemolysis is a rare but severe complication of delayed HTR that occurs most frequently in patients with sickle cell disease and is characterized by the destruction of the recipient's red blood cells as well as transfused cells. Complications such as acute chest syndrome, neurologic complications, and congestive heart failure can follow (Elenga et al. 2008; Talano et al. 2003).

Anaphylactic transfusion reactions manifest with shock, cardiovascular instability, and respiratory distress including stridor. Causes of anaphylaxis include IgA deficiency and haptoglobin deficiency (mediated by anti-IgA and anti-haptoglobin antibodies, respectively), but often the inciting substance is not identified. Autopsy findings may include upper airway edema and pulmonary hyperinflation, but these findings are less common in iatrogenic anaphylaxis than in anaphylaxis caused by food or insect sting, and many cases may have no specific autopsy findings (Pumphrey and Roberts 2000). Serum mast cell tryptase, a marker of mast cell activation, can be measured in a postmortem blood sample; elevated levels support the diagnosis (Pumphrey and Roberts 2000; Nara et al. 2010), although elevated serum tryptase can also occasionally be a nonspecific postmortem finding. Specimens for analysis are a sterile red top vacutainer of blood and a serum separator tube of blood. Serum tryptase levels above the testing laboratory's reference range may suggest mast cell activation. Elevated allergen-specific IgE levels may improve diagnostic specificity (Benjamin 2008); these are also measured from serum collected in the aforementioned vacutainers.

TRALI is among the most common causes of transfusion-related fatalities in children (Stainsby et al. 2008). Children with hematologic malignancies may be especially vulnerable (Sanchez and Toy 2005). Resulting from the activation of recipient neutrophils by donor anti-neutrophil antigen or anti-HLA (human leukocyte antigen) antibodies, TRALI is characterized by acute respiratory distress and pulmonary opacities within a few hours of transfusion. With supportive case, TRALI usually resolves within a few days; however, the mortality rate is approximately 20 %. Autopsy findings in two adults with laboratory-proven TRALI included pleural effusions and proteinaceous fluid filling alveoli, without diffuse alveolar damage (Danielson et al. 2008).

TA-GVHD, in which donor T lymphocytes engraft and attack an immunocompromised or partially HLA-matched recipient, is a rare but well-described transfusion complication that is usually fatal (Stainsby et al. 2008). It presents days to weeks after transfusion with rash, diarrhea, liver dysfunction, and evidence of bone marrow failure. Several pediatric populations are at particular risk for TA-GVHD due to immature or defective cellular immunity including fetuses, neonates (especially very low birth weight neonates), patients with congenital cellular immunodeficiencies such as complete DiGeorge syndrome and severe combined immunodeficiency, and those with acquired cellular immunodeficiencies including leukemia or lymphoma patients, hematopoietic stem cell transplant recipients, and patients receiving fludarabine chemotherapy. TA-GVHD can be prevented by irradiating blood products prior to transfusion. Identification of donor lymphocytes in the circulation or body tissues (usually by molecular methods) is diagnostic (Dwyre and Holland 2008). Histologic autopsy findings are similar to those in other cases of graft-versus-host disease, with cell injury and apoptosis in the skin, gut, liver, and bone marrow, accompanied by CD8+ T cell infiltrates.

Although the risk of infection from blood components has decreased dramatically in recent decades with the advent of improved donor and blood supply screening, viral, bacterial, and parasitic infections can still be transmitted by transfusion. The risk of transmission of hepatitis B is currently about 1 in 500,000 transfusions; HIV and Hepatitis C have a transmission risk of 1 in 2 million. Other less common viral agents that can be transmitted include West Nile, chikungunya, and dengue viruses. Bacterial contamination most commonly occurs in pooled platelets, which are stored at room temperature. Most bacterial contaminants in platelets are skin flora such as staphylococcus and streptococcus. Additionally, cold-tolerant bacteria such as *Yersinia enterocolitica* are occasional contaminants of packed red blood cells. Transfusion-transmitted bacteremia is recognized in approximately 1 in 100,000 platelet transfusions and 1 in 5 million red blood cell transfusions, although the incidence of contamination is significantly higher. Blood-borne parasites can be transmitted in red blood cell units; commonly transmitted diseases include malaria, babesiosis, and Chagas' disease (Perkins and Busch 2010). Diagnosis of infection from blood components requires a high index of suspicion. If suspected shortly after transfusion, culture or molecular examination of the blood unit should be performed.

Medical Devices

Medical devices, including intravascular lines, tubes, and catheters, are nearly ubiquitous among hospitalized patients. Although outright device failure is rare, complications arising from device misplacement, migration, and misuse are widely reported. Indwelling devices may also serve as a source or nidus of infection, as discussed in the section on iatrogenic infection. It is difficult to estimate the incidence of injury or death due to medical devices, but endotracheal tubes and

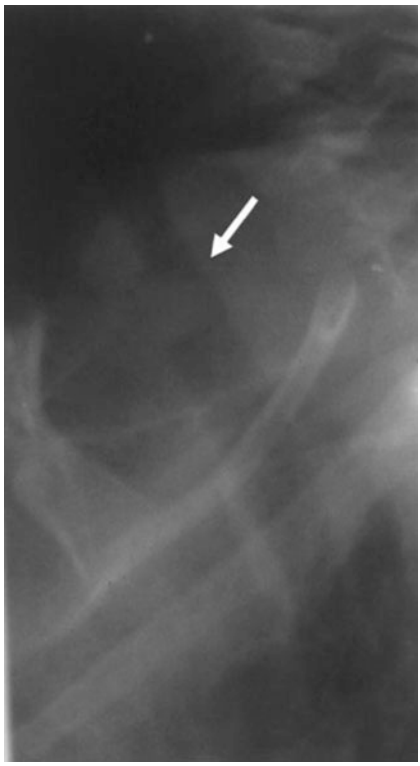

Fig. 28.2 X-ray showing an endotracheal granuloma causing airway obstruction, following accidental removal of the endotracheal tube. The image is a lateral neck radiograph with the vertebral column visible in the *upper right*. The *arrow* indicates a soft tissue density protruding into the radiolucent trachea

vascular catheters appear to be relatively frequent causes of morbidity and mortality. This is perhaps in part because of their widespread use.

Endotracheal tubes can be incorrectly inserted into the esophagus, leading, if undetected, to severe hypoxia. The use of carbon dioxide detection probes has greatly decreased the incidence of this complication (Wyllie and Carlo 2006). There is a particular risk of esophageal intubation in neonates with a tracheoesophageal fistula, a situation which can lead to respiratory arrest and death (Buchino et al. 1986). In low birth weight infants, an endotracheal tube or endotracheal suction catheter can perforate the trachea or bronchus (Holcomb and Templeton 1989; Newman and Oh 1994; Thakur et al. 2000). Once placed, an endotracheal tube can become dislodged if not well secured, especially in very small infants, in whom the total length of the intratracheal segment of tube may be only a few centimeters. Endotracheal tube occlusion, caused by secretions, hemorrhage, or granulation tissue (Fig. 28.2), can be catastrophic if not quickly resolved. A unique cause of occlusion is necrotizing tracheobronchitis, in which tracheal mucosa near the endotracheal tube tip becomes inflamed and necrotic, accompanied by copious thick luminal mucus. The process usually occurs in neonates receiving mechanical ventilation, especially high-frequency ventilation, and can be seen within 3 h of initiating ventilation (Boros et al. 1986; Gaugler et al. 2004;

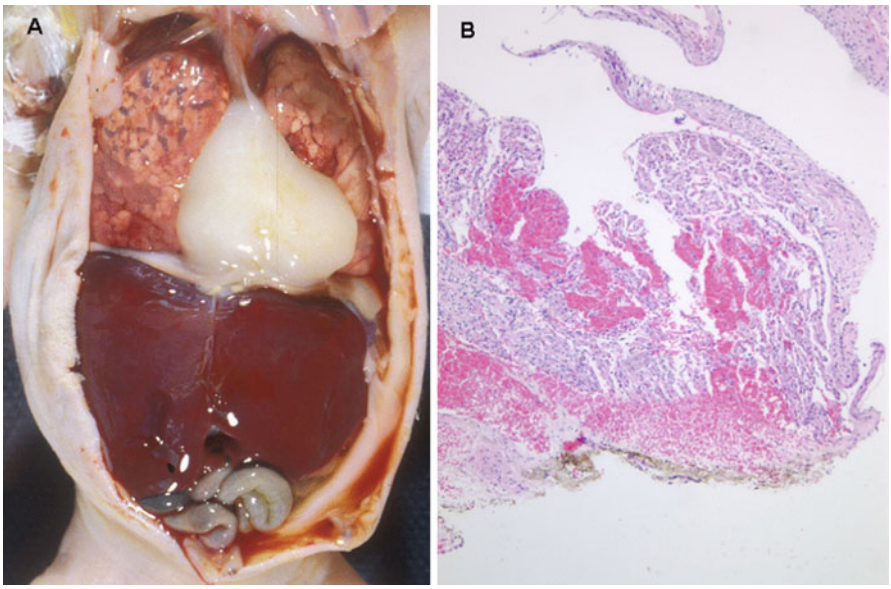

Fig. 28.3 (**a**) Cardiac tamponade occurred in this preterm infant after intralipid fat emulsion was infused via a central venous catheter that perforated the right ventricle. (**b**) Photomicrograph showing right ventricular myocardial hemorrhage at the site of perforation (Hematoxylin and Eosin, H&E ×4)

Metlay et al. 1983; Pietsch et al. 1985). Bronchoscopy, used for the diagnosis or treatment of airway disorders, can cause life-threatening tension pneumothorax (and occasionally pneumoperitoneum) in pediatric patients due to insufflation of oxygen into the airway (Harar et al. 2005; Iannoli and Litman 2002; Boker 2008).

Vascular catheters are subject to misplacement, migration, and incorrect use. Central venous catheters are usually placed with the tip at the cavoatrial junction or within the right atrium. In this site, catheter tips can perforate or erode through vessel or cardiac walls causing hemorrhage, extravasation of infused fluids including parenteral nutrition (Fig. 28.3), or pneumopericardium (Fig. 28.4).

Reports estimate the incidence of neonatal cardiac tamponade secondary to central catheter perforation to be 0.18–1.8 % (Beardsall et al. 2003; Darling et al. 2001; Nadroo et al. 2001; Pezzati et al. 2004), with increased risk of complications in cases where the tip is in the right atrium rather than the vena cava (Darling et al. 2001). Cardiac tamponade frequently occurs several days after the catheter is placed, suggesting that perforation can occur well after initial placement (Nadroo et al. 2001; Pezzati et al. 2004). Tamponade is the most common late cause of catheter-related fatality (Askegard-Giesmann et al. 2009).

In addition to myocardial and caval perforation, central vascular catheters are causes of other injuries. Vascular perforation outside the pericardium can cause bleeding leading to hemothorax, hemoperitoneum (Bagwell et al. 2000), and acute abdomen (Sztajnbok and Troster 2002). Hemothorax is the most common cause of

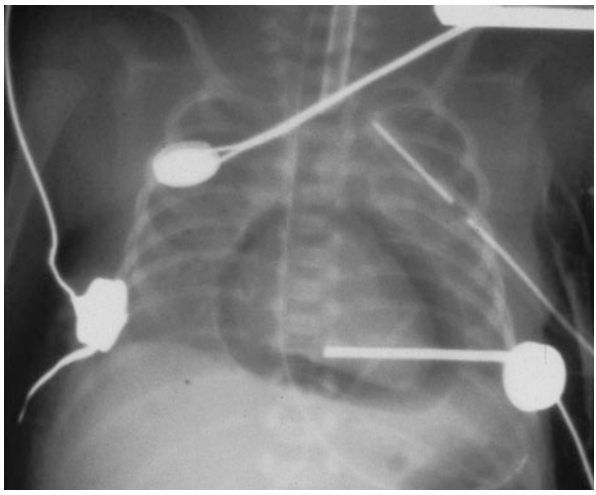

Fig. 28.4 Radiograph depicting pneumopericardium in an infant receiving positive pressure ventilation. The radiolucent area surrounding the heart is created by air in the pericardium

catheter-related fatality within 24 h of catheter placement (Askegard-Giesmann et al. 2009). More rarely, catheters can penetrate adjacent structures such as the liver (Sierre et al. 2007; Yigiter et al. 2008), kidney/renal pelvis (Nadroo et al. 2001), and the extradural (Skinner and Mather 1995) and intrathecal (Fujita et al. 2006) spaces. Liver laceration appears to have a particularly high complication and mortality rate (Sierre et al. 2007; Yigiter et al. 2008). Phrenic nerve injury can follow placement of an internal jugular catheter and may cause morbidity in young infants (Askegard-Giesmann et al. 2009). If a catheter tip becomes displaced, intravenous fluids may be infused into extravascular spaces resulting in a hydrothorax (Bagwell et al. 2000; Maruyama and Koizumi 2006), hydromediastinum (Maruyama and Koizumi 2006), or ascites (Yigiter et al. 2008; Coley et al. 1998). In one instance, catheter location in the epidural space resulted in quadriplegia (Bagwell et al. 2000). Vascular catheters are the leading risk factor for central venous thrombosis in children (Garden and Laussen 2004). Thrombosis in the right atrium can present as arrhythmia or respiratory distress, although over half of atrial thromboses in neonates are asymptomatic (Yang et al. 2010). Coronary sinus thrombosis can lead to sudden cardiovascular collapse and death (Suarez-Penaranda et al. 2000). Other presentations of thrombosis include deep venous thrombosis, superior vena cava syndrome, lymphatic obstruction with chylothorax, or pulmonary thromboembolism (Garden and Laussen 2004; Sandoval et al. 2008).

Catheter fracture, embolization, and tip migration are more uncommon though not extremely rare. In one pediatric series, catheter fracture or embolization was seen in 0.67 % of peripherally inserted central catheters, frequently with embolization into the pulmonary vasculature (Chow et al. 2003). Catheter fragments can also embolize to the right atrium, ventricle, vena cava, or peripheral veins (Surov et al. 2009). In an intact catheter, tip migration into the pulmonary arteries can lead to respiratory distress and lung consolidation (Pignotti et al. 2004).

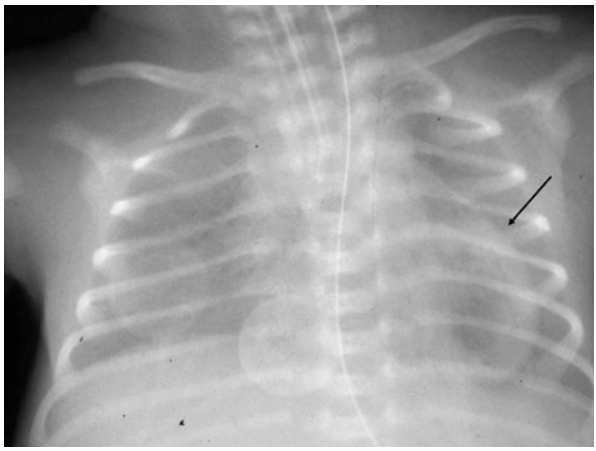

Fig. 28.5 Radiograph depicting an intracardiac air embolism (*arrow*) caused by a nurse inadvertently injecting air into an arterial line. She mistakenly thought she was clearing a nasogastric tube. The *arrow* points to an area of lucency within the left ventricle indicating the presence of air in the ventricle

Errors in infusion or injection can lead to the introduction of air into the vasculature and resultant venous air embolism causing immediate cardiorespiratory collapse and, in some cases, death (Fig. 28.5; Schwartz and Eisenkraft 1993; Laskey et al. 2002; Sowell et al. 2007).

In infants and young children, injected air volumes as small as 0.2–0.4 mL/kg can produce cardiorespiratory instability. Young infants may be at particular risk for paradoxical arterial emboli due to foramen ovale patency (Sethna and Berde 1993). Adults appear more resistant to venous air embolism: estimated lethal volumes of air range from 300 to 500 mL, depending on the rate of injection and clinical comorbidities (Orebaugh 1992); most small air emboli are asymptomatic (Groell et al. 1997). At autopsy, air bubbles can be identified in the heart and large blood vessels. The chest plate should be carefully removed to avoid production of artifactual air bubbles.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is a lifesaving but invasive therapy for cardiac and respiratory failure used most frequently in infants and children. As in cardiopulmonary bypass, blood is circulated via a large cannulas through an external oxygenator and then returned to circulation. Circuit and oxygenator design allow use over an extended period with some ECMO runs lasting weeks. Because of the extensive thrombogenic surface area of the circuit, patients receive systemic anticoagulation, usually heparin.

The most common complications during ECMO are hemorrhage and thrombosis. An autopsy study of 29 pediatric patients who had received ECMO identified hemorrhage in over 50 % of patients, including central nervous system hemorrhage in one-third of patients (Fig. 28.6).

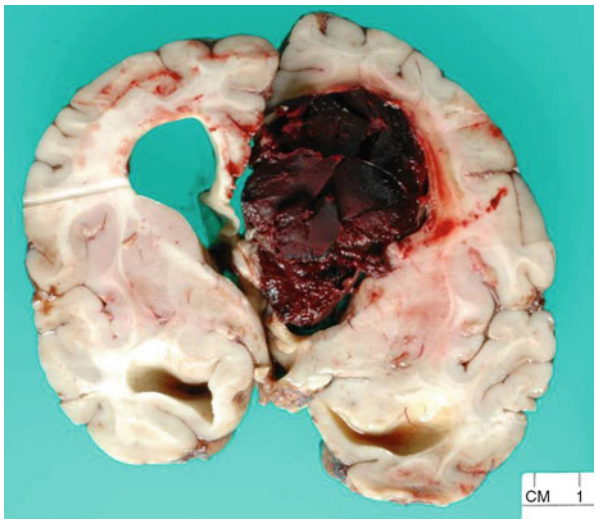

Fig. 28.6 Intraventricular hemorrhage sustained while on ECMO. Blood appears solid because the brain was fixed prior to sectioning

Sixty-nine percent had thrombi, including both large arterial and venous thrombi and microscopic thrombi in the lungs and other organs (Fig. 28.7).

Strikingly, nearly one-third of patients had both thrombi and hemorrhage suggesting that hemostatic balance on ECMO is complex. ECMO patients with congenital cardiac disease seem to be more susceptible to thrombotic complications (Reed and Rutledge 2010). Thrombosis is a particular danger in patients who receive recombinant factor VIIa and/or activated prothrombin complex concentrates for hemorrhage (Bui et al. 2002; Chalwin et al. 2008; Syburra et al. 2010). A notable autopsy cluster of 22 infants with thromboemboli on ECMO revealed that aluminum leaching from the circuit heat exchanger led to the formation of systemic thromboemboli (Vogler et al. 1988).

An unusual pediatric ECMO complication is symmetrical peripheral gangrene or four-limb ischemia without occlusion of large arteries (Ghosh and Bandyopadhyay 2011). The condition is most commonly linked to disseminated intravascular coagulation (DIC) and sepsis. The authors have seen four cases in which infants and children developed symmetrical peripheral gangrene on ECMO following cardiac surgery (Fig. 28.8). Two were septic, but none had clinical or laboratory evidence of DIC.

Other complications of ECMO can arise from cannula placement and vascular obstruction. Neck cannulation for venoarterial ECMO usually requires ligating the right common carotid artery (which can be reconstructed after decannulation). Complications include neurodevelopmental delay and radiological brain abnormalities; significant ipsilateral ischemia is surprisingly rare (Graziani et al. 1997; Trittenwein et al. 2006). Abnormalities of the reconstructed carotid artery can include obstruction, stenosis, and aneurysm formation (Desai et al. 1999; Duncan et al. 2009; Sarioglu et al. 2000). When percutaneous femoral catheters are used,

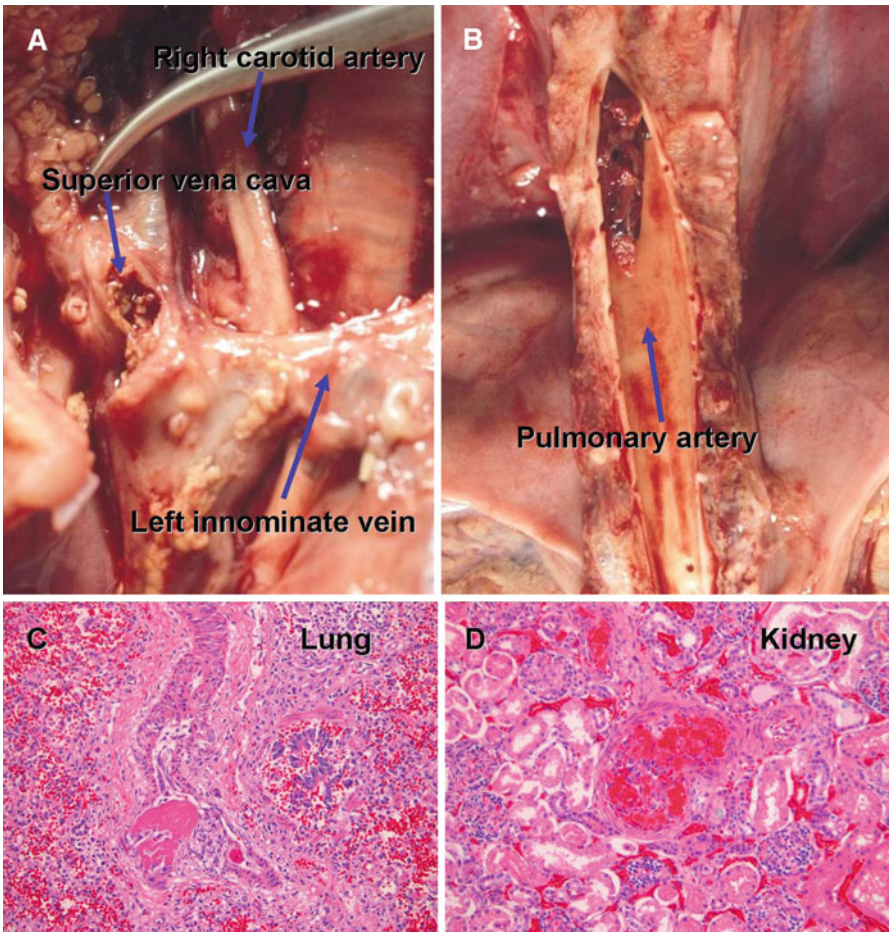

Fig. 28.7 Large venous (**a**) and pulmonary arterial (**b**) thrombi sustained while on ECMO (*arrows*). The lungs are the most common site of microscopic thrombi (**c**), with the kidneys (**d**), another organ where thrombi are often present (Images A and B copyright 2010, R.C. Reed and J.C. Rutledge, *Pediatric and Developmental Pathology*, Society for Pediatric Pathologists, Allen Press, Inc.) (Hematoxylin and Eosin, H&E × 200)

the cannulated leg can develop ischemia, a particularly common complication in children that may require fasciotomy or leg amputation (Gander et al. 2010; Ganslmeier et al. 2011).

Complications of Anesthesia and Surgery

Anesthesia and surgery can lead to a wide variety of complications, some life threatening. The overall complication rate for pediatric anesthesia in a recent study at one children's hospital was 3.0 %, with a higher rate in infants. The most

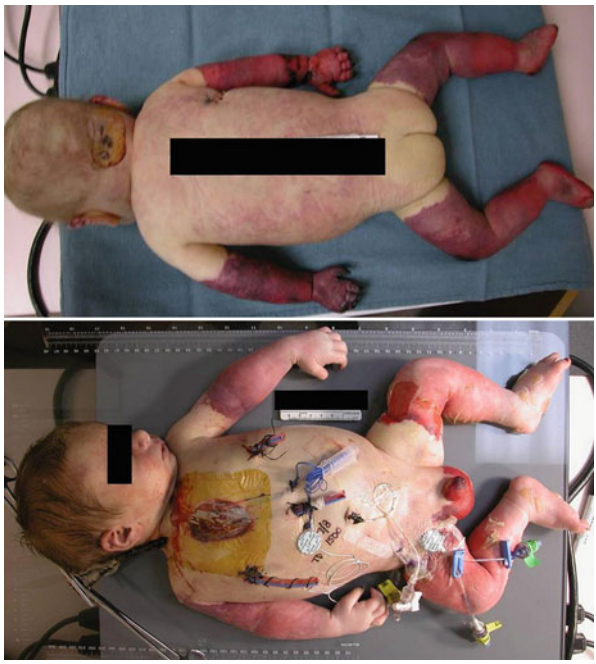

Fig. 28.8 Two infants who developed symmetrical peripheral gangrene while on ECMO. Autopsy examination of the second child revealed no large artery occlusion, but bland fibrin thrombi were present in many capillaries of the skin and deep soft tissue with tissue necrosis. There was no laboratory evidence of DIC. The first child had evidence of serratia and candida sepsis. The second had no antemortem or postmortem evidence of sepsis

common complications were hypoxemia, bronchospasm, and postoperative respiratory depression. Serious complications of anesthesia in children, including cardiac arrest and severe anaphylaxis, are rare (1 in 3,000 and 1 in 6,000, respectively) but do occur (Murat et al. 2004). If complications of anesthesia are suspected as the cause of death, the anesthesia and operative records should be carefully reviewed. Urine in a sterile container and blood in a sterile red top vacutainer should be collected for drug analysis. Of note, inhaled anesthetics generally cannot be detected in blood or urine.

All surgical procedures carry some degree of risk, and the complication rates vary dramatically between procedures. In any procedure, whether open or minimally invasive, complications such as bleeding, infection, and injury to nearby structures can occur. Any open surgery presents the risk for retained instruments and sponges leading to complications such as visceral perforation, fistula formation, or infection (Gawande et al. 2003). One study estimated the incidence of retained surgical tools in pediatric surgery at about 1 in 33,000 cases (Shah and Lander 2009). The estimated incidence in general (adult) surgery is much higher, ranging from 1 in 1,400 to 1 in 19,000 surgeries, with a similar number of additional "near misses" (Shah and Lander 2009; Cima et al. 2008), suggesting that it may be more common than appreciated. Emergency surgery or a change in the planned surgical procedure increases the risk of a retained instrument (Gawande et al. 2003).

Complications of cardiovascular procedures in children are particularly well-documented. Therapeutic cardiac catheterization in children carries a major complication rate of 1.8–4.1 % and a mortality rate of 0.22–0.68 %. Common

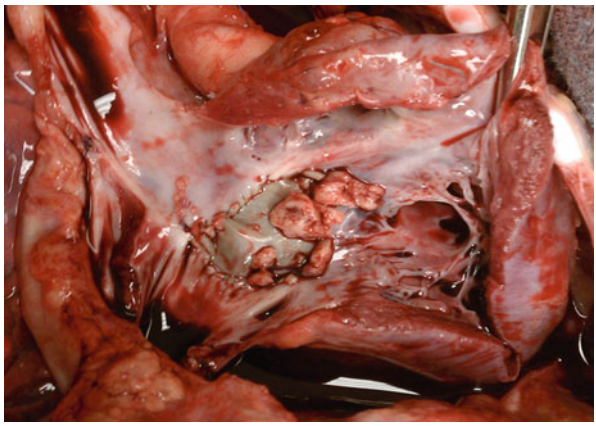

Fig. 28.9 This 11-month-old girl presented with stroke secondary to multiple thromboemboli, 12 days after closure of an atrioventricular septal defect with a bovine pericardial patch. At autopsy, there were large friable fibrin thrombi on both sides of the patch

serious complications include vessel rupture, arrhythmia, and embolic stroke (Agnoletti et al. 2005; Bennett et al. 2005; Mehta et al. 2008). Both open surgery and percutaneously implanted devices can lead to life-threatening complications. Placement of intravascular stents for congenital cardiac abnormalities has a reported early major complication rate of 5.7 % and a mortality rate of 2.3 %, with higher rates again seen in infants. Common complications include stent malposition, migration and embolization, and vessel rupture, the latter the most common cause of death (van Gameren et al. 2006). Right ventricle-to-pulmonary artery shunts, used in first-stage palliation of hypoplastic left heart syndrome, have a 3.0 % incidence of thrombosis, which carries a high risk of mortality (Januszewska et al. 2010). Percutaneous device closure of atrial septal defects is occasionally complicated by erosion of the occluder device through an atrial wall and/or aorta, resulting in cardiac tamponade (Amin et al. 2004). Occluder devices can also embolize or cause thrombosis and thromboembolism requiring surgery (Sarris et al. 2010). Percutaneous pulmonary valve implantation can uncommonly result in homograft rupture with catastrophic bleeding (Lurz et al. 2009). Thrombosis of implanted devices, including valves, patches, and conduits, is another important source of complications in cardiac surgery. Fatal ischemic stroke was seen in a child due to thromboemboli originating on a bovine pericardial patch used to close an atrial septal defect (Fig. 28.9).

Cardiopulmonary bypass is an essential method of support during open cardiac surgery. Complications can arise during cannulation and decannulation (including vascular injury and dissection) as a result of coagulopathy and anticoagulation (including thrombosis and hemorrhage), hypoperfusion or embolic events (including stroke, other neurological injury, and renal failure), and/or mechanical malfunction (including air embolism and pump failure) (Ailawadi and Zacour 2009). In one large pediatric series, the most common cause of death following cardiopulmonary bypass surgery was low cardiac output followed by arrhythmia, infection, and pulmonary complications (Zhu et al. 2006).

Cardiac surgery carries a particularly high risk of mortality for low birth weight neonates (birth weight <2,500 g) (Curzon et al. 2008). Common complications include bloodstream infections (23 % of low birth weight infants undergoing cardiac surgery), neurological complications including periventricular leukomalacia (21 %), and arrhythmias requiring treatment (20 %) (Ades et al. 2010).

Complications of cardiac surgery can result from altered cardiothoracic anatomy, injury to adjacent structures, and implanted devices. Several case reports describe myocardial infarctions in infants and children due to coronary artery compression after placing a stent in the pulmonary trunk or right pulmonary artery (van Gameren et al. 2006; Gewillig and Brown 2009; Hamzeh et al. 2009; Perret et al. 2008). Intraoperative phrenic nerve injury can lead to diaphragmatic paralysis; this occurs in about 5 % of children undergoing cardiac surgery, especially arterial switch and Blalock-Taussig shunt operations (Akay et al. 2006; Joho-Arreola et al. 2005). Diaphragmatic paralysis is also a rare complication of tracheoesophageal fistula repair and other thoracic procedures (Henderson and Spigland 2010). Thoracic duct injury causes chylothorax in 1.3–3.8 % of children undergoing cardiac surgery (Chan et al. 2005; Katanyuwong et al. 2009; Milonakis et al. 2009) and can also complicate tracheoesophageal fistula repair (Sy et al. 2001).

Other types of surgery and interventional procedures carry risks of morbidity and mortality. Endoscopy is performed in children with increasing frequency. Although generally a safe procedure, life-threatening complications occur in 0.02–0.09 % of pediatric procedures (Iqbal et al. 2008) with an overall complication rate of about 1.1 % (Thakkar et al. 2008). The most common complications are perforation, usually of the colon or esophagus, and bleeding (Iqbal et al. 2008; Thakkar et al. 2008). Colonic perforation presents as peritonitis and/or pneumoperitoneum and usually requires surgical repair. Notably, esophageal and colonic perforations can occur in the absence of biopsy or other direct manipulation of the mucosa (Iqbal et al. 2008). Laparoscopic surgery is replacing open laparotomy for many commonly performed pediatric surgical procedures. Although this approach generally carries decreased morbidity compared to open methods, complications specific to laparoscopy are reported. Placement of trochars and needle can injure intra-abdominal organs, especially the intestine, and can perforate blood vessels, including the aorta and vena cava (Guloglu et al. 2004; Schafer et al. 2001). In addition to hemorrhage, gas embolism can be a life-threatening sequela, leading in some cases to cardiac arrest or paradoxical systemic emboli. The most common route of entry seems to be via a patent umbilical vein (usually in neonates), or (though not always) secondary to abdominal insufflation (Kudsi et al. 2009; Lalwani and Aliason 2009; Mattei and Tyler 2007; Taylor and Hoffman 2010). Laparoscopy can also cause extensive subcutaneous emphysema (Coelho et al. 2010).

Frequently performed pediatric surgeries such as inguinal herniorrhaphy, tonsillectomy, and appendectomy have low but measurable morbidity and mortality rates. Inguinal hernia surgery is a very safe procedure, rarely complicated by extensive subcutaneous emphysema (in laparoscopic procedures), injury to pelvic organs, and infection (Coelho et al. 2010). Tonsillectomy can result in major complications including delayed postoperative hemorrhage and dehydration in

0.7–3.4 % of cases, with intracapsular tonsillectomy presenting fewer complications than traditional electrocautery methods (Gallagher et al. 2010; Schmidt et al. 2007). More unusual complications include negative-pressure pulmonary edema, which affects patients with long-standing airway obstruction (Johnson et al. 2002; Thomas et al. 1999), nasopharyngeal stenosis, and Eagle syndrome (stylohyoid ligament ossification causing facial pain or dysphagia) (Johnson et al. 2002). Appendectomy can be complicated by wound and intra-abdominal infections occurring in 3.1–6.0 % of cases, with fewer wound infections when a laparoscopic approach is used (Liu et al. 2010; Paya et al. 2000; Sauerland et al. 2010). Rarer complications include injury to intra-abdominal organs and blood vessels (Guloglu et al. 2004; Schafer et al. 2001) and small intestinal obstruction or ileus (Liu et al. 2010).

Enteral feeding tube placement, another common procedure in pediatric patients, can be accomplished as nasogastric tube placement or percutaneous gastrostomy. Nasogastric tubes can be misplaced in the respiratory tract or placement can lead to esophageal or gastric injury. Erroneous placement in the trachea or bronchi can lead to pneumothorax or fatal pneumonia (Metheny et al. 2007). Esophageal injuries include formation of a pharyngeal pseudodiverticulum or blind tract through the mucosa ending in submucosal tissues, and in more severe cases, transmural esophageal perforation with pneumomediastinum and air or food leak into the chest (Sudhakaran and Kirby 2001). Gastric perforation is less common but can also occur (Metheny et al. 2007). Following esophageal or gastric perforation, the catheter can migrate in the mediastinum or retroperitoneum, perforating structures such as the pericardium (Hanafy Eel et al. 2006) or the urinary bladder (Mattar et al. 1997). Percutaneous gastrostomy carries a significant complication rate with one series reporting major complications in 12.6 % of procedures in children (Vervloessem et al. 2009). Common major complications include peritonitis and other major infections, new or worsened reflux, and gastrocolic fistula (Vervloessem et al. 2009). Less common but serious complications include injury to the small intestine, liver, or spleen. Endoscopic complications include esophageal perforation and hemorrhage (Vervloessem et al. 2009; Schrag et al. 2007). Several series indicate that the overall procedure-related mortality rate is 0.2–0.9 % (Vervloessem et al. 2009). Late complications of percutaneous gastrostomy, including excessive granulation tissue and buried bumper syndrome, affect up to half of pediatric patients in some series (Vervloessem et al. 2009; Naiditch et al. 2010; Segal et al. 2001).

Nosocomial Infections

Nosocomial infections are a common complication of hospitalization and a significant contributor to morbidity and mortality in patients. In intensive care nurseries, the average estimated incidence is 11–17 hospital-acquired infections per 100 patients; pediatric intensive care units (PICUs) have an average incidence of 11–13 per 100 patients. Of note, there can be considerable variation in infection rate

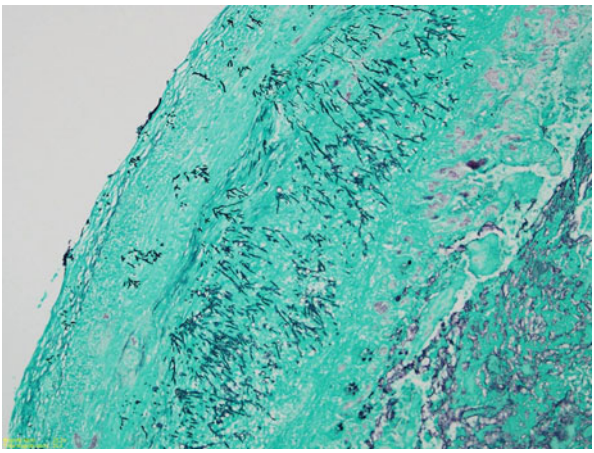

Fig. 28.10 Fungal infection of open abdominal wound in a 24-day-old preterm infant with a ruptured omphalocele. At autopsy, fungi invaded all exposed organs, including the small intestine (shown here), with necrosis and hemorrhage of involved tissues. Wound cultures grew *Aspergillus fumigatus* (Grocott-Gomori's methenamine silver stain, GMS × 4)

between hospitals (Banerjee et al. 2006). Bloodstream infections are the most common hospital-acquired infection for infants and children, followed by pneumonia (Gaynes et al. 1996; Klevens et al. 2002; Richards et al. 1999). Neonates are also susceptible to urinary tract, ear, nose, throat, and gastrointestinal infections (Gaynes et al. 1996; Sohn et al. 2001), while infants and children in pediatric intensive care units are more vulnerable to urinary tract, soft tissue, and surgical site infections (Fig. 28.10; Richards et al. 1999; Grohskopf et al. 2002).

Hospital-acquired bloodstream infections in children are strongly associated with central vascular catheters, and 91 % of PICU patients with bloodstream infections have central catheters (Richards et al. 1999). The most common infectious agent in both neonates and children is coagulase-negative Staphylococcus (Gaynes et al. 1996; Richards et al. 1999; Sohn et al. 2001; Grohskopf et al. 2002; Rabalais et al. 1988), followed by *Enterococcus* species, *Candida* species, and *Staphylococcus aureus* (Gaynes et al. 1996; Richards et al. 1999; Grohskopf et al. 2002; Rabalais et al. 1988). Bacterial contamination of intravenous medication or parenteral nutrition can cause outbreaks of bloodstream infections within a single hospital unit. In recent years, multiple neonates in intensive care units have died after receiving total parenteral nutrition contaminated by *Enterobacter cloacae* (Tresoldi et al. 2000), *Enterobacter hormaechei* (Campos et al. 2007), and *Serratia marcescens* (Arslan et al. 2010), and glucose and water contaminated with endotoxin (Centers for Disease Control and Prevention (CDC) 1998; Garrett et al. 2002). Bacterial, fungal, and viral nosocomial infections can occur as outbreaks within a hospital or single hospital unit due to contaminated instruments (Faden et al. 2005), water (Naze et al. 2010), or soap (Rabier et al. 2008) or due to transmission by colonized or infected health-care workers (Huang et al. 2002; McAdams et al. 2008).

Other nosocomial infections have a similar strong association with invasive devices. Nosocomial pneumonia in children occurs almost exclusively in the setting

of mechanical ventilation: 95 % of hospital-acquired pneumonias in the PICU are in children on ventilators (Richards et al. 1999). The most common causes are *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Richards et al. 1999; Grohskopf et al. 2002). Similarly, 77 % of PICU patients with urinary tract infections have an indwelling urinary catheter. The most infectious agent is *Escherichia coli* (Richards et al. 1999). Surgical site infections are particularly common following cardiovascular surgery; the most common causes include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and coagulase-negative Staphylococci (Richards et al. 1999). Peritonitis is a major complication of peritoneal dialysis and occurs more frequently in children, especially young children. Although the direct mortality rate is relatively low (1–1.2 %), it is the most common reason for cessation of peritoneal dialysis in children. Coagulase-negative Staphylococci and *Staphylococcus aureus* are the most common causes (Chadha et al. 2010).

If infection is suspected in a hospital death, bacterial, fungal, and viral cultures should be collected as clinically appropriate. Routine sampling of lung tissue, as noted earlier, is recommended. The spleen can be cultured if blood is unavailable. In particular, blood for aerobic and anaerobic bacteria and fungus (drawn from the vena cava or heart), urine for bacteria and fungus, and tissue from areas of suspected infection or abscess can be cultured. Tissue and fluid tend to give positive results more frequently than swabs/culturettes.

Nonaccidental Death in the Hospital

Although the overwhelming majority of pediatric deaths in the hospital are due to disease or complications of therapy as discussed above, other nonaccidental deaths can occur in the hospital. Suicide is a very rare cause of in-hospital death for children, but cases do occur, particularly among older adolescents on inpatient psychiatric wards. Schizophrenia and depressive symptoms are the most common diagnoses. Even though a previous suicide attempt is a risk factor for a subsequent attempt, a significant number of patients (25–57 %) who attempt or commit suicide during a hospital admission have no history of previous suicide attempts (Bowers et al. 2010). Many patients deny suicidal thoughts and ideation, even in the last medical/psychological examination prior to the attempt (Busch et al. 2003). Methods tend to depend on opportunity, with hanging and jumping from a height common methods in most hospitals (Bowers et al. 2010).

Although Munchausen syndrome by proxy, or factitious illness by proxy in children, is discussed elsewhere, a special mention should be made of this phenomenon as a known cause of nonaccidental death in the hospital. In a landmark 1997 study, children in whom induced illness was suspected underwent covert video surveillance during a hospital admission. Surveillance revealed abuse in 33 of 39 children, including intentional suffocation in 30, poisonings, and a deliberate arm fracture. Disturbingly, the 39 patients had 41 siblings of whom 12 had previously died suddenly and unexpectedly. In several of these cases, a parent subsequently confessed to suffocating one or more

children (Hall et al. 2000). Common causes of death include suffocation and drug overdose. When investigating a possible case of Munchausen syndrome by proxy, or factitious illness by proxy in children, interviews with caregivers and evidence from video surveillance may be crucial in determining that death was intentional rather than natural or accidental.

Conclusion

Unexpected death during hospitalization is a relatively common event and one that pediatric and forensic pathologists should be prepared to encounter. The clinical history, including past medical history, hospital course, and surgical, radiologic, and laboratory findings, is crucial in guiding the autopsy and the interpretation of autopsy findings. Many causes of unexpected death in the hospital may be difficult to detect at autopsy in the absence of clinical suspicion. Notable examples include electrolyte imbalances, drug errors, and transfusion reactions. Some situations may require collection or preservation of pre- or postmortem fluids or tissues, such as serum to detect drug levels or vitreous humor or urine to determine glucose and ketone levels. In some cases, special dissection techniques may be required, e.g., dissection under water to detect pneumothorax.

Investigation of unexpected hospital deaths can provide important feedback to physicians, nurses, and others involved in the care of the patient. This information guides the treatment of future patients with similar conditions and provides a measure of quality control that cannot be replicated with other methods. The autopsy report provides the patient's family with an explanation and a narrative of their child's clinical course and death and may assist in providing closure. Finally, the autopsy frequently provides the initial observations of important therapeutic complications and therefore guides refinements to surgical technique, medical devices, and therapeutic procedures. Approaching every unexpected hospital death with this in mind ensures that the autopsy report can be a thorough, informative, and meaningful medical record.

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Pediatric Toxicology

29

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Contents

Abstract

The preponderance of reported exposures to potentially toxic substances each year occurs in children. While many of these exposures are presumed accidental in nature, it is sometimes difficult to discern the cause and intent of a given

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event. Statistical evaluations generally demonstrate a low homicidal poisoning risk for children; however, such evaluations may not be complete in respect to investigation. Purposeful childhood poisoning is not a new phenomenon, with a number of significant historical events reported; in fact, at one time such acts may have been an accepted practice. The outcomes of accidental and deliberate poisoning in children may be distinct from that of adults based on a number of variables, including toxicokinetic and toxicodynamic differences. Many of these differences are developmentally based; for example, liver-enzyme biotransformation capabilities may be significantly different in young children compared to adults; additionally, blood–brain barrier development is not complete at birth. In general, the younger the child, the greater the likelihood of observable differences. With reference to postmortem forensic toxicological issues, every unexpected or unexplained child death should be presumed to be toxicological in nature. Of importance are a thorough scene examination, a complete autopsy to include unique sampling of fluids and tissues, and a toxicological examination that hones in on particular concerns for the pediatric population.

Introduction

The concept that children are nothing more than small adults has no basis in clinical medicine. As evidence of this, the medical specialty pediatrics is dedicated to the care and treatment of children while entire hospital complexes are constructed that focus on the pediatric population. Additionally, clinical laboratory medicine related to children has established reference intervals to capture the uniqueness of this group of patients (Soldin et al. 2011). In respect to the use of medications, dose considerations are typically separate and distinct from those in the adult population based on known pharmacokinetic and pharmacodynamic differences (Takemote et al. 2011). From a toxicological perspective, it too is recognized that children's responses to known exposures of potentially harmful substances do not necessarily mirror that of adults. Unfortunately, due to a lack of controlled experiments, many of these differences are recognized only through empirical means. Thus, exposure of children to the plethora of medicinal and non medicinal substances can result in both predictable and unpredictable toxicities.

A poison is defined as any substance which, when ingested, inhaled, or absorbed or when applied to, injected into, or developed within the body, by its chemical action may cause damage to structure or function (Dorland's Illustrated Medical Dictionary 1985). As an extension of this definition, poisoning is the administration of a toxicant, either accidentally or deliberately.

Toxicology is the scientific discipline dealing with the adverse effects of chemicals on living beings. It has been termed the study of poisons. Forensic toxicology is a subspecialty of toxicology that deals with the analysis of biological specimens and the subsequent interpretation of findings in respect to human

performance and poisoning issues, both in living and deceased individuals. Many of the interpretive issues in forensic toxicology are based on controlled studies in adults and/or findings in adults with known histories, e.g., dose taken, suicidal intent, recognized impairment, or other pathophysiological derangements; typically, few, if any, such studies or information are readily available in children. It is not possible to logically extend the observations in adults to children due to, in part, some of the issues mentioned above. Additionally, the biological responses and sensitivities of children to poison exposure often requires specialized analyses. These myriad of issues render pediatric forensic toxicology exceptionally challenging.

Through examination of the historical aspects of poisoning in children, the toxicokinetic and toxicodynamic differences to poison exposure in children compared to adults, and specific preanalytical and analytical issues related to children, significant improvement in the understanding of toxicological findings in pediatric patients is possible. Additionally, an understanding of the medicolegal and social issues of childhood poisoning is essential to place toxicological findings in context.

Statistics

There exists a plethora of national, state, and local statistics and databases concerning childhood poisoning (O'Brien 2010). Many of these data points come from various sources thus causing a number of reported findings for the same statistic. In some situations, the reporting of poisoning, in children and adults alike, is voluntary, while in other situations such reporting is mandatory (Shepherd and Ferslew 2009), thus allowing for significant differences in the number of cases in any given database. Further complicating this issue is the choice of a clinician to designate a diagnosis as a poisoning. As such, getting a solid footing on the depth of childhood poisoning is somewhat clouded. Even given these factors and other limitations, the available data are demonstrative of the extent of the problem.

When evaluating reported poisoning cases in children, it must be understood that the term poisoning is not necessarily pejorative in respect to whether a given exposure was accidental, non accidental, or homicidal. For example, an unintentional over medicating of a child by a parent is still considered a poisoning. While superficially not acknowledging such differences may seem unwise, there is often a lack of forthrightness regarding the exposure from parents and caregivers, thus making such distinctions impossible.

Each year in the United States (USA), there are two million or so voluntary reports of exposure to chemicals, including drugs, to poison control centers (PCCs). More than half of these reports involve children (Bronstein et al. 2008), with a preponderance occurring in children less than 3 years of age. Often, two distinct age distributions can be detected: 1–5 years and 6–19 years. The former group tends to be normally distributed, while the latter group is skewed toward the older ages. This same conclusion was reached in a statistical evaluation of forensic cases involving the deaths of children (Campbell and Collins 2001).

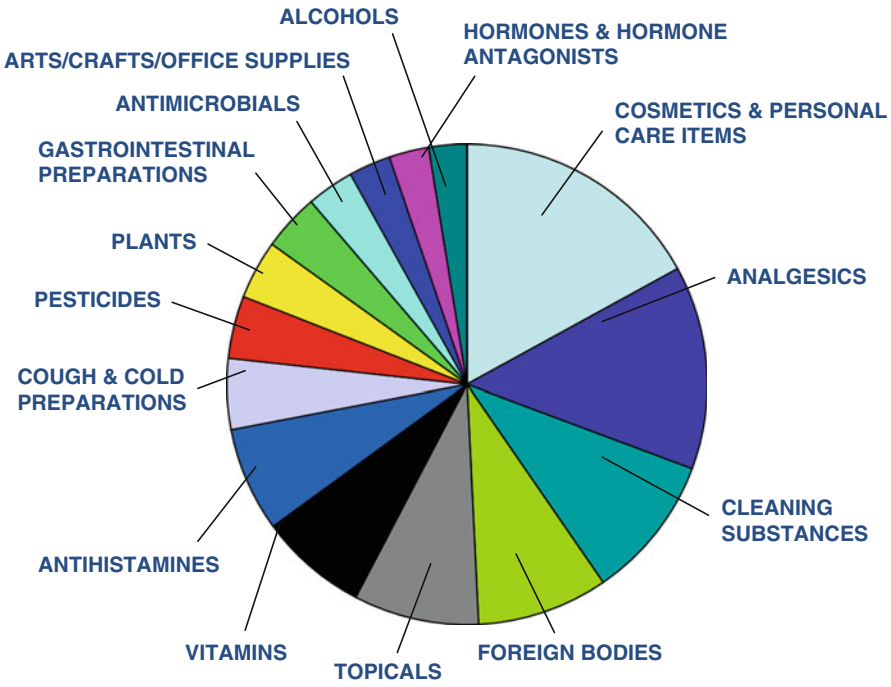

Fig. 29.1 Typical variety of substances in pediatric poisonings reported by PCCs and approximate percentages of each substance (Bronstein et al. 2010)

The younger group generally reflects either purposeful administration by parents or caregivers or developmental inquisitiveness accompanied by ambulation. On the other hand, in older children, experimentation with drugs and other agents tends to predominate, along with the maturing of suicidal intentionality (Pfeffer 1997).

The majority of children exposed to drugs and other chemicals reported to PCCs each year recover from these events. Figure 29.1 shows a common breakdown of substance types in children <5 years old as reported by PCCs. In a review of data from a 5-year period (1985–1989), out of approximately 3.8 million exposures in children <6 years old, there were about 2,100 major outcomes and 111 fatalities (Litovitz and Manoguerra 1992). It must be cautioned however that not all poisoning fatalities are captured in these data, for example, medical examiner cases, thus leading to an underestimation of the actual frequency. Table 29.1 shows the percentage of all fatalities attributed to children broken down by age group as reported in the 2009 Annual Report of the American Association of Poison Control Centers. Childhood fatalities due to poisoning represented approximately 2–4 % of all fatalities since 1992 (Bronstein et al. 2010). This percentage has held relatively constant for many years. It is of interest to note that an assessment of the substances commonly

Table 29.1 Percentage of all poisoning fatalities by pediatric age group (Bronstein et al. 2010)

Age group	Number of fatalities	% of all fatalities[a]
≤ 5 years	37	3.2 %
6–12 years	10	0.9 %
13–19 years	48	4.1 %

[a]Total fatalities due to poisoning (all ages) = 1,158

encountered in fatalities reported by PCCs shows age specificity; in the younger children, approximately 40 % were pharmaceuticals, while about 60 % were non pharmaceuticals (Litovitz and Manoguerra 1992). For deaths in children <5 years old, analgesics, batteries, and hydrocarbons were responsible for most multiple- and single-substance exposures (Bronstein et al. 2010). The range of substances from medical-examiner/coroner cases is, as would be expected, much more diverse than from PCCs (Campbell and Collins 2001). This is, in part, due to the amount and quality of toxicological testing performed. Data from individual centers as opposed to national databases are often more revealing in respect to pediatric poisoning. In one report, 8.4 % of children brought to one hospital's emergency department with Apparent Life-Threatening Events (ALTEs) were found to have significant, positive toxicological screens; about half this number was positive for over-the-counter cold preparations, with no indication that the child was on such medication and no caregiver admitting administering a medication (Pitetti et al. 2008).

The idea that childhood poisoning can represent a form of child abuse was first suggested in 1962 (Kempe et al. 1962). The term "Munchausen by Proxy" was coined by Meadow in 1977, and poisoning was recognized as one means of facilitating this syndrome (McClure et al. 1996). Until around 1990, only scattered reports of such deliberate poisonings had appeared in the medical literature (Rogers et al. 1976; Dine and McGovern 1982; Hickson et al. 1989). Thereafter, many such reports have appeared in the medical and forensic literature. At autopsy, if child abuse is suspected, toxicological examination should take place as recommended by Weston in 1968 (Rogers et al. 1976). Thus, the concept of non accidental poisoning of children is, remarkably, relatively new in respect to the scientific literature. That such poisonings have occurred throughout history, however, is not new.

Homicidal poisonings in the USA are relatively rare. For the period of 1999–2005, the overall reported rate for homicidal poisonings was 0.26/million person years (total absolute number = 523). In infants, the rate was 2.05/million, 8–9 times greater than the general population with a racial trend toward African–American infants (5.3/million vs. 1.8/million Caucasian infants). Children aged 1–4 years also had an elevated rate at 0.49/million. Children ≥5 years had homicidal poisoning rates comparable to the general population (Shepherd and Ferslew 2009). Given historical and empirical evidence, including medicolegal and social issues as well as this author's experience, the rate of non accidental poisonings in the pediatric population, especially infants, is most likely underreported (Middleberg 2004).

Historical Perspectives

The concept of a child existing as a recognized independent person with individual rights is a relatively modern construct. Historically, children were often perceived as property and accordingly had few, if any, rights (Hart 1991), and deMause (1998) described the varied mistreatments of young human beings throughout history. Adults have used many means to inflict injury to children, with poisoning representing one such method. While the purposeful poisoning of children no doubt preceded recorded history, a number of known records lend credence to the use of poisons as a means of filicide throughout man's existence. The following, while not comprehensive, illustrates some noteworthy events leading to the use of poisons in children.

The nefarious use of poisons in ancient times is well documented and undoubtedly included children as victims. As political and social structures took form, intentional poisoning became prevalent. For example, in what had become a decadent Roman society in the eyes of many at the end of the first century A.D., Juvenal and others openly denounced the practice of mothers poisoning stepchildren (Cilliers and Retief 2000), thus demonstrating a prevalent ill-fated process of that time. During this same time period, Nero poisoned to death his 14-year-old stepbrother Britannicus with what is believed to be cyanide, based on the rapidity of the death (Blyth 1885). Additionally, the governing family rule of the Roman Empire was *Patria Potestas* (Father's Power) whereby families were patriarchal with the oldest living male descendant maintaining legal authority over his descendants, including the power of life and death of not only his children but of his children's children (Saller 1986). In some situations, it was the father's duty to kill a child, especially if the child was deformed. While direct reference to the means of killing is not readily identified, given the widespread use at the time, poisoning assuredly was one means of completing the assigned task.

The Middle Ages came with an enormous amount of discovery in respect to poisons. As compounds were identified, potions, powders, etc. were developed and exploited not only during this time but particularly during the Italian and French Renaissance (Collard 2008). The art of poisoning during the Renaissance period was more or less perfected by women, often for inheritance gain. Women would take ransoms to kill, teach other women how to poison, and run "poisoning clubs" to gain wealth and notoriety, with arsenic often being the substance of choice. One of the more infamous poisoners during this time was Catherine Deshayes Monvoisin, who was also known as "La Voisin (the neighbor)." While many adults were her victims, she is also credited with having poisoned some 2,000 infants (Gallo 2008). For these noteworthy efforts, she was burned at the stake more or less bringing to an end a period of ruthless poisoning (Somerset 2004).

After the Renaissance, poisoning continued, but in what appears to be a more random fashion. This changed somewhat during the Victorian period in England. During this period, the predominant victims of poisoning were children under 5 years of age, generally from poor families. The expression "I'll poison you out of the road" was one familiar to this population. Oftentimes, children of that time

became poisoning victims so parents could collect insurance premiums. In one grisly accounting, Rebecca Smith poisoned eight of her babies to death and was hanged as a result (Watson 2004). Perhaps the most famous murderess of that time was Mary Ann Cotton. Using arsenic as a weapon, she is credited with the killing of four husbands, 12 children (some of her own and others stepchildren), one sister-in-law, and one lodger. She was hanged in 1873 (Lane and Gregg 1995).

Poisoning cases of note involving children in the twentieth century demonstrated a more sophisticated use of a given agent. Two examples show the thought that the perpetrators used with this form of silent weaponry. In 1974, Ronald Clark O'Bryan became known as "The Man Who Killed Halloween." In suburban Houston, after taking out two $20,000 insurance policies on his two young children, O'Bryan replaced some of the contents of five powder candy–containing straws with cyanide. His son ate the candy and subsequently died, while his daughter did not eat the candy. Fortunately, no other children consumed the candy before police were able to investigate. O'Bryan was put to death by lethal injection after spending more than 9 years on death row (Glenn 2004; Babineck 1999).

In a period suspected to range from 1978 to 1982, Genene Jones was investigated for the suspicious deaths of 47 children and causing injuries to others. As a pediatric intensive care unit nurse who worked the night shift, an inordinate number of deaths occurred during her work time. After leaving the hospital following an internal investigation, she took a job as a nurse in a local pediatric office. Following the death of a 15-month-old under her care in the office, toxicological examination demonstrated the presence of succinylcholine in the child. Following a trial, Jones was convicted of murder for one death and subsequently found guilty of injuring another child. She was sentenced to 99 years for murder and a concurrent 60 years for the administration of heparin resulting in the injury of another child. She is suspected of having used digoxin as another poisoning agent in relation to the deaths of other children (Ramsland 2007; Elkind 1983).

The poisoning of children has continued into the twenty-first century with a mixture of sophisticated and unsophisticated means (Shepherd and Ferslew 2009). It is unlikely, given the stealthy means of delivery, the time delay associated with most poisons, and the ever-increasing challenges of detection that man will ever cease to use this mode of injury provocation and killing.

General Toxicological Principles

Introduction

A number of factors distinguish children from adults when considering toxicology. As children mature, many of the differences lessen, but children continue to develop both physically and mentally through adolescence. In general, the younger the child, the greater the expected disparity in kinetic and dynamic toxicological responses. The basis of such differences is steeped in developmental processes that begin in utero. Toxic insult to the developing fetus generally results in four

potential perturbations: embryolethality, developmental issues, growth retardation, and functional deficits. A major determinant of which occurs and the resultant effects are based on the timing of the toxic insult relative to the stage of development. Many structural and functional deficits occur due to exposures during organogenesis (4th to 8th weeks post-gestation) (Moore and Persaud 2003). However, other periods of development can still produce unwanted outcomes. Exposures later in fetal maturation often result in various deficits short of structural abnormalities. Thus, even in the seemingly normal child at birth, the effects of toxic insult may not be observed for years. For example, from approximately 1940–1970, diethylstilbestrol (DES) was given to some 10–15 million pregnant women in the mistaken belief that it would prevent miscarriage. In the late 1960s, a number of young women (14–21 years old) developed clear-cell adenocarcinoma of the vagina, a disease that up to then had only been seen in older women. Other vaginal abnormalities, e.g., adenosis, were also observed. Affected males developed epididymal cysts, hypotrophic testes, and poor sperm quality. Epidemiological studies traced these delayed effects to DES (Giusti et al. 1995). As a result of this toxic outcome, DES became one of the first recognized endocrine disruptors (Scheuplein et al. 2002; Newbold 2008).

Within the pediatric population, differences in responses occur not only due to biological variation but due to continued developmental issues. Ultimately, such differences result in toxicokinetic and toxicodynamic endpoints that dictate whether a given toxic insult in an otherwise normal child results in an adverse outcome. A number of the differences not only among children of different ages but also between children and adults are worth understanding in order to put toxicological findings in deaths involving this population into perspective. It should be realized, however, that pathological conditions can result in significant perturbations to the normal maturation and functioning of the following factors that affect xenobiotic exposure. The effects of such disease processes are beyond the scope of this chapter.

Size

The metamorphosis of children from birth to adulthood is rather remarkable. Never again, until perhaps late in life, will such significant changes occur over a relatively short period of time. What is most obvious with respect to change is size; i.e., over an 18-year or so period, an approximate 5.5-fold increase in weight and a 3-fold increase in surface area occurs (Rodman 1994). Blood volume increases approximately 16-fold between birth and adulthood (Fig. 29.2). These factors alone affect toxicological parameters that can result in significant toxicity in a child whereas no toxicity would be expected in an adult. For example, it can be calculated based on height, weight, and total body water (TBW) that a single, standard alcohol-containing drink would result in a blood alcohol concentration of 18 mg/dL (0.018 %) in an average adult and approximately 100 mg/dL in an average 6-month-old, enough to induce hypoglycemia

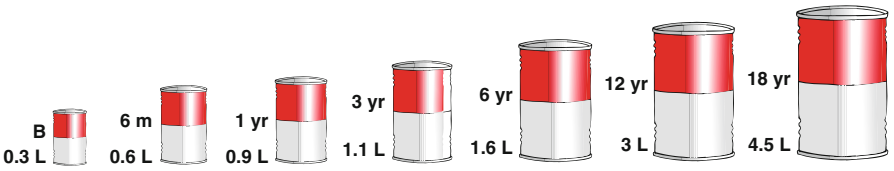

Fig. 29.2 Approximate changes in blood volume with age. *B* birth, *m* month, *yr* year(s) (Linderkamp et al. 1977)

(http://emedicine.medscape.com/article/1010220-clinical#a0217). With respect to specific pharmacological and toxicological effects, size is a major predictor of clearance and volume of distribution for many compounds in children (Anderson and Holford 2011). However, the use of allometric parameters to predict such things as drug metabolism is confounded by the very changes associated with maturation (Bjorkman 2006).

Toxicokinetics (TK)

Toxicokinetics is often defined as what the body does to a toxin (a substance of natural origin, e.g., snake venom) or toxicant (a man-made substance, e.g., diazepam). For ease of purpose, the term toxicant will be used to cover both kinds of substances. The general processes associated with toxicokinetics are absorption, distribution, metabolism, and excretion. It is the combination of all of these processes that determines the ultimate fate of a toxicant once an exposure takes place. A detailed explanation of each of these processes is neither possible nor completely relevant here. However, certain aspects of toxicokinetics are important in distinguishing outcomes of toxic exposures in children compared to adults (Alcorn and McNamara 2003). What follows are some of the important differences that can affect concentrations and other aspects of toxicants in children and ultimately the role of a toxicant in the mode and manner of death of a child.

Generally, most toxicokinetic parameters reach adult capability in the healthy child by the age of 10 years. There are some exceptions to this, as noted below. Most of the significant differences occur in children less than 6 years of age, many during the first year of life. It can be anticipated, however, as greater knowledge is gained in areas such as toxicogenetics and receptor biochemistry, subtle but significant differences throughout the childhood maturation process will become evident and perhaps influential in toxicant action.

While many ways exist to demonstrate differences between children and adults with respect to toxicokinetics, the method of Makri et al. (2004) is used here to group children by developmental stages.

Pre-embryonic/Embryonic/Fetus

The pre-embryonic, embryonic, and fetal periods are defined from conception to 2 weeks, 2–8 weeks gestational age, and 8 weeks gestational age to birth,

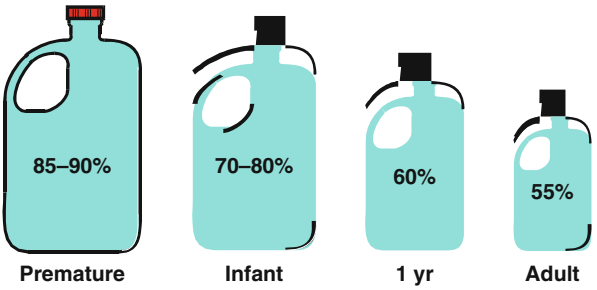

Fig. 29.3 Approximate differences in total body water as a percent of body weight during development (International Life Sciences Institute 1963; Raghaven et al. 1998; Koren 1997)

respectively (Scheuplein et al. 2002). The effects of toxic exposures during the first 2 weeks post-gestation can result in a range of effects from termination to continued development with non observable effects. Thereafter, a spectrum of effects can occur (Makri et al. 2004). Clearly, during these stages, conceptus exposure is via maternal exposure. What can be overlooked is that maternal exposure cannot only be acute or chronic but may also be remote in time; i.e., sequestration of toxicants in body stores, e.g., fat, and release into general circulation can also result in effects on the developing child. For example, lead accumulation in the long bones of a mother can be released during pregnancy, thus not only potentially causing a spontaneous abortion but exposing the fetus, with the concomitant resultant adverse effects of lead, e.g., learning deficiencies (O'Halloran and Spickett 1992/1993). Metabolic processes in the developing fetus are immature and display varying degrees of activity involving various cytochrome P-450 (CYP) enzymes; but, for the most part, the fetus cannot rely upon its own biotransformation processes for significant metabolic protection (Blackburn 2013). In some situations, this may be of benefit to the fetus when bio activation of a substance via hepatic metabolism leads to toxic metabolites (Makri et al. 2004).

Glomerular filtration and tubular secretion are immature at birth. This indicates that renal elimination in the fetus is poor resulting in increased residence time of many toxicants (Alcorn and McNamara 2002). The fetal hepatobiliary system is also immature, despite the ability to form some bile acids, thus precluding this process as a mechanism to handle xenobiotics. In its stead, cholephiles must be handled by both the maternal hepatobiliary system and the placenta (Macias et al. 2009). Other factors involved in fetal toxicity include distribution of the toxicant, often associated with total body water (Fig. 29.3), and development of the blood–brain barrier.

Neonate and Infant Periods

A neonate is defined as a newborn up to 1 month old, whereas an infant is aged from 1 month to 1 year (Moore and Persaud 2003). The first 3 months of life following a normal gestational pregnancy bring significant changes in maturation to factors affecting the handling of toxicants. For the neonate not in need of medical care, exposure to substances generally occurs via feeding of breast milk or formula and inhalation (Makri et al. 2004). Many drugs and other toxicants are secreted into

breast milk. It is estimated, however, that for most substances, with notable exceptions (cf. Breastfeeding), less than 1 % of a maternal dose is transferred to the child (Schreiber 2001). As with all known exposures, the risk versus benefit must be viewed, and in the case of breastfeeding, the recognized benefits appear to outweigh the risks in most cases.

At birth, placental transfer of xenobiotics ceases, thus putting the burden of handling not only new exposures but remaining circulating concentrations of toxicants from in utero exposure onto the neonate. Qualitatively, shortly after birth, biliary and renal functions rapidly increase. Many other necessary elements to sustain a viable, developing child also begin or mature shortly after birth (Scheuplein et al. 2002).

Absorption. While much focus is placed on the absorption of chemicals after oral consumption, it must be kept in mind that exposure can take place by other routes, including rectally, inhalationally, parenterally, and dermally (Tetelbaum et al. 2005). The absorption of a given substance can be markedly affected by the route of administration. Factors that affect absorption include gastric and intestinal pHs, gastric emptying time and peristalsis, metabolic processes, whether the means of absorption is passive or active, bile acid and salt activity, digestive-enzyme secretion, skin thickness, and lung development and maturation (Scheuplein et al. 2002). While each of these factors could be discussed in detail, what follows is a brief summary of the issues that should be considered when determining the effects of any given substance in a case involving a neonate or infant.

At birth, the pH of the gastric contents will be as high as it will naturally be during life, with a mean pH of 6.6 (range, 1.4–7.8) (Miclat et al. 1978). The pH then rapidly drops to 1–3 over a 24-h period but does not reach consistent adult levels until approximately 3 years of age. This can affect absorption of various agents based on Henderson-Hasselbalch chemistry. For example, there would be an expected increase in absorption of acid-labile and basic substances following oral administration of such compounds to the early neonate, with a concomitant decrease in absorption of acidic compounds. That such differences can occur has been demonstrated with acid-labile penicillin and related compounds, whereas absorption of phenobarbital is lower in neonates and infants compared to older children and adults. Some of these differences may be due to metabolic differences (Koren 1997; Tetelbaum et al. 2005). In some cases, however, despite these considerations, neonates and infants often absorb certain agents to the same or greater degree than adults. Gastric emptying is also relatively slow to develop, not reaching adult levels until at least approximately 6 months of age. Such a delay would predictably result in increased absorption of a given agent, but this has not been demonstrated to be so in every case (Scheuplein et al. 2002; Koren 1997).

The skin represents a primary barrier to the absorption of various xenobiotics, especially those that are lipophilic. The first signs of keratinization of the skin begin at 22–24 weeks post-gestation, and the stratum corneum becomes well defined at about this same time period, more fully developed at 34 weeks, but still not as mature as older children and adults (Blackburn 2013). Toxic epidemics due to

percutaneous absorption of toxicants in neonates have been noted and include exposure to betadine (iodine), hexachlorophene, and phenol (Bearer 1995; Evans and Rutter 1986).

Subcutaneous and intramuscular administrations of substances in the neonate and infant are influenced by such factors as decreased muscle mass, increased water content of muscle, and altered blood flow. This can lead to delayed or unpredictable absorption for some compounds, e.g., some cephalosporin antibiotics (Johnson 2011; Koren 1997).

Distribution. The process by which a xenobiotic moves from the site of absorption to other areas of the body is termed distribution. Many factors affect distribution, including blood flow, total body water, body fat, storage of toxicants in tissues, protein binding, blood–brain barrier development, and tissue affinity (Rozman and Klaasen 2001). Total body water can have wide extremes based on age and is greatest in premature babies (Fig. 29.3) reaching adult levels after about 1 year of age. Most of the water in neonates and infants is extracellular (International Life Sciences Institute 1963; Raghaven et al. 1998; Koren 1997). Body fat also follows an age-based pattern with premature children and neonates having the lowest, reaching average adult levels by around 5–10 years of age (Schmelzle and Fusch 2002; Gallagher et al. 2000; Laurson et al. 2011). Protein binding is in general lower in neonates. One consequence of this is a greater amount of drug in the free form, thus creating a greater dose–response effect. Additionally, endogenous substances, e.g., bilirubin, that are present in neonates may compete for protein binding and can therefore preclude the binding of xenobiotics. Compounds known to be affected by decreased protein binding include phenytoin, salicylates, and ampicillin (Johnson 2011; Koren 1997). There exists controversy as to whether the blood–brain barrier is fully developed at birth, mainly due to the difficulty in performing experimental evaluations. Evidence seems to indicate that at least at 4 months and older, there is little difference in this barrier compared to adults. In younger children, differences might exist, and given the fatty nature of the brain, this organ can serve as a depot for some substances (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500009793.pdf; Makri et al. 2004).

Metabolism (*Biotransformation*). While the liver is considered the organ where most biotransformation takes place, it must be understood that there are many sites within the body where such processes occur, including the kidney, gastrointestinal tract, lung, skin, and testes. In classic pharmacology and toxicology, metabolism is broken down into phase I and phase II. Phase I involves an initial change to a substance typically via oxidations, reductions, etc. and includes the cytochrome P-450 isoforms. Phase II (conjugations) reactions involve attachment of another chemical moiety to the substance with the intent of hastening elimination, but this is not always the end result. Compounds do not have to undergo phase I or phase II processes to be eliminated from the body, and compounds can undergo only phase I metabolism, only phase II metabolism, or both. Biotransformation of a substance should not be confused with the term detoxification. Often, biotransformation leads to a more reactive species toxicologically or results in the formation of toxic by-products, e.g., free radicals (Parkinson and Ogilvie 2008; Gregus 2008).

The ontogeny of drug-metabolizing enzymes is complex, especially given the sheer number of enzymes, and related polymorphisms, involved in the process. Many enzymes of phase I and phase II metabolism, including many cytochromes, are active in utero; however, most do not reach adult capabilities until after birth (Blake et al. 2005). Interestingly, shortly after birth, some enzyme activity exceeds that of adults, but for the most part, enzyme activity is less than that of adults. It is not possible to draw universal conclusions as to when each enzyme involved in metabolism reaches adult levels. Excellent reviews of the subject were produced by Hines (2008) and de Wildt (2011). It should be recognized, however, that some enzyme activity is not reached until adulthood. The differential development of these enzyme systems can lead to varied outcomes following exposure to a particular substance, ranging from less toxicity to greater toxicity compared to an adult. For example, chloramphenicol was found to induce the often fatal gray-baby syndrome due to the immature glucuronidation pathway in neonates (Choonara and Rieder 2002). On the other hand, the toxicity of acetaminophen is reported to be mitigated in children due to an increased ability for sulfation (Penna and Buchanan 1991). An additional factor to consider, not only with neonates and infants but with all children and adults, is possible toxicogenetic influences, e.g., ultra rapid metabolism of codeine to morphine in young, breast-fed infants (Neville et al. 2011). Many of these factors result in different half-lives, not only between children and adults but between children (Table 29.2).

Oxidation of many alcohols and aldehydes, including ethanol, is catalyzed by alcohol dehydrogenase (ADH) (Parkinson and Ogilivie 2008). There are seven genes that encode for ADH, thus producing multiple forms of the enzyme. Class I ADH appears to play the most significant role in alcohol metabolism in humans. ADH is found in multiple locations within the body, with a preponderance, both in quantity and importance, in the liver (Jones 2008a). Like other enzymes, development of ADH activity is not complete at birth. Fetuses tend to have ADH activity approximately 10–100 times less than adults depending on the age of the fetus. Children tend to reach adult levels of activity around 5 years of age (Pikkarainen and Raiha 1967). Aldehyde dehydrogenase or aldehyde oxidase (AOX) metabolizes aldehydes, but in particular acetaldehyde, the metabolite formed after alcohol dehydrogenase activity on ethanol. Acetaldehyde is responsible for the development of many of the untoward effects of alcohol, including liver damage, throbbing headache, and facial flushing. Some individuals, especially associated with some ethnicities, e.g., some Japanese, have mutant forms of AOX thus making drinking of ethanol-containing beverages not pleasurable (Jones 2008a). Neonates have 10–15 % of the activity of AOX as adults, with a linear increase in activity to adult levels reached at 1 year of age (Hines 2008). Based on toxicological principles alone, the exposure of children, especially neonates and infants, to alcohol is contraindicated.

Intestinal flora is also involved in the degree of absorption and metabolism of both endogenous compounds and xenobiotics. Such influences generally take place in the ileum and colon. At birth, gastrointestinal flora colonization begins with that obtained from the mother during birthing. Thereafter, feeding and environmental

factors affect continued colonization with bacterial flora reaching that of adults by 4 years of age. Factors such as breastfeeding versus bottle-feeding contribute to which bacteria predominate. Metabolic reactions by gut flora are generally reductive or hydrolytic in nature (Blackburn 2013; Alcorn and McNamara 2003; Strolin Benedetti and Baltes 2003).

Excretion. While the body, even in neonates and infants, possesses multiple means of excretion (breath, sweat, hair, etc.), the two most quantitatively important means of excretion are urine and bile (fecal). Renal function important to toxicants can be divided into glomerular filtration and tubular secretion. Both processes reach adult capability at around 1 year of age. However, failure to account for the progressive maturation of these processes after birth can result in toxicity, and such is the case with aminoglycosides administered to the very young, and this is due to decreased urinary excretion (Kearns et al. 2003). All of the processes involved in enterohepatic circulation are immature at birth, including bile synthesis, conjugation, transport, secretion, and reabsorption. Maturation of these processes occurs at about 1 year of age (Scheuplein et al. 2002). As a result, toxicants eliminated by this route may have prolonged residence times in young children.

In summary, during the neonatal and infancy periods, a great deal of change is observed in factors affecting toxicokinetics. These changes, along with those that continue in other age groups, can lead to both qualitative and quantitative differences in parent compound and metabolites found in the fluids and tissues of these children compared to adults. Forensic toxicological analyses in cases involving this age group must take such factors into account in order to not under- or over interpret findings.

Preschool (1–6 year) Period

With respect to toxicokinetics, this period sees a continued maturation of many of the processes described in the *neonate and infant* stages. Gastric motility and transit time now exceed adult levels, and this may lead to faster absorption of substances. Some serum-binding proteins (albumin) reach adult levels during this time frame, while others do not. Distribution of toxicants is still affected by such factors as total body water, which remains greater than that of adults. While some metabolic processes, e.g., most phase-I processes, are mature by this stage, others continue to develop, e.g., glucuronidation (Makri et al. 2004).

Child (6–12 year) Period

The majority of processes involved in toxicokinetics have matured by the end of this stage. A few remaining immature processes include increased gastric motility and emptying (Makri et al. 2004). That toxicokinetics can be influenced by physical activity, personal choices, and behaviors becomes a factor in this stage. In other words, environmental factors play integral roles in xenobiotic exposure and alterations in metabolic processes. Children of this age group enter school, begin to experiment independent of parental oversight, develop hobbies, etc., all of which can influence toxicokinetic outcomes. Clearly, from this point forward, and while

Table 29.2 Differences in elimination half-lives of selected compounds at various ages (Spino et al. 1993; Kerger et al. 2006; Milbrath et al. 2009; Wimmerová et al. 2011)

Drug/toxicant	Neonate	Infant	Children	Adult
Caffeine	103 h	-	-	6 h
Chloramphenicol	8–15 h	15–22 h	2.3–3.4 h	1.5–5 h
Diazepam	25–100 h	10 h	25 h	15–25 h
Meperidine	22 h	-	-	3–4 h
Mepivacaine	8.7 h	-	-	3.2 h
Nortriptyline	56 h	-	-	18–22 h
2,3,7,8-Tetrachlorodibenz-*p*-dioxin (TCDD)	1.6 year	-	-	3.2 year
Polychlorinated biphenyls (PCBs)	-	0.1–1.2 year	4.5–10.6 year	0.1–22 year

having had some influence in early years, the complexity of interactions of humans with their environment adds to the difficulty in predicting toxicokinetic parameters.

Adolescents (12–19 year)

Most basic factors previously discussed that affect toxicokinetics are mature by the adolescent stage. Gastric motility remains faster than in adults (Makri et al. 2004). However, hormonal influences on organ function, including metabolic processes, produce quantitative differences in how children in this age group handle toxicant exposure compared to younger children and adults. Size and surface area differences do not account for such observations. For example, the anti-inflammatory antipyrine has been shown to have an intermediate clearance between that of young children (<12 year) and adults in the adolescent. Gender differences are now seen with respect to toxicokinetics, most likely due to pubertal changes (Rodman 1994).

Practical Applications

A number of examples exist that highlight the practical value of understanding toxicokinetics in respect to potential outcomes in children:

1. Mothers using methadone while pregnant have given birth to neonates with prolonged QTc syndrome, most likely attributable to developmentally low CYP2B6 and CYP3A4, both being involved in the metabolism of methadone (de Wildt 2011).
2. Half-lives of many common therapeutic agents are significantly different in young children compared to adults (Table 29.2). Failure to take such differences into account can lead to toxicity or ineffective responses in children, up to and including death.
3. Valproic acid, a useful anticonvulsant drug in children, can cause hepatotoxicity due to increased metabolite formation via CYP2C9 and CYP2A6. This empirical observation may be due to increased enzyme activity leading to greater toxic metabolite formation (de Wildt 2011).

4. In a controlled study comparing the effectiveness of two antibiotic treatment protocols in premature newborns, penicillin/sulfisoxazole versus oxytetracycline, it was noted that there was a significantly greater number of deaths in those enrolled in the former treatment protocol. Of significance was the formation of kernicterus with the penicillin/sulfisoxazole regimen. The mechanism appears to involve competition between sulfisoxazole and bilirubin for serum albumin. Once displaced from albumin and with a decreased ability to glucuronidate, this population is at an increased risk of developing toxic sequelae of bilirubin (Silverman et al. 1956; Dunn et al. 1964).
5. Benzyl alcohol (BA) has been used as an antibacterial component in sodium chloride solutions for intravenous administration. A series of premature infants developed a "gasping syndrome" prior to dying after receiving injections of this material. This condition was characterized by severe metabolic acidosis, a striking onset of gasping respiration, and a constellation of other effects, including renal failure. BA gets biotransformed to benzoic acid, which is subsequently conjugated with glycine to form the readily excreted hippuric acid. A major contributing factor to the onset of this condition is the immature metabolic processes to safely handle benzyl alcohol in the premature child (Gershanik et al. 1982).
6. Diphenhydramine-related deaths in children were extensively reviewed by Baker et al. (2003). This compound has greater clearance in children than adults, thus partially explaining why children who are administered diphenhydramine have a lack of sleep response to the compound (Roehrs et al. 1993). It may also explain why children may be overdosed with the drug accidentally by parents. That is, as normal doses do not induce the desired effect of sleep, more of the drug may be given.

Toxicodynamics (TD)

Toxicodynamics can be defined as the resultant effects of toxicant action. More specifically, TD encompasses all the processes leading to toxic effects and includes the following: binding and affinity to receptors, interactions with DNA, altered gene expression, modulation of mediator substances (e.g., second messengers), interactions with or modulation of hormones, induced cell proliferation, cytotoxicity, and chronic changes in laboratory values, organ function, and histopathology (Heinrich-Hirsch et al. 2001). Developmental toxicodynamics relates the interaction between TD to age-related maturation of the structure and function of biological systems and the effects following toxic exposures (Mulla 2010). Unlike toxicokinetics, the number of studies related to TD in children is relatively sparse, in part due to ethical considerations. Often, such studies are performed in sick children, thus adding additional variables in trying to draw significant conclusions regarding a particular substance. That disease states can alter TK parameters has been well established (Dagan et al. 1993). Mandatory or incentivized requirements for testing of drug or toxicant safety in children in the USA and elsewhere have improved substantially but still have certain limitations that do not equate to equal regulation regarding drug use in adults (Thaul 2012; Sinha 2008).

Table 29.3 Some common toxicodynamic outcomes in children compared to adults (Mulla 2010; American Society of Health-System Pharmacists 2012)

Observed effect compared to adults	Potential consequence	Potential cause
Increased/decreased potency	Unexpected effects at small or large doses or exposures	Receptor or target organ sensitivity, immature biochemical pathways
Increased/decreased efficacy	Under or exaggerated effects	Receptor or target organ sensitivity, immature biochemical pathways, toxicokinetic differences, not understood mechanisms
Target organ-specific toxicity or reduced toxicity at a given target organ	Damage to a specific target organ with related sequelae or lack of expected damage to a target organ	Susceptibility (e.g., the brain) or lack of sensitivity to developing organs or organ systems
Paradoxical effects	Unexpected outcomes, e.g., stimulation due to antihistamines	Underdeveloped target organs, cellular processes, receptors, modulators

When considering TD in children compared to adults, the spectrum of responses can vary significantly (Table 29.3). It should be understood, however, that it is often difficult to isolate TD differences without consideration of TK differences. Further, the mere exposure of a child, no matter what the age, to a toxicant does not have to result in toxic sequelae (Straff 2004). Many of these TD differences can be attributed to maturational issues related to receptor affinity, density, or signal transduction. Additionally, effects of toxicants on biochemical pathways may be different in children. The combined adverse effects of toxicants in the developing child put critical systems, e.g., nervous, endocrine, reproductive, and immune, at particular risk (Mulla 2010). It is therefore critical that age-specific dosing regimens be developed based on critical factors expressed by both TD and TK (Kearns et al. 2003).

The effects of toxicant exposure on children, especially young children, may not be manifested until later in life. This is a function of the inability to observe or detect such effects, which can be subtle, resulting from toxicant-induced maturational changes in organ development over time. Ultimately, TD effects are usually substance specific (Straff 2004).

While much focus of TD and TK effects is centered on the very young child, adolescents are particularly prone to long-term sequelae from exposure to drugs of abuse, including alcohol, as well as environmental and other agents. While many biochemical and physiological maturational processes are complete by adolescence, some are not as well developed. For example, the mesocorticolimbic circuitry continues to develop during this time period in human development. Specifically, processes interweaving various neurotransmitters, e.g., dopamine, with the limbic system, play critical roles in attention, decision-making, and motivational and emotional regulation. Interference with this critical

developmental process may be associated with novelty-seeking and risk-taking behaviors, including substance abuse. Adding to this complex maturational process is the influence of hormonal changes, which besides the physiological effects may ultimately affect interactions with peers that interplay with the previously mentioned behaviors (Stansfield and Kirstein 2005; Spear 2002). Children often are willing to experiment without concern for, or without careful consideration of, the consequences, with or without perceived peer influence (Bauman and Ennett 1996). Therefore, careful screening and education of children as young as 9 years of age for substance abuse is critical to help ward off possible long-term sequelae (DuRant et al. 1999). Such effects are not limited to drugs of abuse, as other toxicological agents, including environmental agents, can also interfere with other critical developmental factors (Gauderman et al. 2004). Lastly, and significantly, the use of abused substances by this age group is associated with increased rates of attempted suicide and death by suicide (Garlow et al. 2007; Kelly et al. 2004, 2002).

Examples of TD Effects in Children with Forensic Implications

1. *Environmental tobacco smoke* (*ETS*). Exposure to ETS has been associated with a number of adverse effects in children. Smoking during pregnancy is associated with lower birth rates, premature labor, miscarriage, and higher infant-mortality rates. Additionally, an increased risk of asthma development even in the first year of life has also been associated with maternal smoking of cigarettes (Weitzman et al. 1990). ETS also appears to be related to an increased risk of sudden infant death syndrome (SIDS) and exacerbation of asthma in children (European Environment Agency 2002; Chilmoncyzk et al. 1993). There exist sex-based differences in the effects of smoking on lung function in adolescents with girls appearing to be more susceptible than boys. Nonetheless, both sexes have associated with them airway obstruction and slowed growth of lung function in adolescence with early-onset cigarette smoking (Gold et al. 1996). Early-onset cigarette smoking is also correlated with early progression of decreased lung function and disease (Apostol et al. 2002). At least one in five 12th graders is a smoker in the USA (Johnston et al. 2012).
2. *Opioids*. A complete discussion of the effects of opioids on children is not possible here; however, certain relevant issues are worth noting. When discussing opioids and children, it must be understood that exposures occur in three general ways: purposeful administration by a medical professional, parent, caregiver, or other individual, unintentional self-administration (e.g., toddlers accessing parental medication), and intentional self-administration (e.g., recreational use). From its member sites, the American Association of Poison Control Centers in the USA reported about 29,000 visits to emergency rooms due to opioid exposure in children $\leq$5 years of age from 2001 to 2008. These visits resulted in 20 deaths (Bond et al. 2012). It should be expected that these numbers have increased due to the proliferation of opioids for pain management in more recent years.

   The developing fetus is subject to significant effects due to maternal exposure to opioids. The appearance of neonatal abstinence syndrome (NAS),

a withdrawal-type reaction, is not uncommon in neonates of opioid-using mothers. Signs and symptoms of NAS include central nervous system (CNS) hypersensitivity, respiratory distress, autonomic dysfunction, and gastrointestinal (GI) disturbances. The severity of NAS is based on which opioid has been used, the dosage, the time since the mother's last dose, the exposure duration, and the state of health of the neonate. NAS generally appears within 72 h of birth but could be as long as 2–4 weeks, with effects lasting from 6 days to 8 weeks (Blackburn 2013; Kaltenbach et al. 1998).

For medical purposes, it was once believed that children do not experience pain as significantly as adults. This theory has been debunked as it has been shown that neonates attain peripheral, spinal, and supraspinal afferent pain transmission by 26 weeks post-gestation, although descending inhibitory pathways develop later (Berde and Sethna 2002). Differences in pharmacokinetic parameters can influence TD outcomes of opioids, especially adverse outcomes up to and including death. For example, the elimination half-life of morphine is reported to be 7–10 h in preterm neonates, 7–13 h in term neonates, 1–4 h in infants and other children, and 2–4 h in adults (Olkkola et al. 1995). The changes in half-life are at least partially attributed to increased glucuronidation capabilities in the developing child (McRorie et al. 1992). Therefore, age-related changes in the elimination half-life of morphine must be taken into account when rendering opinions as to postmortem blood findings after a given dose. Based on maturational processes associated with the lungs and respiratory–reflex responses, the use of opioids in neonates and infants may result in increased risk of opioid-related respiratory depression with differences compared to adults eliminated after 3–6 months (Berde and Sethna 2002).

In summary, TK parameters of opioids in neonates tend to be different from those in adults, with elimination being slower, but reaching, or exceeding, adult proportions in the first year of life. Metabolism in neonates may be slower than adults, but may exceed that of adults, in preschool and early school years. This may result in the need for higher dosages, a consideration in evaluating cases where children are prescribed opioids. There does not appear to be substantial differences in toxicodynamics of opioids in children compared to adults except in the neonatal period (Olkkola et al. 1995).

In 2011, it was reported that less than 1 % of adolescents in the USA use heroin. On the other hand, of 8th, 10th, and 12th graders, 1.8 %, 3.9 %, and 4.9 %, respectively, used oxycodone and in relation to hydrocodone, 2.1 %, 5.9 %, and 8.1 %, respectively (Johnston et al. 2012). As this author has handled many cases with unexpected opioid findings in children of various ages, it appears that other than infants, adverse effects of these drugs leading to death would be expected to be similar to those in adults.

3. *Stimulants*. The abuse of stimulants is a worldwide problem. Additionally, stimulants are used medically in the treatment of a number of disorders. In respect to children, exposure to stimulants leading to adverse effects occurs both in medically prescribed and recreational uses. While there are a number of

legitimate and illicit stimulants available to patients and abusers alike, the focus here will be on two types:

(a) *Amphetamine-type stimulants*. Within this class of substances are commonly recognized drugs of abuse, including amphetamine, methamphetamine, the methylenedioxy-class (e.g., MDMA [ecstasy], MDA [Eve]), and the newer "bath salts" (e.g., MDPV). Additionally, there are a number of prescription therapeutic agents routinely used in children, such as amphetamine and methylphenidate (Ritalin®), for such conditions as attention deficit hyperactivity disorder (ADHD). As with other pharmacological classes, the use of stimulants in children with ADHD has been described as a paradoxical effect, although controversy remains whether this is so (Gualtieri and Johnson 2006; Massanari et al. 1997; Green and Warshauer 1981; Robbins and Sahakian 1979; Sahakian and Robbins 1977). Over-the-counter preparations containing phenylephrine, ephedra alkaloids, and pseudoephedrine are also readily available.

Interestingly, first-time users of methamphetamine tend to be female, thus potentially affecting those of child-bearing age. In 2009, 6.7 % of individuals seeking treatment for methamphetamine abuse in the USA were pregnant, and while the mere presence of a substance does not necessarily correlate with a cause of death, methamphetamine was reported in a series of intrauterine or stillborn deaths (Stewart and Meeker 1997). Children born to mothers using methamphetamine during pregnancy can exhibit a withdrawal syndrome less severe than that with opioid use, often requiring no pharmacological intervention. Such children tend to be small for gestational age at birth, have lower birth weights, be shorter in stature (at least up to 3 years old), and have decreased arousal and poor grasping skills, at least until 3 years old, attention and memory issues, and other sequelae (Winslow et al. 2007; American College of Obstetricians and Gynecologists' Committee Opinion 2011; LaGasse et al. 2012). As a result, developmental behavioral problems have been reported with greater externalizing and ADHD problems with 5-year-olds whose mothers had prenatal exposure to methamphetamine (LaGasse et al. 2012). Long-term effects of prenatal exposure to amphetamines have not been studied extensively, but, despite confounders, academic and physical delays were reported in a series of mothers who abused amphetamine during pregnancy (Cernerud et al. 1996). The root cause of many of the effects of amphetamines appears to be related not only to selective damage to dopamine and 5-HT terminals but also to neuronal and endothelial cell bodies (Yamamoto et al. 2010).

Another often neglected aspect related to adverse effects on children is living in homes where methamphetamine and other stimulants are abused and/or made. Associated results of such exposure include inadvertent poisoning (including death), trauma, neglect, abuse, and adverse psychological effects (Oral et al. 2011; Winslow et al. 2007).

The abuse of amphetamine-type stimulants is reported to start in children less than 12 years of age (Vancouver Sun 2010; Herman-Stahl et al. 2006;

Antoon et al. 2001). The adverse effects of abused amphetamine-type stimulants in adolescent children would be expected to be the same as those in adults.

The use of prescription stimulants within the pediatric population is widespread, especially in children aged 5–14 years (Cox et al. 2003). That such medications are also abused is well recognized (McCabe et al. 2004; Poulin 2001). The adverse effects of prescribed stimulant use in children range from less severe (insomnia, irritability, anxiousness, nightmares, etc.) up to, and including, death. In a relative sense, the use of prescribed stimulants appears to be safe from a cardiac perspective (Winterstein et al. 2007). However, sudden cardiac-related adverse effects, including death, after prescription stimulant use have occurred. From 1992 to 2005, the US Food and Drug Administration (FDA) reported 11 sudden deaths in children using methylphenidate. In a retrospective study, Gould and colleagues (2009) determined a significant association between sudden unexplained death and the use of stimulant medication in children and adolescents. This study excluded other reported adverse effects including stroke and acute myocardial infarction.

Over-the-counter stimulants have also been associated with adverse effects, including death, in children and adolescents (Dart et al. 2009). There are a number of potential sources of these stimulants. Herbal and supplement products containing ephedrine (ephedra alkaloids) have been associated with deaths in all ages. For this reason, the US FDA banned the selling of such products in 2004. Nevertheless, stimulants remain in over-the-counter products, e.g., influenza and cold remedies and weight loss products and may be masked by alternate names, e.g., Ma Huang. In 1999, Middleberg reported on differences between postmortem pseudoephedrine findings in infants compared to adults, demonstrating a difference in the concentrations associated with deaths. The safety of such products in infants was subsequently supported by other investigators following postmortem toxicological analysis (Wingert et al. 2007; Marinetti et al. 2005). After an FDA advisory panel recommendation in 2007, manufacturers voluntarily removed the labeling of products for infants containing pseudoephedrine and other cough and cold medications (Reinberg 2007).

(b) *Cocaine*. As a stimulant, cocaine possesses many of the same toxicodynamic properties as amphetamines. Cocaine readily passes through the placenta and, once in the fetus, can pass through the fetal blood–brain barrier. As a vasoconstrictor, maternal use of cocaine can lead to placental constriction, placental hemorrhages, and infarcts and abruption (Gouin et al. 2011). As a result, neonates exposed to cocaine may demonstrate low birth weights, decreased body length, smaller head circumference, and cerebral infarcts. There do not appear to be established withdrawal behaviors in neonates born following in utero exposure to cocaine, but even so signs, including irritability, restlessness, tachycardia, and sleep disturbances, have been reported (Blackburn 2013). Long-term sequelae of in utero exposure to cocaine appear to be focused on specific cognitive impairments and

behavioral problems, although an increased risk of sudden infant death has been reported (Singer et al. 2004; Rosenberg et al. 1991; Chasnoff et al. 1987; Shannon et al. 1989). Cocaine passed in breast milk has reportedly caused intoxication in exposed neonates, including tachycardia, tachypnea, hypertension, irritability, and tremulousness (Chasnoff et al. 1987). The half-life of cocaine in neonates is longer than in adults (Blackburn-Tucker 2013).

Cocaine exposure in young children and adolescents may be both passive, e.g., sidestream smoke, and active, e.g., found around the house or for recreational use (Shannon et al. 1989). It is estimated that 2.9 % or less of children in the 8th, 10th, and 12th grades use cocaine (Johnston et al. 2012). Adverse effects of cocaine in children are fundamentally the same as those in adults, including cardiovascular and cerebrovascular pathologies, addiction, and death (Rao et al. 2007; Shannon et al. 1989). It has been demonstrated that there is an increased risk of suicide among adolescent cocaine abusers (Garlow et al. 2007).

4. *Alcohols and inhalants*. The exposure of children of all ages to alcohols and inhalants is long-standing. Such exposures not only have been as a result of accidental and recreational use but also through folk and traditional medicine (Smitherman et al. 2005; Mennella 2002). Regardless of the reason for exposure, alcohols and inhalants pose significant short-term and long-term effects physiologically, pathologically, and psychosocially.
   (a) *Ethyl alcohol* (*Ethanol*; *Alcohol*). The US Centers for Disease Control and Prevention (CDC) reported that about 12 % of pregnant women use alcohol at some point during pregnancy, with a small percentage being binge drinkers ($\geq$4 drinks in one sitting). Fetal alcohol syndrome (FAS) is a condition that falls under the broader term of fetal alcohol spectrum disorder (FASD) (Frost et al. 2011). Characteristics of children born with FAS include facial dysmorphism, limb defects, cardiovascular defects, growth development issues, microcephaly, epicanthal folds, maxillary hypoplasia, short nose, thin upper lip, and mental retardation. It is believed that maternal alcohol use is the leading cause of mental retardation. Fetal alcohol effects (FAE) is a lesser form of FAS associated with less alcohol use (e.g., 1–2 oz per day). Manifestations of FAE include behavioral and learning difficulties that continue into adolescence (Moore and Persaud 2003). The current thought is that there is no level of drinking that is safe to the developing child in utero (Blackburn 2013). There is evidence that newborns metabolize alcohol at half the rate of adults (Idanpaan-Heikkila et al. 1972). This may be important in that the use of alcohol by breastfeeding mothers as a means of increasing milk production, milk letdown, and relaxation of mother and infant is still prevalent. In fact, of a group of surveyed lactating women, 25 % were advised to drink alcohol by a physician. Unfortunately, it has been demonstrated that the use of alcohol in lactating women causes less milk production, infants to consume about 20 % less milk, decreased sleep by the infant, and decreased motor-skill maturation (Mennella 2002).

Alcohol remains one of the most widely used psychoactive substances in the USA among children. Remarkably, Johnston et al. (2012) reported that within 30 days of surveying students, 13 %, 27 %, and 40 % of 8th, 10th, and 12th graders, respectively, consumed at least one alcoholic beverage. While the totality of use of alcohol among these age groups in 2011 appears to be lower than in previous years, the consumption of alcohol by children remains a problem. Due to continued maturation of brain regions associated with drug reinforcement, it can be expected that patterns of alcohol abuse would be different in adolescents compared to adults. Long-term effects on neural and endocrine system maturation are also expected (Spear 2002). Neuropsychological effects, including short-term memory deficits, are associated with early to mid-adolescent heavy drinking (Brown et al. 2000). Pathologically, adolescents with alcohol-related problems have smaller hippocampal volumes, with women more prone to brain shrinkage (De Bellis et al. 2000; Hommer et al. 1996a, b). Children (ranging from infants to adolescents) that are exposed to alcohol have an increased risk of developing hypoglycemia (Lteif and Schwenk 1999; Ragan et al. 1979). The mortality rate in children with alcohol-induced hypoglycemia is reported to be as high as 25 % (Ernst et al. 1996).

(b) *Isopropyl alcohol* (*IPA*; *Isopropanol*). IPA is an alcohol that has a diverse set of uses and is found in a range of products, including nail polish, hair spray, and antifreeze. It is also sold as a stand-alone product containing 62–72 % IPA (Stremski and Hennes 2000). In 2004, there were approximately 4,500 cases of children <6 years of age who were exposed to IPA and reported to poison-control centers, with an additional 676 cases of children between 6 years and 19 years of age (Watson et al. 2005). The use of IPA as a means of controlling fever in children is a practice that should be discouraged as toxicity from this practice is widely reported (Arditi and Killner 1987; Garrison 1953). More children under 6 years of age are exposed to isopropyl alcohol than ethyl alcohol, methanol, and ethylene glycol. The substance is rapidly absorbed from the gastrointestinal tract and can lead to gastrointestinal irritation, CNS depression, hypotension, and coma (Riordan et al. 2002; Erickson and Brent 2005). Many exposures in children are believed to occur from inhalation of IPA vapor. While coma is not an infrequent occurrence, deaths from isopropyl alcohol in children are rare.

(c) *Inhalants*. Adolescents are significant abusers of inhalants in the USA and elsewhere. Inhalants tend to be abused by younger adolescents with use declining as the youths age. This is facilitated by the ready availability of the range of products containing inhalants, their relative cost, their legal status, and the high from abuse being rapid and short-lasting (Kurtzman et al. 2001). Outbreaks of inhalant abuse occurred in the late 1950s and continue to be an issue today (Bass 1970). The terms applied to inhalant abuse include sniffing (sniffing or snorting fumes from containers), bagging (sniffing or inhaling fumes from substances sprayed into a bag), and huffing (inhalant-soaked rag stuffed in the mouth). Other means of inhalant

abuse include spraying aerosols directly into the nose or mouth and inhaling volatiles within balloons (National Institute on Drug Abuse 2012). The most commonly abused inhalants include glue; shoe polish; volatile fuels such as propane, butane, and gasoline; aliphatic hydrocarbons and aromatics (e.g., toluene and xylenes); alkyl halides (e.g., 1,1,1-trichloroethane); and nitrites (e.g., amyl nitrite). While most of the compounds are CNS depressants, the nitrites are vasodilators (Wu et al. 2004; Kurtzman et al. 2001).

In recent years, there has been a trend toward decreased inhalant abuse among adolescents with approximately 4–7 % of 8th to 10th graders using an inhalant at least once within 1 year of being surveyed (Johnston et al. 2012). Inhalant abuse is not necessarily transient as one survey demonstrated that of those adolescents abusing inhalants, 77 % did so for more than 1 year, 47 % for more than 2 years, and 10 % for over 6 years (Neumark et al. 1998).

The toxicity of inhalants is varied and can be acute and chronic. Grossly, inhalants can act as CNS depressants, asphyxiants, suffocants, proconvulsants, arrhythmogenic agents, hyper- and hypotensive agents, and choking agents (National Institute on Drug Abuse 2012). Effects are wide-ranging from euphoria to coma and death. Mechanisms of acute death following inhalant abuse have been attributed to anoxia, vagal inhibition, respiratory depression, and cardiac arrhythmia. The preponderance of deaths appear to be due to inhalant-induced myocardial sensitization to catecholamines (Shepherd 1989; Bass 1970). In this respect, it is not uncommon for a history that includes inhalation followed by acute activity, e.g., running, prior to collapse. Chronic abuse of inhalants can lead to cognitive dysfunction and dementia as well as changes to brain structure, e.g., cortical atrophy and widespread cerebellar damage from toluene abuse. An excellent review of the pathology by organ systems was prepared by Kurtzman et al. (2001). Table 29.4 lists some inhalants and potential toxic effects. Lastly, inhalant abuse by pregnant women can lead to significant adverse developmental and morphological derangements in the child (Jones and Balster 1998; Dinwiddie 1994). While inhalant abuse is more prevalent in isolated regions and socioeconomically disadvantaged areas, it crosses all demographic settings, both rural and urban, as well as ethnicities in the USA. Historically, American Indian and Alaska Native youth have had a higher use incidence of inhalants, but like all inhalant abusers, there is a downward trend in use by American Indian youth in recent years (Williams et al. 2007).

Carboxyhemoglobin (*COHb*) *and methemoglobin* (*MetHb*). Young children tend to be more susceptible to toxic sequelae of exposure to carbon monoxide (CO) and methemoglobin-inducing agents. Reasons for this sensitivity may be based on young children's higher basal metabolic rate with consequent higher tissue-oxygen demand (Liebelt 1999). Children less than 6 months old may also have significant amounts of fetal hemoglobin, which binds CO more avidly than adult hemoglobin, thus significantly increasing the half-life of the carboxyhemoglobin moiety as well as the concentration of COHb (Snook 2005; Abelsohn et al. 2002). Therefore, given equal

Table 29.4 Acute and chronic effects of some commonly abused inhalants (NIDA 2012; Pfeiffer et al. 2006; Dinwiddie 1994; LiPuma et al. 1982)

Substance(s)	Where found	Acute effects	Chronic effects
Nitrites	"Poppers" (a slang term used to reflect nitrite abuse)	Vasodilation, sudden death – cardiovascular	Suppressed immunologic function, RBC injury
Butane, isobutane, propane	Propellant for many aerosols	CNS depression, sudden death – cardiac, asphyxiation	Myocardial fibrosis
Freons	Refrigerants	CNS depression, sudden death – cardiac, asphyxiation, sudden cooling/cold injury to airways	Liver damage
Methylene chloride	Solvents	CNS depression, sudden death – cardiac, asphyxiation, carbon monoxide poisoning	Cardiac muscle damage
Nitrous oxide	Mini-tanks, laughing gas	CNS depression, pneumomediastinum, interstitial emphysema, death	Polyneuropathy, interference with cobalamin metabolism
Toluene	Solvents	CNS depression, sudden death	Brain damage (ataxia, impaired cognition, loss of equilibrium, loss of brain tissue, loss of hearing and vision), liver damage, renal damage
Trichloroethylene	Degreasers	Sudden death	Liver disease (e.g., cirrhosis), hearing and vision problems, reproductive problems

exposures, children may develop higher concentrations of COHb and/or be more susceptible to the effects of the toxin than adults. While a direct correlation between COHb levels and toxic sequelae across all age groups is not possible, in children, COHb of >25 % has a high degree of syncope associated with it and a higher degree of altered mental status and seizures compared to adults (White 2000). It can be expected that a wide disparity in COHb will be seen in fatalities in the pediatric population. It should be noted that with some spectrophotometric-based measurement techniques, e.g., some co-oximeters, interference of fetal hemoglobin may produce falsely elevated COHb levels (Vreman et al. 1998).

There are a host of methemoglobin-inducing agents consisting of dietary and environmental substances (e.g., meat preservatives and naphthalene), industrial chemicals (e.g., aromatic amines and nitrites), and drugs (e.g., dapsone, rifampin) (Osterhoudt 2005). Methemoglobin is a form of hemoglobin where the ferrous

iron (Fe^{+2}) is converted to ferric iron (Fe^{+3}). In this form, MetHb cannot transport oxygen (Wright et al. 1999). Children less than 6 months of age are more susceptible to MetHb-inducing toxicities because (Osterhoudt 2005)

(a) Their Hb is more susceptible to oxidative stress.
(b) They are lacking significant enzymes necessary to reduce MetHb.
(c) Fetal Hb may be more easily oxidized than normal Hb.
(d) Fetal Hb has a greater affinity for oxygen; thus, it will not release oxygen to tissues as easily (left shift in the oxygen dissociation curve).
(e) MetHb causes an increase in oxygen affinity of the remaining normal Hb, aka the "Bohr effect" (this same phenomenon holds for COHb as well).

Unfortunately, postmortem methemoglobin determination and interpretation is confounded by the artifactual formation of MetHb as part of the decomposition process (Reay et al. 1984). Thus, interpretation of MetHb in infants must be done carefully; however, this should not preclude the use of such testing when appropriate.

Space precludes a comprehensive discussion of all agents, individually or by toxicological class, to which children are exposed. It should be kept in mind that children do not necessarily react to exposures as do adults, as evidenced by the examples above. Due to the relative dearth of data regarding the effects of many agents on children, circumstances of death are of great importance in the interpretation of toxicological findings. In this vein, the scene investigation and history are critical.

It should also be kept in mind that recreational toxicological exposures of children can be part of fads. As such, the list of abused substances may rapidly change and often defies logic. For example, the use of dextromethorphan in large doses to get high requires the consumption of large amounts of cough syrups that do not taste pleasant, yet this did not prevent such a fad from occurring in the early 1990s that, despite coverage in the general media and the medical literature regarding the potential adverse effects, resulted in significant toxicities and homicides with effects mimicking those of phencyclidine (Schwartz 2005; Murray and Brewerton 1993; Logan et al. 2012). It can be expected that children of all ages will continue to be exposed to toxic agents via maternal exposure, accident, or experimentation. It is therefore incumbent upon the forensic toxicologist and pathologist to remain current in trends, consider toxicological causes of death from the outset of a death, and use all information to assess the impact of such exposures.

"Forensic" Issues

Forensic toxicological cases involving the pediatric population have unique considerations that should be recognized. The previous discussion highlighted some of the basic toxicological differences between children and adults. The following discussion stresses some of the unique issues and concepts in postmortem forensic pediatric toxicology.

Table 29.5 Steps to allow for proper assessment of findings in postmortem pediatric forensic toxicology cases

1. Treat all deaths of children when not explained by obvious means as possibly toxicological in nature
2. Scene investigation should include a thorough inventory of medications (prescribed, non-prescribed, and herbal) and household products, e.g., cleaning substances and pesticides. This should include examination of trash cans, cabinets, handbags, and plants. Discrete spaces, e.g., safes and attics, should not be overlooked
3. For cases involving neonates and infants, blood and urine from the mother and father should be collected if possible. Additionally, breast milk should be collected from refrigerators or other storage locales
4. A detailed history should be obtained that includes:
   a. The last time that the child was seen alive
   b. An account of the child's whereabouts for at least 72 h prior to death, including the state of health
   c. A detailed chronology of events leading to the death, including the child's behavior
   d. Parental (and child, where applicable) work sites and hobbies
   e. Caregivers and caregiver site location, e.g., near a landfill
5. The complete autopsy should include careful observation of:
   a. Unusual odors and colors, especially in gastric and intestinal contents and solid organs
   b. Careful observation of stomach and intestinal contents for unusual objects, e.g., button batteries
   c. Morphological changes to brain structure, e.g., atrophy of specific areas
   d. Microscopic changes to organ structure, especially the brain, heart, kidney, liver, and nerves
6. Specimen collection should include fluids (blood, bile, vitreous, urine) and tissues (solid organs, skeletal muscle). Hair, when available, should be collected in every case and saved. In lieu of hair, whole fingernails should be collected

Scene Investigation, Autopsy, and Specimens

It is this author's experience that cases involving postmortem toxicological findings in children are often unexpected, especially in young children. In this regard, failure to consider the possibility of death due to toxicological means from the outset often results in a lost opportunity to explain such findings. That is, insufficient scene investigation, incomplete autopsy analyses, and insufficient specimen collection often require these steps to be performed again. Unfortunately, depending on how much time goes by before receipt of toxicology findings, requisite evidence is altered or removed or the body has been embalmed and/or buried, or worse, cremated. To circumvent adverse issues related to scene investigation, autopsy, and specimen collection in relation to toxicology, the steps listed in Table 29.5 are recommended.

Toxicological Analyses

The forensic toxicological examination of specimens in pediatric patients should include testing that may not be routine in adults. Due to certain susceptibilities of

Table 29.6 Toxicological analyses to consider in deaths involving children

Substance	Explanation
Carboxyhemoglobin, methemoglobin	Young children are particularly sensitive to exposure to carbon monoxide and methemoglobin-inducing agents. Concentrations not normally causing adverse effects in adults may be fatal in young children
Drugs of abuse (comprehensive)	Children are often unknowingly exposed to such agents due to presence in the home or through sidestream smoke. Children in homes where drugs of abuse are synthesized may have in vivo by-products or reagents associated with the synthesis of the intended agents. Adolescents may often experiment with such agents
Therapeutic agents (comprehensive)	Given the myriad of therapeutic agents, both prescription and nonprescription, present in the home and available to children by other means, such agents should be included in all toxicological examinations of children. Younger children who die in the hands of caregivers should always be screened for therapeutic substances since such agents may be used to sedate a child
Metals	Younger children may become toxic due to exposure to batteries, toys, etc. that contain toxic metals. Signs and symptoms of toxic metal exposure may mimic other pathologies precluding their diagnosis in the living patient
Botanicals, fungi (e.g., belladonna alkaloids, amatoxin)	Where and when appropriate, screening for toxicants found in plants, mushrooms, and other flora may be appropriate. Often, pathological signs and symptoms precede death
Alcohols and inhalants	Given the prevalence and widespread use of alcohols and inhalants in the pediatric population, such testing should be performed in all unexplained pediatric deaths
Environmental agents (pesticides, solvents, etc.)	Given the rapid toxicity of many such compounds and the inability to detect most of these substances on routine toxicological screening, such agents must be considered in unexplained pediatric deaths
Miscellaneous tests	Given specific histories and clinical pictures, consultation with a toxicologist to develop analyte-specific assays should be considered

children to various toxicants, especially younger children, testing protocols should be established to encompass a relatively broader range of substances. Additionally, inborn errors of metabolism should be excluded in unexplained deaths where toxicological agents were detected. For example, propionic acid was misidentified as ethylene glycol in a child with methylmalonic acidemia (Shoemaker et al. 1992). Additionally, given the serious nature of the often unexpected toxicological findings in children, laboratories must use techniques that incontrovertibly identify toxicants. In one case, while not in a child, 2,3-butanediol was misidentified as ethylene glycol when its presence was most likely due to the former substance being used as a denaturing agent in alcohol preparations (Jones et al. 1991). Table 29.6 outlines analyses that should be considered in cases involving children.

Analytical tools available to competent forensic-toxicology laboratories should include methods that characterize substances based on their molecular structure. Commonly, in order to facilitate this need, techniques based on mass spectrometry are used, including gas chromatography–mass spectrometry (GC-MS), liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS), liquid chromatography–time of flight (LC-TOF), and inductively coupled plasma–mass spectrometry (ICP-MS). It should be recognized, however, that techniques based on mass spectrometry are not the only acceptable analytical tools.

Postmortem Calculations

Attempts have been made to apply pharmacokinetic calculations used in the living to postmortem findings. Often, these calculations are attempted to determine dose and other relevant information. Retrospective pharmacokinetic calculations from postmortem toxicological findings except but in few situations (e.g., alcohol in some cases) have no scientific basis and are fraught with peril (Jones 2008b). This conclusion is based on a combination of incomplete information and postmortem factors. For example, only in rare situations is a complete history of exposure known in a given individual. That is, what dose was taken, how often, TK and TD interactions (see below), route of administration, and tolerance are rarely known. Reducing such issues to basic pharmacokinetic formulas is neither practical nor advised. Factors including postmortem redistribution, postmortem diffusion, protein-binding changes, embalming, and body movement all contribute to the difficulty of interpreting postmortem toxicological findings and further hinder the applicability of pharmacokinetic equations to such findings (Pelissier-Alicot et al. 2003; Ferner 2008). These issues are even more striking in cases involving children as the required pharmacological variables for such calculations are often not known at all, thus even making prospective calculations difficult. Postmortem diffusion has not, to this author's knowledge, been extensively studied in children. One might surmise, however, that such a process would be of greater significance in this population due to physical space limitations, immature biological barriers, and other factors, e.g., water versus fat content. Lastly, even when such calculations may have some validity, e.g., alcohol-related calculations, specific variables related to children should be recognized. For example, in using calculations that involve total body water, it must be understood that TBW determination is different in children and adults (Wells et al. 2005).

Breastfeeding

It is recognized today that breastfeeding is the healthiest form of nourishment for the neonate and infant (Schreiber 2001; Howard and Lawrence 1998). It is also recognized, however, that many women who give birth are also on necessary medications and/or abuse various substances or may be exposed to environmental agents. The questions then become:

Table 29.7 Some examples of drugs contraindicated during breastfeeding (Committee on Drugs 2001; Berlin and Briggs 2005)

Substance	Effects
β blocking agents	Hypotension, bradycardia, tachypnea
Salicylates	Metabolic acidosis
Lithium	Drug transferred to child, narrow therapeutic index
Antineoplastic agents	Child at risk due to rapidly dividing cells and tissues
Immunosuppressants	Potential immune suppression, neutropenia

1. Does the risk of exposure to a substance outweigh the benefits?
2. Does a particular substance get into breast milk?
3. Did the nursing child receive enough of a dose to cause illness or death?

As to whether the risk of exposure to a substance outweighs the benefit, this must be determined on a case-by-case basis between the patient and her physician. In respect to drugs of abuse, these substances are contraindicated during lactation. A complete list of drugs and environmental agents and recommendations for use during lactation can be found in the report of the Committee on Drugs of the American Academy of Pediatrics (2001). Specific therapeutic agents associated with significant adverse outcomes to the neonate and infant are provided in Table 29.7.

Drugs and other toxicants enter breast milk by a variety of different mechanisms. Briefly, milk is produced in mammary tissue, and toxicants traverse alveolar mammary cells to get into the milk. The processes involved in this transfer include transcellular diffusion, passive and ionophore-facilitated diffusion, intracellular diffusion (larger molecules), and other mechanisms (Berlin and Briggs 2005). Many substances make their way into breast milk, thus exposing breastfeeding children to these agents. However, the mere presence of a substance in breast milk does not portend any given adverse effect(s) in the suckling child (Committee on Drugs 2001; Berlin and Briggs 2005). There are a number of pharmacokinetic variables that are used to define the passage of drugs into breast milk; however, use of these variables to calculate the dose received by a child should not be performed in living or postmortem cases for many of the same reasons given in the section on "Postmortem Calculations". Of particular confounding note is that toxicant accumulation in breast milk and the infant occur over time, thus making it virtually impossible to determine not only how much toxicant the mother was exposed to but if the amount of substance in an infant came from a one-time or multiple exposure. Further hindering such calculations are generally unknown elimination kinetics in the suckling child as well as how much milk was consumed in any given feeding. Multiple other variables make such calculations tenuous at best.

Whether the illness or death of a child is due to passage of toxicants in breast milk is not easily discerned, especially with drugs of abuse. Often, drug abusers live in conditions that are less than ideal. In this respect, drugs in the general environment of a young child are not surprising, creating exposure possibilities via airborne concentrations, smoke, residue on parents' hands and face, etc. Therefore,

accounting for the presence of a drug of abuse in a young child must preclude other means of exposure than just breast milk. Further, the presence of a drug of abuse in a child due to breast milk should not obviate other considerations for the cause of death. Nevertheless, the prosecution of women accused of having passed drugs in breast milk resulting in the death of their child has occurred (Riparbelli 2011; Hutchison 2011; Ariagno et al. 1995).

It should be kept in mind that many environmental agents also get absorbed into breast milk. While interpretation of such findings in a child is challenging, they may be no less important than those of drugs (Leung et al. 2006; Landrigan et al. 2002).

Placental Transfer of Toxicants

The placenta acts as a point of demarcation between the maternal and fetal units. Between the maternal and fetal bloodstreams is a barrier consisting of layers of syncytiotrophoblasts, cytotrophoblasts, connective tissue, and endothelium, thus creating distinct maternal and fetal blood systems. However, at the placental–uterine junction there is sharing of blood whereby vital nutrients and other essential transfers to the fetus occur, and exchange of waste materials from the fetal bloodstream to the mother occurs (Barr et al. 2007; Ostrea et al. 2004). In respect to xenobiotics, there are few compounds that do not cross the placenta; it is merely a matter of the mechanism, the degree, and at what rate (Blackburn 2013). It should be understood, however, that in utero exposure can occur via other compartments as well, e.g., yolk sac, fetal membranes, fallopian tubes, and uterine lumen (Thadani et al. 2004). The feto placental–maternal circulation is not established until approximately the tenth week of pregnancy. Therefore, exposure of the embryo to xenobiotics during this time period must occur through extracellular fluid for any effects to occur. Thereafter, agents, potentially including their metabolites, will pass through the placenta at varying degrees with the placenta offering more protection against some agents compared to others. Many of the studies demonstrating passage of xenobiotics through the placenta have been done in animals. The relevance of such studies to humans is often questionable as the human placenta can be both anatomically and physiologically different from that of other species (Syme et al. 2004).

The majority of xenobiotics will pass through the placenta into the fetus by passive diffusion, although facilitated and active processes have also been demonstrated. Factors affecting passive diffusion through the placenta include maternal clearance of an agent, molecular weight of an agent, lipid solubility of an agent, charged state of the agent, degree of protein binding, and affinity of a given agent to placental tissue. Significant accumulation of an agent in placenta will cause a depot of that agent in the placenta (Syme et al. 2004). Other maternal, placental, and fetal characteristics also affect xenobiotic transfer, including changes in placental structure through pregnancy, e.g., thinning of placental membranes as pregnancy progresses, pathological processes, blood flow, and umbilical venous pressure. Facilitated diffusion is not considered a significant means for toxicant passage;

however, active transport has been associated with drug transfer via various transporters, including the APT-binding cassette (ABC) group (including p-glycoprotein, multidrug resistant proteins [MRP-1, MRP-2, MRP-3] and breast cancer resistance protein [BCRP]), monoamine transporters (e.g., serotonin transporter [SERT], norepinephrine transporter [NET]), and organic cation transporters (e.g., OCTN2). The interference of a transporter by a xenobiotic can affect the passage of other agents, including vital nutrients, to the fetus either directly by a specific reaction with the transporter or indirectly by interfering with cell-signaling pathways or transmembrane ion gradients that can adversely affect transporter function. Interestingly, amphetamines are transportable to the fetus via the SERT transporter whereas cocaine and nontricyclic antidepressants bind to this transporter with high affinity and therefore are not transferred to the fetus; cocaine can pass into the fetus, however, by other means than the SERT (Syme et al. 2004; Ganapathy et al. 1999). Ultimately, compounds that are low in molecular weight, lipid-soluble, non ionized, and minimally protein-bound have a much better chance of passing from mother to developing child. The rate-limiting step in passage of these latter compounds is blood flow, whereas that of compounds that are polar or that have other characteristics that render them unlikely to cross the placenta easily is diffusion rate. Lastly, once in the fetus, due to differences in pH, fetal metabolism, etc., a substance may be "trapped" in the fetus due to changes in polarity, charge, protein binding, etc. of the parent compound or metabolites (Blackburn 2013).

The placenta has metabolic activity, although it appears that such activity is relatively minor in respect to allowing passage of agents to the fetus. Some phase I and II metabolic processes are carried out by the placenta and vary according to gestational age. Additionally, these processes generally do not function quantitatively to the same degree as the adult human liver (Zhou et al. 2008). A number of CYP isoforms are present in the placenta, including CYPI, CYP2, CYP3, and CYP4 with some inducible by cigarette smoking and other environmental exposures (Pasanen 1999; Hakkola, et al. 1997; Pelkonen et al. 1972). In respect to drugs of abuse, amphetamine, cocaine, codeine, phencyclidine, etc. have been shown to be metabolized by human placental microsomes. Significant phase-II metabolic processes identified in the placenta include glucuronidation (only UGT2 appears to be present at birth) and glutathione conjugation, while epoxide hydrolysis, sulfation, and acetylation are present but have limited utility (Collier et al. 2002; Pacifici and Rane 1981). It should be kept in mind that such metabolic processes can lead to more toxic substances, thus potentially exposing the fetus to greater risk of poor outcomes, whether immediate or delayed until after birth (Ostrea et al. 2004).

Placental transfer of drugs, especially drugs of abuse, has potentially significant forensic implications related to the developing fetus, where outcomes can range from no effects to death in utero to significant postpartum pathologies for the child. Additionally, legal issues surrounding child custody and care in cases of children born after in utero exposure to drugs of abuse are commonplace and complex. The effects of placental transfer of drugs of abuse are often confounded by other factors, e.g., coadministration of various agents, poor socioeconomic factors, poor access to or use of prenatal health care, and poor nutrition, thus making practical

interpretation of effects somewhat complicated (Garcia-Bournissen et al. 2007). Besides the direct effects of placental transfer of drugs of abuse on the child, indirect effects are also well known. For example, cocaine can cause decreased uteroplacental blood flow and abruptio placentae (Thadani et al. 2004; Meeker and Reynolds 1990). Additionally, exposure to environmental agents, e.g., metals and dioxins, must be taken into consideration in any evaluation of a poor pregnancy outcome where toxicity is under consideration.

Interpretation of postmortem findings of drugs of abuse in a fetus or newborn is complex in regard to the impact of transplacental administration. Ostrea et al. (2004) provide an excellent compilation of effects of therapeutic agents via placental transfer, while Rayburn (2007) provides a similar compilation for drugs of abuse known to cross the placenta. As a few examples, alcohol and inhalant solvents, e.g., toluene, readily pass the placental barrier. Cocaine and metabolites also cross the placenta; however, cocaine is also sequestered in the placenta, offering perhaps some protection to the fetus against the compound. In a study involving pregnant monkeys, fetal exposure following maternal intravenous administration of cocaine was less than 30 % that of maternal exposure. Even so, both the mother and the fetus may be at additional risk of cocaine toxicity since plasma cholinesterase, a primary enzyme involved in cocaine metabolism, is decreased during pregnancy and in the fetus (Garcia-Bournissen et al. 2007; Zhou et al. 2001). As mentioned earlier, cocaine also binds to the SERT transporter, potentially causing indirect toxicity by inhibiting transport of serotonin and other vital substances using the SERT, to the developing fetus. Cocaine also interferes with the transfer of vital amino acids. This same concept holds for other drugs of abuse that interfere with normal transporter function, e.g., interference of amino acid transport by cannabinoids and nicotine (Ganapathy et al. 1999). These latter processes can lead to indirect toxicities at the nutritional level. That opioids cross the placental barrier is evidenced by the classic neonatal abstinence syndrome (NAS); however, it can be expected that not all opioids will cross the placenta to the same degree. For example, buprenorphine appears to be sequestered in the placenta, thus limiting how much gets to the fetus; additionally, only a small amount of buprenorphine metabolism appears to take place in the placenta. Nevertheless, both buprenorphine and norbuprenorphine are measureable in newborns, but due to the sequestering, there is some indication that NAS may be less than with methadone in situations where these compounds are used in addicted mothers (Kacinko et al. 2008; Nanovskaya et al. 2002).

Exposure of a developing child to any given agent of toxicological interest can be measured in biomaterials. Useful samples for testing include urine, blood, meconium, hair, cord blood, umbilical cord, oral fluid, and amniotic fluid. All specimen types have their limitations, either analytically based, e.g., extraction difficulty or false-positive screening, or toxicologically based, e.g., detection windows and collection difficulty. Interpretation of such findings must be done with care and caution (Gray and Huestis 2007). Nevertheless, deaths and other serious sequelae due to in utero exposure of the developing child to drugs of abuse have been reported (Rayburn 2007; Huestis and Choo 2002; Meeker and Reynolds 1990).

Drug Interactions and Toxicogenetics

Drug and toxicant interactions are complex and involve both TK and TD interactions (Pleuvry 2005). Space precludes a detailed discussion on this subject; however, some basic information should be kept in mind when considering toxicological findings in children. On a TK level, interactions between two or more substances can affect the absorption, distribution, metabolism, and/or elimination of another substance. From a TD perspective, interactions of toxicants may be additive (where the sum total of an interaction is merely additive), potentiative (where one agent may not cause a toxic response but increases the normal toxic response of another agent), synergistic (where one agent interacts with another agent to cause an effect greater than the sum of expected effects), or antagonistic (where one substance inhibits the action of another) (Eaton and Gilbert 2008). Unfortunately, too often, the term synergistic is used in respect to interpretation of forensic toxicological findings despite no proof that such an interaction occurred. The better term to use is "at least additive" when two substances are present that can induce similar effects. Together, TK and TD interactions can result in no change in response to a given agent, too little response, or too much response.

Given the relative immaturity of many enzyme systems and other important processes for the handling of xenobiotics in children, drug and toxicant interactions may be of increased importance in this population. For example, a given enzyme system in a child may already be quantitatively less capable of metabolizing a substance. So, if compound "A" requires a particular enzyme system to be metabolized, the presence of another compound that preferentially uses the same enzyme system would increase the likelihood of toxicity of compound A. In adults, alternate pathways may eliminate this concern, but such alternate systems may be immature in the developing child.

Toxicogenetics is an evolving science. Basically, toxicogenetics takes into account inheritable means of differential toxicant disposition. Many of the discussions today focus on the polymorphisms associated with the P-450 cytochromes, although polymorphisms related to other metabolic processes also exist (Johansson and Ingelman-Sundberg 2011; Holmgren et al. 2004; Druid et al. 1999). These polymorphic differences may cause differences in toxicokinetic profiles of substances (Smith 2009). That is, some individuals may be slow metabolizers of a given substance, while others are rapid or ultra rapid metabolizers. In toxicology, if a substance is metabolized to a toxic by-product, ultra rapid metabolizers are at increased risk of toxicity. On the other hand, if toxicity is associated with the intact substance, then slow metabolizers are at increased risk of toxicity. By identifying polymorphisms of enzymes used to metabolize a given substance, theoretically, toxicity might be avoided by not exposing an individual to a given substance that predictably would result in a poor outcome. Unfortunately, genotype does not necessarily equate to phenotype based on additional factors, e.g., environmental confounders (Ikediobi et al. 2009). Nevertheless, in certain situations, identification of a given polymorphism might help explain an adverse response in a given individual (Ferreiros et al. 2009).

Interpretation of Results

The interpretation of postmortem toxicological findings in children less than 6 years of age is challenging, as can be seen from the information provided throughout this chapter. In children greater than 6 years of age, for the most part, adult data can be used to aid in interpretation. Even so, care should be taken in respect to the differences noted between these populations. There is a relative dearth of postmortem toxicological data in young children, in part due to the relatively smaller percentage of cases. As such, anecdotal case reports are often used for perspective. Extreme caution should be used, however, in applying any given anecdotal case study to another case, especially when the case numbers are small. There are some reports involving children where a significant number of cases have been reported. Such studies are of greater significance in terms of literature value (Maron et al. 2009; Baker et al. 2003; Jumbelic et al. 1997; Hanzlick 1995; Hanzlick and Davis 1992).

As with all cases involving toxicological findings, pediatric cases must be put into context of the entirety of information, perhaps even more so, given the consequences of cause and manner of death. In this respect, all resources should be used for interpretive purposes. It is this author's experience that in order to facilitate proper interpretation of postmortem toxicological findings in children, a team approach is required with all stakeholders meeting together. A toxicologist experienced with pediatric cases should be involved to ensure that the requisite scientific considerations are fully explored.

Acute or chronic exposure *may* be deduced using hair analysis, fingernails, and/or gastric and intestinal contents. Route of administration, except in rare instances, cannot be determined by toxicological results alone.

Medicolegal Issues

Deaths involving children elicit great pain and suffering in most cultures, with those including poisoning being no exception. After it is concluded that a toxicant played a role in the death of a child, the question usually becomes whether the exposure was accidental or intentional. Such determinations are usually not straightforward and require a great deal of investigation and information gathering to adequately address the issues at hand. This author has been asked many times to assist in such determinations, and while drawing strict guidelines around this issue is difficult, it is possible to deduce certain broad interpretations. Most prominently, age plays a significant factor in determining whether any given exposure was accidental or intentional.

Very young children (< 6 months) tend to play a passive role in exposure to toxic agents, with exposures generally occurring via a parent, caregiver, or sibling. When exposure due to passive means, e.g., sidestream cocaine smoke and breastfeeding can be ruled out, deaths due to poisoning in this age group are, by definition, intentional. While intentionality is a given, many such deaths are accidental in nature and may stem from a simple need for a parent to help a child afflicted with a cold. In other cases, the intentionality is less clear (Middleberg 2004). For example, in one case

a mother gave a cold and influenza preparation to an infant via its bottled formula in order to keep the child sedated (author's case); while the administration of the drugs was intentional, the outcome of death was not. In such cases, charges of child endangerment are common.

As children become ambulatory and up to adolescence, accidental versus intentional exposure becomes less clear. Since these children can play a more active role in the administration of toxicants, care must be used in the medicolegal setting. Consideration should be given to the fact that children up to about 5 years of age tend to be orally fixated and curious and will put most things in their mouths. For example, a child could self-consume a brightly colored liquid that contains ethylene glycol that was seemingly properly stored in a garage, an accidental exposure. On the other hand, parental dosing of an over-the-counter preparation to treat signs and symptoms of an upper-respiratory infection is intentional; again, however, poor outcomes may be considered accidental even though there was intentionality in administration.

Adolescent exposures to toxicants are generally intentional in that either the child is aware of the administration (e.g., medication, recreational purposes, or suicide) or there is attempted poisoning.

In summary, intentional administration of drugs to children of all ages occurs for a number of purposes, including a parentally perceived need to help a child, to discipline a child, to bring attention to the parent or caregiver (e.g., Munchausen by Proxy [McClure et al. 1996]), or to purposely injure or kill a child (Middleberg 2004). While it could be argued that, short of purposeful administration in order to cause harm, all other exposures are accidental, this is a medicolegal issue. In trying to bring clarity to the various concerns, the following tend to draw into question the intent of a given administration:

1. Claims of an accident or unknown illness, recurrent unexplained illness
2. History of unexplained acute or chronic illness
3. Delay in seeking medical care
4. Case history that is inadequate, contradictory, and/or changing
5. Previous hospitalizations for toxicant exposure or injury
6. Blame placed on a third party

Lastly, cases involving the findings of toxicants in children have a number of social issues associated with them. For example, prosecutors may be reticent to bring serious criminal charges based on equivocal medical evidence, despite other evidence, out of fear that a jury will not believe that someone would purposely harm a child (Cornwall 1998). As evidence of this, in one geographic area of the USA, only 1 in 14 deaths over a 5-year period that were assigned to abuse or neglect resulted in successful criminal prosecution (Frederick 2003).

Conclusion

Pediatric poisonings leading to death occur with some regularity, perhaps more so than recognized. Such cases may be accidental or intentional in nature. In order to determine the effect(s) of any given exposure to a child, the differences between

this population and adults must be considered. Such differences that must be taken into account include size, toxicokinetics, and toxicodynamics. Other unique issues, e.g., breastfeeding, toxicant interactions, and assignment of toxicokinetic variables, must also be considered. Failure to understand the role these differences can make can lead to inaccurate interpretation of toxicological findings in children. As a relative dearth of toxicological data exists for pediatric cases, especially in very young children, interpretation of findings necessarily requires significant ancillary information to be incorporated into the decision-making process. Only then can proper assignment of the cause and manner of death have medicolegal significance.

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Pediatric Natural Deaths

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Contents

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Abstract

Autopsies are important in the investigation of childhood deaths. Most natural deaths are unlikely to come to the attention of the forensic pathologist, particularly in cases where death occurs in hospital. During the neonatal period (up to 28 days of age), deaths most commonly occur as a result of prematurity and related conditions, chromosomal abnormalities, or congenital malformations. Beyond the neonatal period, trauma-related deaths and sudden infant death syndrome are more common. In terms of natural acquired diseases of childhood, certain conditions are prevalent based on age and may be encountered at autopsy. Common acquired diseases that cause death in infants and children up to 5 years of age include pneumonia and other respiratory diseases, other infectious diseases, and malignancies. In older children, mortality due to natural disease declines substantially with trauma being the major cause of death, and malignancies the major cause of acquired disease. Sudden and/or unexpected deaths in which a natural disease state was previously unknown are most likely to come under the jurisdiction of the medical examiner or coroner and may be related to an underlying natural disease. Depending on the underlying disease process, the approach can differ, and therefore familiarity with common causes of death during childhood is important in order to focus the autopsy so that special techniques can be used along with obtaining proper ancillary testing to arrive at an accurate diagnosis and cause of death.

Introduction

Worldwide, the leading causes of death in neonates (birth to 28 days of age) are preterm birth complications, intrapartum-related complications, sepsis or meningitis, pneumonia, congenital abnormalities, other disorders, tetanus, and diarrhea. Globally, 7.6 million children died before the age of 5 years in 2010 with 64 % dying from infections. The major infections causing death in children include pneumonia, diarrhea, and malaria (Liu et al. 2010). Cancer is listed as the fourth most common cause of death in the industrialized world in children less than 15 years of age (American Academy of Pediatrics Committee on Environmental Heat 2003). In the United States (USA), from data obtained from the Center for Disease Control (CDC) National Center for Health Statistics (NCHS) mortality data for 1999–2009, the leading cause of death (all causes) in childhood (excluding neonates) was attributed to external causes (Centers for Disease Control and Prevention and National Center for Health Statistics 1999). In the neonatal period (up to 28 days following birth), the leading cause of death involved conditions that originated in the neonatal period, followed by congenital malformations, deformations, and chromosomal abnormalities, and diseases of the circulatory system with primary pulmonary

hypertension being number one. Beyond the neonatal period, congenital malformations including chromosomal abnormalities, trauma including child abuse, and sudden infant death syndrome (SIDS) are some of the most common causes of death and will be covered elsewhere in the text. Table 30.1 depicts the five most common childhood-acquired diseases categorized by pediatric age groups in the USA. This chapter will focus on acquired childhood diseases that cause death outside the neonatal period that are likely to be encountered by the forensic pathologist, and approaches to autopsy examination. The topics are not intended to be exhaustive but instead to include common natural diseases and their features that are likely to be encountered at autopsy.

Childhood Infections

Acquired diseases that are commonly encountered in infants up to 1 year of age include sequelae of conditions that originate in the perinatal period. Acquired diseases of the respiratory system (ICD-10 disease codes J00–J99), of which the majority include pneumonia and other respiratory infections followed by all other infectious diseases (ICD-10 codes A00–B99), are the most prevalent causes of death in infants up to the age of 1 year in the USA. Aside from respiratory infections, other types of infectious diseases that cause death appear to predominate in infants less than 1 year of age and continue to be a leading cause of morbidity and mortality in young children. Of the infectious causes of death, globally, diarrhea and malaria follow pneumonia in children less than 5 years of age. Other infectious diseases with increased mortality in children worldwide include meningitis, AIDS, and measles (Liu et al. 2010). In a recent US autopsy study evaluating causes of death in previously healthy or near-healthy children presenting to a children's hospital, more than half of the deaths occurred in children less than 1 year old, and infectious causes were the leading cause of death. In this study, the greatest number of deaths was attributed to bacterial infections with an almost equal distribution of sepsis and meningitis (Taggart and Craver 2006).

Septicemia

Sepsis is associated with high mortality rates in children. Sepsis, severe sepsis, and septic shock represent a continuum that reflects the inflammatory response to infection. In addition to a response to infection, systemic inflammatory response syndrome (SIRS) can occur from noninfectious life-threatening conditions (e.g., burns, trauma). Sepsis produces a biphasic inflammatory response in which the acute phase is marked by a rise in stress hormones that causes an increase in mitochondrial and metabolic activity followed by an altered hormonal profile that

Table 30.1 Most common causes of death in the USA 1999–2009 (by age and disease categories) (Centers for Disease Control and Prevention and National Center for Health Statistics 1999)

Age group	Cause of death (ICD-10 codes)
28 days to <1 year	1. Respiratory system diseases (J00–J99) a. Respiratory infections (J00.0–J18.9, J20.0–J22.9, J85.0–J86.9) b. Other disorders of lung including cystic lung disease (J98.4) 2. Certain infectious and parasitic diseases (A00–B99) a. Septicemia (A40.0–A41.9, B37.7) b. Diarrheal disease (A04.7–A09.9) c. Meningitis (A39.0–A39.4, A87.2–A87.9, B00.4) 3. Digestive system diseases (K00–K93) a. Noninfectious gastroenteritis and colitis b. Acute vascular disorders of intestine 4. Circulatory system diseases (I00–I99) a. Cerebrovascular diseases (I60.0–I79.9) b. Primary (I27.0) and secondary pulmonary hypertension (I27.2) 5. Nervous system diseases (G00–G99) a. Systemic CNS atrophies/demyelinating diseases (G10.0–G14.9, G35.0–G37.9) b. Meningitis/encephalitis (G00.0–G00.9, G03.0–G03.9, G04.0–G04.9)
1–4 years	1. Malignant neoplasms (C00–C97) a. Lymphomas and leukemias (C81.0–C96.9) b. Nervous system tumors (C69.0–C72.9) c. Adrenal tumors (C74.9) 2. Respiratory system diseases (J00–J99) a. Respiratory infections (J00.0–J18.9, J20.0–J22.9, J85.0–J86.9) b. Asthma (J45–J46) 3. Nervous system diseases (G00–G99) a. Meningitis/encephalitis (G00.0–G00.9, G03-0–G03.9, G04.0–G04.9) b. Seizures (G40.0–G41.9) c. Cerebral palsy (G80.0–G80.9) 4. Circulatory system diseases (I00–I99) a. Cerebrovascular diseases (I60.0–I79.9) b. Endocarditis/myocarditis (I33.0, I40.0–I40.9, I51.4) c. Cardiomyopathy (I42.0–I42.9) 5. Certain infectious and parasitic diseases (A00–B99) a. Septicemia (A40.0–A41.9, B34.0–B34.9, B37.7) b. Diarrheal disease (A02.0–A09.9) c. Meningitis (A39.0–A39.4, A87.2–A87.9, B00.4)
5–9 years	1. Malignant neoplasms (C00–C97) a. Nervous system tumors (C69.0–C72.9) b. Lymphomas and leukemias (C81.0–C96.9) c. Bone and soft tissue (C40.0–C49.9) 2. Nervous system diseases (G00–G99) a. Cerebral palsy (G80.–G80.9) b. Seizures (G40.0–G41.9) c. Meningitis/encephalitis (G00.0–G00.9, G03.0–G03.9, G04.0–G04.9) 3. Respiratory system diseases (K00–J99) a. Respiratory infections (J00.0–J18.9, J20.0–J22.9, J85.0–J86.9) b. Asthma (J45–J46)

(*continued*)

Table 30.1 (continued)

Age group	Cause of death (ICD-10 codes)
	4. Circulatory system diseases (I00–I99) a. Cerebrovascular diseases (I60.0–I79.9) b. Endocarditis/myocarditis (I33.0, I40.0–I40.9, I51.4) c. Cardiomyopathy (I42.0–I42.9) 5. Endocrine, nutritional, and metabolic diseases (E00–E90) a. Metabolic diseases (inborn errors of metabolism) (E70.0–E83.9, E85.0–E90.0) b. Cystic fibrosis (E84.0–E84.9) c. Diabetes mellitus (E10.0–E14.9)
10–14 years	1. Malignant neoplasms (C00–C97) a. Lymphomas and leukemias (C81.0–C96.9) b. Nervous system tumors (C69.0–C72.9) c. Bone and soft tissue (C40.0–C49.9) 2. Nervous system diseases (G00–G99) a. Cerebral palsy (G80.–G80.9) b. Seizures (G40.0–G41.9) c. Meningitis/encephalitis (G00.0–G00.9, G03.0–G03.9, G04.0–G04.9) 3. Circulatory system diseases (I00–I99) a. Cerebrovascular diseases (I60.0–I79.9) b. Cardiomyopathy (I42.0–I42.9) c. Conduction disorders and arrhythmias (I44.0–I49.9) 4. Respiratory system diseases (J00–J99) a. Asthma (J45–J46) b. Respiratory infections (J00.0–J18.9, J20.0–J22.9, J85.0–J86.9) 5. Endocrine, nutritional, and metabolic diseases (E00–E90) a. Metabolic diseases (inborn errors of metabolism) (E70.0–E83.9, E85.0–E90.0) b. Cystic fibrosis (E84.0–E84.9) c. Diabetes mellitus (E10.0–E14.9)
15–19 years	1. Malignant neoplasms (C00–C97) a. Lymphomas and leukemias (C81.0–C96.9) b. Bone and soft tissue (C40.0–C49.9) c. Nervous system tumors (C69.0–C72.9) 2. Circulatory system diseases (I00–I99) a. Cardiomyopathy (I42.0–I42.9) b. Conduction disorders and arrhythmias (I44.0–I49.9) c. Cerebrovascular diseases (I60.0–I79.9) 3. Nervous system diseases (G0–G99) a. Cerebral palsy (G80.–G80.9) b. Seizures (G40.0–G41.9) c. Meningitis/encephalitis (G00.0–G00.9, G03.0–G03.9, G04.0–G04.9) 4. Respiratory system diseases (J00–J99) a. Asthma (J45–J46) b. Respiratory infections (J00.0–J18.9, J20.0–J22.9, J85.0–J86.9) 5. Endocrine, nutritional, and metabolic diseases (E00–E90) a. Cystic fibrosis (E84.0–E84.9) b. Metabolic diseases (inborn errors of metabolism) (E70.0–E83.9, E85.0–E90.0) c. Diabetes mellitus (E10.0–E14.9)

results in a decrease in energy production, metabolic rate, and normal cellular responses (Singer et al. 2004). SIRS involves the release of pro-inflammatory mediators in response to infection or injury and/or ischemia. The pro-inflammatory response is often followed by a compensatory anti-inflammatory mediator release. An imbalance between the pro- and anti-inflammatory mediators results in an immunologic imbalance with systemic inflammation. Most children who die from sepsis generally have the most severe form – septic shock with evidence of multiple-organ failure that can include acute respiratory distress syndrome, disseminated intravascular coagulation, and ischemic injury to multiple organs. When sepsis is suspected, it is important to consider obtaining cultures of blood, cerebrospinal fluid (CSF), and tissues. More recently, some have advocated obtaining blood for the determination of biochemical sepsis markers such as procalcitonin, although reliable postmortem reference values are lacking (Tsokos 2007; Riedel et al. 2011). Autopsy findings in some cases of sepsis are often nonspecific (Tsokos 2007). In a majority of cases, there should be some nidus of infection (e.g., pneumonia) identifiable on postmortem examination. An example is *Neisseria meningitides* sepsis. In such cases, typically there are skin changes (e.g., petechial or purpuric rash), cloudy or purulent meninges, and bilateral hemorrhagic adrenal necrosis (Waterhouse-Friderichsen syndrome), although Waterhouse-Friderichsen syndrome is not specific for Neisseria sepsis. In cases of treated or partially treated sepsis, there may not be a clear-cut nidus of infection; however, there typically is evidence of end-organ damage with varying changes throughout the body (Torgersen et al. 2009). Cultures from the blood, cerebrospinal fluid (CSF), and/or tissues should be considered particularly when the etiologic agent is unknown. The culture results often may be the only evidence of sepsis found on postmortem examination. The yield of other postmortem testing for infectious organisms has improved with detection of infectious agents by polymerase chain reaction (PCR), immunofluorescence, and detection of early antigen-fluorescent foci using postmortem tissue samples as has been shown in evaluating sudden unexpected deaths in infancy with consistent use of ancillary investigations (Weber et al. 2008, 2010).

Postmortem Macroscopic and Microscopic Examination

In general, skin changes can include ulcerations, cellulitis, erythema, petechial hemorrhages, purpura, ecchymoses, bullae (both intact and ruptured), and skin desquamation. Typically there is peripheral, dependent, or diffuse edema. On internal examination, pleural, pericardial, and peritoneal effusions may be present. On examination of the organs, there may be little to no abnormal changes, or marked changes resulting from the dissemination of infection, or changes related to hypotension and septic shock. It is not uncommon to see petechiae or hemorrhages on the organ surfaces, particularly the pleura, heart, and thymus. The liver and spleen may be enlarged, softened, and have wrinkled capsules. On sectioning, the spleen may show deliquescence (liquefaction). The liver parenchyma may have accentuation of the lobular architecture, centrilobular hemorrhage, and necrosis. In severe cases of sepsis, there may also be evidence of cholestasis or steatosis. The lungs, heart, liver, spleen,

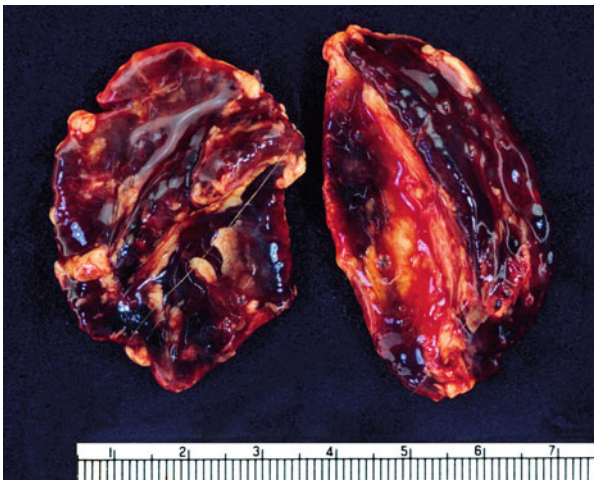

Fig. 30.1 Bilateral adrenal glands with diffuse hemorrhage (Waterhouse-Friderichsen syndrome)

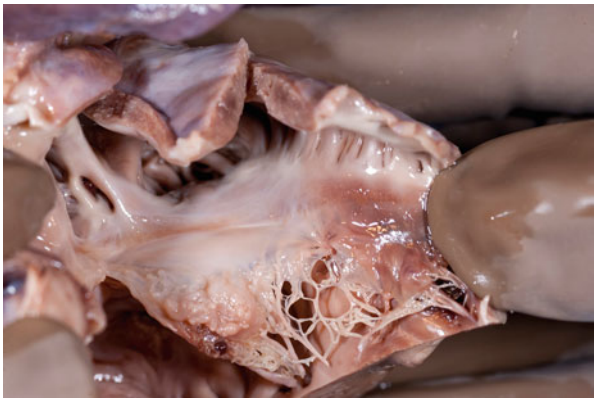

Fig. 30.2 Tricuspid valve with vegetations on the flow side of the valve leaflets

and kidneys may contain infarcts. In the lungs, there may be evidence of edema and congestion, pneumonia, abscess, or diffuse alveolar damage. Diffuse adrenal hemorrhage can be seen in some cases of bacterial sepsis, most notably in association with *Neisseria meningitidis* sepsis (Fig. 30.1). The kidneys may have scattered infective foci in the cortex with sparing of the medulla indicating hematogenous spread of infection. The heart may be dilated and contain diffuse or localized red-blue lesions or valvular vegetations (Fig. 30.2). The esophagus, stomach, and bowel walls may be thickened, edematous, and congested. There may be bloody material in the intestinal lumen. There may be fat necrosis or hemorrhage in, or surrounding, the pancreas. The brain may have evidence of edema or hemorrhage within the parenchyma (Fig. 30.3).

In bacterial sepsis, microscopically, seeding of the bacteria in one or multiple organs can be present. Fibrin microthrombi may be seen within the microvasculature of various organs. Increased numbers of segmented neutrophils may be present

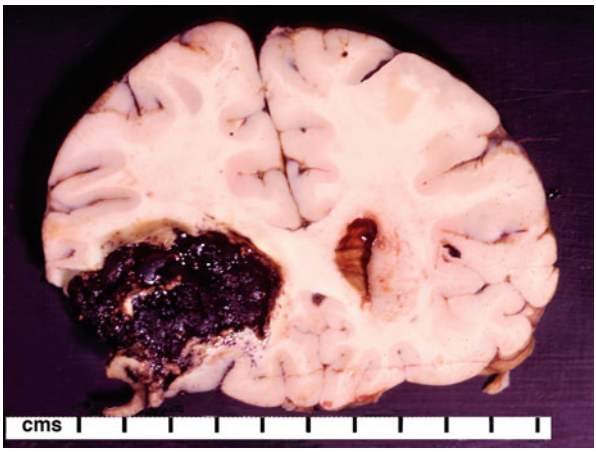

Fig. 30.3 Coronal section from the brain of a patient with endocarditis showing an acute parenchymal hemorrhage resulting from a septic embolus in the left middle cerebral artery territory. The hemorrhage extends into the lateral ventricle

within the microvasculature, in particular the lungs and hepatic sinusoids. The bone marrow may show an increase in myeloid precursors (so-called left shift). Edema and mixed inflammation can sometimes be seen in the myocardium or there may be valvular endocarditis (Fig. 30.4a, b). Cellular injury and evidence of apoptosis may be seen in multiple organs.

Ancillary Testing

Because the histopathologic features and morphology of infectious organisms are often nonspecific, in order to identify the etiologic agent, cultures, serological tests, immunohistochemistry studies, in situ hybridization assays, molecular studies, and electron microscopy may be warranted. For the best results, the autopsy should be performed as soon as possible following death, and stringent precautions (sterile technique) should be used for obtaining specimens for ancillary studies (Centers for Disease Control and Prevention and National Center for Health Statistics 1999). Refrigeration shortly after death at 4–10 ^{o}C helps slow the postmortem migration of endogenous microorganisms.

Appropriate culture media, collection containers, and equipment should be available prior to starting the case, and samples should be transported to the appropriate laboratory for testing as quickly as possible. If the sample can be transported quickly to the laboratory, a sterile container can often be used for many of the tissue-culture samples. When fungi are suspected, sealing the sterile container with parafilm or a tight screw top is desirable to avoid bacterial overgrowth.

Percutaneous samples can be obtained after antiseptically cleaning the skin. Upon opening the chest, blood for cultures or other studies can generally be obtained from the inferior vena cava, ascending aorta, subclavian vessels, or right atrium after carefully opening the pericardium without contaminating the underlying structures. If blood is to be used for toxicology, samples from both a peripheral site and central site are desired as some drugs undergo postmortem redistribution.

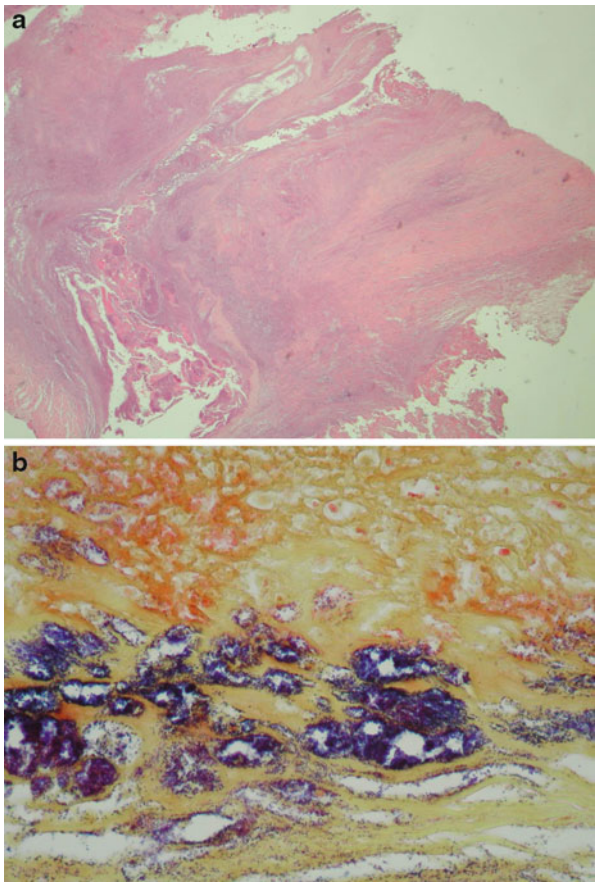

Fig. 30.4 (**a**) Vegetation with acute bacterial endocarditis (Hematoxylin and Eosin, H&E × 4) showing acute inflammatory cells and fibrin (**b**) vegetation, high-magnification Gram stain showing Gram-positive bacteria consistent with acute bacterial endocarditis (×4)

Using aseptic technique a needle can be introduced and blood aspirated into a sterile syringe. If serum samples are desired and will be stored for any length of time, it is useful to centrifuge the blood.

Swab cultures from grossly purulent tissues can be collected with the use of cotton-tipped applicators. If possible, tissue samples for microbiology studies should be obtained in situ after the surface of the organ is wiped dry and cleaned with an iodine-containing disinfectant or seared with a hot spatula (note that this technique is more likely to aerosolize infectious organisms). A sterile scalpel and forceps should be used to cut the surface of the organ and obtain the tissue samples from beneath the surface. The tissue can then be placed in the appropriate collection container for transport to the laboratory.

CSF can be obtained with an appropriately long needle by standard percutaneous posterior lumbar puncture, aspiration through the spinal foramina between the first

and second lumbar vertebrae following organ evisceration, or aspirating from the lateral ventricle after separating the cerebral hemispheres. Alternatively, the body can be placed in a prone position with a block under the chest to flex the neck and a needle inserted into the skin at the junction of the occiput and atlas (C-1) at the atlantooccipital joint. The needle is angled toward the bridge of the nose, and once there is a loss of resistance indicating entry into the cisterna magnum, CSF can be aspirated.

Fresh tissue samples obtained with aseptic technique at autopsy and frozen can be stored and later used as a source for multiple studies in particular PCR for infectious diseases, especially when a small number of organisms are present, or when the particular microorganism is difficult to culture or takes a long time to grow in culture. Frozen tissue samples can also be later used for electrophoresis, Western blot, Southern blot, DNA studies, high-pressure liquid chromatography (HPLC), gas chromatography–mass spectrometry (GC-MS), and enzyme assays (Kapur 2001).

Both immunohistochemistry (IHC) and in situ hybridization (ISH) using paraffin-embedded tissue can be used to diagnose and study infectious diseases. The sensitivity of IHC is greater than ISH because IHC detects specific antigens which are more abundant in infectious organisms, while ISH uses specific probes that detect nucleic acids which are less abundant than antigens. Formalin fixation can decrease the sensitivity of IHC due to cross-linking of proteins; therefore fixation should not exceed 2 weeks before embedding.

Diarrheal Infections

Acute gastroenteritis is a leading cause of morbidity and mortality worldwide. Most cases can be linked to contaminated water and food supplies. Although improvements in the management and prevention of infectious gastroenteritis have reduced the number of deaths over the past several decades, the number of hospitalizations remains high even in developed countries. The causative agents of diarrhea in developing countries include rotaviruses, Norwalk-like viruses, enteric adenoviruses, enterotoxigenic *Escherichia coli*, Campylobacter species, cytotoxigenic *Clostridium difficile*, and Cryptosporidium. Viral diarrhea tends to occur in the winter or dry seasons. In tropical areas in developing countries, the mortality from diarrheal infections is estimated at 4.6 million deaths per year (12,600 deaths per day in children), and in some areas the mortality exceeds 25 % in children less than 5 years of age. Outbreaks of diarrheal disease occur in child-care centers with rotavirus infections occurring in children under 2 years of age and *Giardia lamblia* infection in older children (Guerrant et al. 1990). Rotavirus infection accounts for approximately 1.2 million deaths worldwide in children less than 5 years of age (Tate et al. 2012). Rotavirus selectively infects small-intestinal mature enterocytes without disrupting crypt cells which results in repopulation of the surface epithelium by immature secretory cells. The loss of absorption and increase in secretory cells result in a net secretion of water and electrolytes that combines with an

osmotic diarrhea from poor absorption of nutrients. Acute diarrheal infections in children can quickly result in severe dehydration and metabolic acidosis that can result in death. In some cases, the child may appear to be adequately hydrated and therefore an acute gastroenteritis may not be suspected. In such cases, dehydration may be overlooked (Staat et al. 2005). Various body fluids can be used for biochemical testing; however, vitreous fluid is the most stable and can be used for many metabolic tests. In suspected cases of infectious gastroenteritis, consideration to evaluate electrolytes in vitreous fluid should be entertained along with the possibility of obtaining gastric or intestinal contents for ancillary studies to determine the etiologic agent. Rotavirus infection can be made by rapid antigen testing of stool by enzyme immunoassay (EIA) or latex agglutination tests. Rapid latex and Dot-ELISA tests can be utilized and are both sensitive and specific for rotavirus. More recently, the ImmunoCard STAT® Rotavirus kit has become available. The ImmunoCard STAT® Rotavirus kit is an easy, rapid, cost-effective test that detects monoclonal antibodies to rotavirus in stool samples. RT-PCR is useful for investigating genotype prevalence (Goodgame 2001).

Postmortem Macroscopic and Microscopic Examination

On macroscopic examination, the findings in the gastrointestinal tract may be nonspecific or quite variable. Although the gastrointestinal tract rapidly autolyzes postmortem, in cases of suspected gastroenteritis, it is important to obtain fecal samples if ancillary testing is sought and to fix sections of the gastrointestinal tract as quickly as possible. With acute viral enterocolitis, the bowel may appear dilated and filled with flocculent fluid. After emptying the intestines and stomach and for better preservation, it is helpful to rinse the samples in formalin rather than water. Most infections show a nonspecific pattern of damage to the surface epithelium. Acute enterocolitis appears as diffusely red with a thickened mucosa. Alternatively, in cases of *Clostridium difficile* or amoebic enterocolitis, multiple discrete plaques (pseudomembranes) or mucosal ulcerations may be present.

In acute infective enterocolitis, there is a predominance of acute over chronic inflammation with neutrophils in the crypt epithelium rather than crypt lumen, a lack of crypt architectural abnormalities, and edema (Shepherd 1999). The small intestine may exhibit modest blunting of the villous architecture with associated acute inflammation and edema. Well-formed granulomas are a feature of some infectious enterocolitides. In particular yersiniosis, chlamydia, and tuberculosis can cause granulomatous disease, often with necrosis which is not usually seen in other noninfectious enterocolitides such as Crohn disease. Infection by clostridial species can show epithelial characteristics similar to cholera with mucus depletion of the crypts but with epithelial damage that can be necrotizing.

Ancillary Testing

When determination of the pathogenic organism is desired, samples for cultures or other tests should be obtained. Because most children with acute infectious enterocolitis die from dehydration and/or acidosis, consideration should be made to determine postmortem vitreous electrolyte values. For studies of electrolytes,

Table 30.2 Common postmortem vitreous electrolyte patterns with dehydration

Type of dehydration	Sodium (mmol/L)[a]	Chloride (mmol/L)[a]	Creatinine (mg/dL)[a]	Urea nitrogen (md/dL)[a]
Hypernatremic	>155	>135	Elevated	>40
Isonatremic	Normal	Normal	Elevated	Elevated
Hyponatremic	<135	<105	Maybe elevated	Elevated

[a]Vitreous reference range for sodium is 135–150 mmol/L, for chloride is 105–135 mmolL, for creatinine is 0.6–1.3 mg/dL, and for urea nitrogen is 8–20 mg/dL (Collins 2011)

vitreous fluid can be easily drawn from the posterior chambers of the eyes. Vitreous is the specimen for analysis and is preferred over blood samples because of the postmortem breakdown and autolysis that occurs in serum. Although potassium is unstable in vitreous, sodium, chloride, creatinine, and urea nitrogen can remain stable for up to 120 h following death. Because vitreous glucose levels decrease postmortem, the vitreous is not useful for identifying hypoglycemia. Variables such as postmortem interval, temperature, and patient age can affect vitreous components. Analysis for glucose, ketones, alcohols, and certain drugs can also be performed on vitreous. Table 30.2 shows some typical dehydration patterns that can be interpreted from vitreous analysis.

Meningitis

Infectious organisms can enter the central nervous system (CNS) by hematogenous spread, direct implantation, or local extension or through the peripheral nervous system (PNS). The most common portal of entry is by hematogenous spread. Meningitis is an inflammatory process of the leptomeninges and CSF. When the inflammation extends to involve the brain parenchyma, it is referred to as meningoencephalitis. Infectious meningitis/meningoencephalitis can be divided broadly into three categories on the basis of the inflammatory infiltrate. In acute pyogenic or bacterial meningitis, *Escherichia coli* and group B streptococci are the most common bacterial etiologic agents in neonates; *Hemophilus, Streptococcus pneumoniae*, influenza (particularly in developing countries with no access to the vaccines for pneumococcus and *Hemophilus influenza* type b), and *Neisseria meningitidis* are most common in infants and children; and *Neisseria meningitidis* is the most common bacterial pathogen in adolescents and young adults. Acute aseptic meningitis is most often caused by viruses and is generally a benign disease with seasonal variation. In most instances, children who die with aseptic meningitis have concurrent systemic illness (e.g., enteroviral infection with concurrent myocarditis and hepatic necrosis with coagulopathy. The most common viral etiologic agents of aseptic meningitis include echoviruses, Coxsackie A and B viruses, herpes simplex viruses, mumps and measles viruses, adenoviruses, arboviruses, and more recently lymphocytic choriomeningitis virus. Viral

meningitis is most prevalent in children less than 5 years of age, and the most common etiologic agents in this age group are enteroviruses. The third major category encompasses the chronic bacterial meningoencephalitides including tuberculosis, neurosyphilis, and Lyme disease. The morbidity and mortality depend on a number of factors including infectious agent, age, health state, and how quickly the diagnosis and treatment occur. Pediatric meningitis is most common in children under the age of 4 years and peaks between 3 and 8 months of age. The overall mortality for bacterial meningitis is 5–10 %. In neonates, the death rate is 15–20 %, and in older children it is 3–10 %. The highest mortality rates are with *Streptococcus pneumoniae, Hemophilus influenza* type b, and *Neisseria meningitidis* (Muller 2012). Although the worldwide prevalence of tuberculosis in children is difficult to assess, it is estimated that 40,000 tuberculosis-related deaths occur annually, and 1 of every 300 untreated primary cases of tuberculosis develops tuberculous meningitis. The prevalence of tuberculous meningitis is highest in children less than 5 years of age (Ramachandran 2011). If an etiologic agent is sought at the time of autopsy, CSF and tissue for culture and other ancillary studies should be obtained as soon as possible following death.

Postmortem Macroscopic and Microscopic Examination

In cases of acute bacterial meningitis, in the very early stages, there may be little or no discernable exudate. Typically in fulminant cases, there may be edema, the CSF is generally cloudy, and the leptomeninges can be cloudy, thickened, or contain a purulent exudate. The meningeal vessels are often prominent and engorged. On sectioning, there may be purulent fluid or an exudate in the ventricles, and in cases of meningococcemia, there can be hemorrhage in the ventricles and small thrombotic infarcts. The location of the exudate can be a hint to the underlying etiology. In cases of Hemophilus, the exudate is located at the base of the brain, whereas with pneumococcal meningitis, the exudate tends to be most prominent over the cerebral convexities near the sagittal sinus. There are no distinct findings seen in aseptic meningitis, often consisting of only edema. With chronic bacterial meningoencephalitis, there may be a gelatinous or fibrinous exudate present most commonly at the base of the brain and white granules scattered over the leptomeninges.

Microscopically in acute bacterial meningitis, large numbers of neutrophils can be seen within the subarachnoid space and sometimes the ventricles that are associated with necrotic debris. Purulent material may be seen in the choroid plexus. Inflammatory cells are often seen surrounding the leptomeningeal blood vessels and periventricular white matter (Fig. 30.5a, b). There may also be fibrinoid necrosis of small vessels in the periventricular white matter. Intracellular and extracellular bacteria can usually be seen or demonstrated by special stains. Cases of aseptic meningitis microscopically can range from no microscopic abnormalities, to a mild to moderate lymphocytic infiltrate within the leptomeninges and a scant perivascular lymphocytic infiltrate, microglial nodules, and neuronophagia; to acute necrotizing encephalitis (Fig. 30.6).

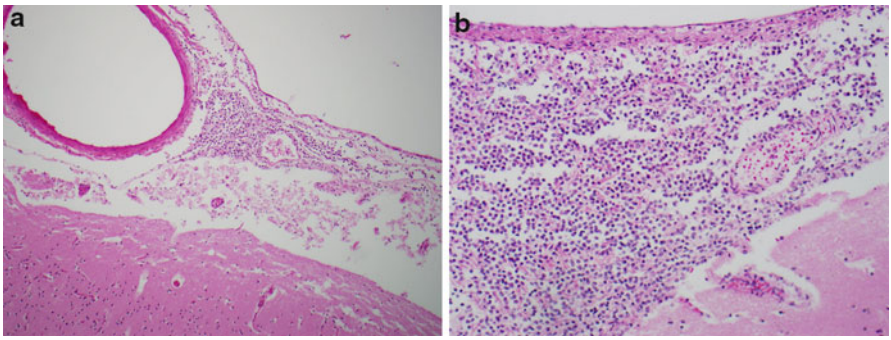

Fig. 30.5 (**a**) Leptomeninges, medium-magnification H&E stain with acute bacterial meningitis (Hematoxylin and Eosin, H&E ×10) (**b**) leptomeninges, high-magnification H&E stain showing a dense acute inflammatory infiltrate (Hematoxylin and Eosin, H&E ×20)

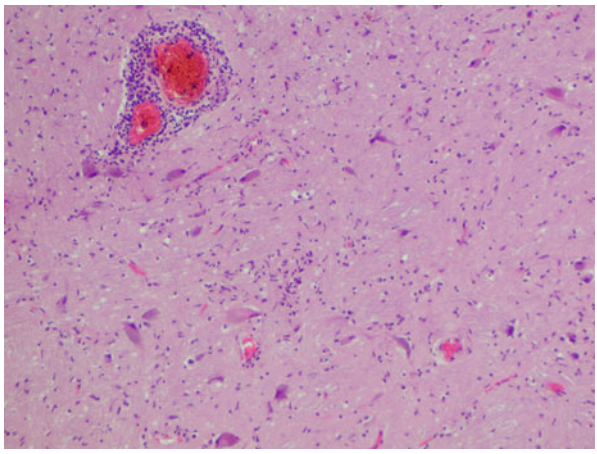

Fig. 30.6 Photomicrograph of brain in a child with acute viral encephalitis, high-magnification H&E stain showing perivascular lymphocytic infiltrate and microglial nodules (Hematoxylin and Eosin, H&E ×20)

Ancillary Studies

If CSF can be collected early in the postmortem interval, the yield may be better. Studies have shown that mononuclear cell counts increase in relation to the postmortem interval, and the cells can become vacuolated after about 12 h postmortem. Cisternal and ventricular CSF typically have none to only a few cells, compared to lumbar CSF (Morris and Harrison 2006). Although assessment of mononuclear cell counts may be variable, the existence of neutrophils in postmortem CSF may be helpful in determining the presence of infection, and therefore cell counts should be considered; however, obtaining CSF samples for culture and/or DNA and RNA extraction for PCR may prove more beneficial in helping to determine the infectious etiology.

Fresh tissue for snap freezing should also be considered in cases of suspected meningoencephalitis. This can allow for further testing using molecular techniques.

Malaria

The estimates of disease burden from malaria vary widely. For 2008, the World Health Organization estimated that 80 % of deaths from malaria occurred in children younger than 5 years of age with the majority of deaths in sub-Saharan Africa (Crawley et al. 2010). Substantial overlap with HIV infection exists and is associated with fatality. The symptoms of severe malaria caused by all species are the same symptoms recognized in sepsis. Headache, chills, muscle aches, vomiting, and anorexia are common. Impaired consciousness, seizures, respiratory distress, severe anemia, hypoglycemia, metabolic acidosis, and hyperlactatemia are the most frequently reported clinical and laboratory features reported in children with severe falciparum malaria.

Postmortem Macroscopic and Microscopic Examination

Most autopsy series addressing malaria as a cause of death are in adult populations, and the macroscopic findings have been found to be nonspecific. The method of diagnosis consists of histopathologic findings of malarial pigment-laden red blood cells in the capillaries of multiple organs and visualization of the parasites on Giemsa-stained peripheral smears (Menezes et al. 2012). Nested PCR can be used to identify the parasite in paraffin-embedded tissue samples, and immunofluorescence can also be used to identify the parasites in infected red blood cells.

Respiratory Infections

Of the diseases that cause death in children, the most common are respiratory infections and in particular lower respiratory-tract infections (i.e., pneumonia). Pneumonia is one of the most common infections worldwide with a high morbidity and high mortality, particularly in developing countries. *Streptococcus pneumoniae* is the most common bacterial cause of pneumonia. Viruses cause approximately 95 % of pneumonias in infancy and are the most common cause of pneumonia in all age groups. Influenza A, influenza B, respiratory syncytial virus, adenovirus, and parainfluenza virus 1, 2, and 3 are the most common respiratory viruses causing pneumonia. In industrialized countries upper and lower respiratory viral infections have a mortality of 1–3 % among children less than 5 years of age, and in developing countries the mortality reaches 10–15 % (Alter et al. 2011).

In children aged from 3 weeks to 15 years, lower respiratory-tract viruses and *Streptococcus pneumoniae* are common pathogens that cause community-acquired pneumonia. Chlamydia is also common in these age groups, although pneumonia is caused by *Chlamydia trachomatis* in infants less than 3 months of age, whereas *Chlamydia pneumoniae* is more common in children older than 3 months. *Bordetella pertussis* is also responsible for causing pneumonia in infants less than 3 months of age, and in children aged from 4 months to 15 years, *Staphylococcus aureus* and *Mycoplasma pneumoniae* are common pathogens (Alter et al. 2011).

In older adolescents, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Streptococcus pneumoniae* are also common causes of pneumonia, with *Mycoplasma pneumoniae* being the most common cause (Alter et al. 2011).

In cases of clinically diagnosed or suspected pneumonia, it is important to review the clinical record and in particular imaging and laboratory studies. Sections from the lungs should be aseptically sampled, placed in a sterile container, and sent for microbial evaluation. Samples have the best yield if they are collected as early as possible in the postmortem interval. In collecting the sample, cleansing or searing the lung surface and sampling deep areas will also give the best results. Samples for viral evaluation should be collected into appropriate containers and media.

Postmortem Macroscopic and Microscopic Examination

Bacterial pneumonias can either have patchy consolidation (bronchopneumonia) or involvement of large areas or an entire lobe (lobar pneumonia), or both patterns can overlap. Bronchopneumonia is often multilobed and bilateral, and lobar pneumonia can be boggy and intensely congested, densely red, firm and airless (red hepatization), or with a confluent grayish-brown dry appearance (gray hepatization). Bacterial pneumonias can progress and cause abscess formation, empyema, and bacteremic dissemination with endocarditis, meningitis, or suppurative arthritis.

Atypical (viral and mycoplasma) pneumonias may be patchy or involve entire lobes. The lung often appears intensely congested (dark red/blue) and subcrepitant. Pleuritis, empyema, and pleural effusions are not typically associated with viral or mycoplasma pneumonias. With atypical pneumonias, there may be superimposed bacterial infection showing either patchy consolidation, lobar consolidation, or both, as in primary bacterial pneumonias. With influenza respiratory infections, mucosal edema and hyperemia, tonsillitis, vocal-cord edema, and abundant mucus may be present.

Histologically, in bacterial bronchopneumonias there is suppurative inflammation consisting of neutrophils that fill the bronchi, bronchioles, and alveoli (Fig. 30.7). In the early stage of lobar pneumonia, vascular engorgement and fluid, sparse neutrophils, and abundant bacteria can be seen in the alveoli. In the red-hepatization stage of lobar pneumonia, there is a confluent acute inflammatory infiltrate with red blood cells, neutrophils, and fibrin filling the alveoli. Resolution with a lack of the red cells and a persistent fibrinopurulent exudate is seen in the stage of gray hepatization.

The histological pattern of most viral and mycoplasma pneumonias depends on the severity of the infection. The trachea and bronchi are often inflamed. Atypical pneumonias characteristically involve the interstitium with a mononuclear infiltrate consisting of lymphocytes, histiocytes, and occasional plasma cells. In acute infection, neutrophils may also be present, and there can be proteinaceous material within the alveoli and hyaline membranes similar to those seen in hyaline-membrane disease. Certain viruses may cause epithelial necrosis (e.g., herpes simplex, varicella, and adenovirus), epithelial giant cells with nuclear or cytoplasmic

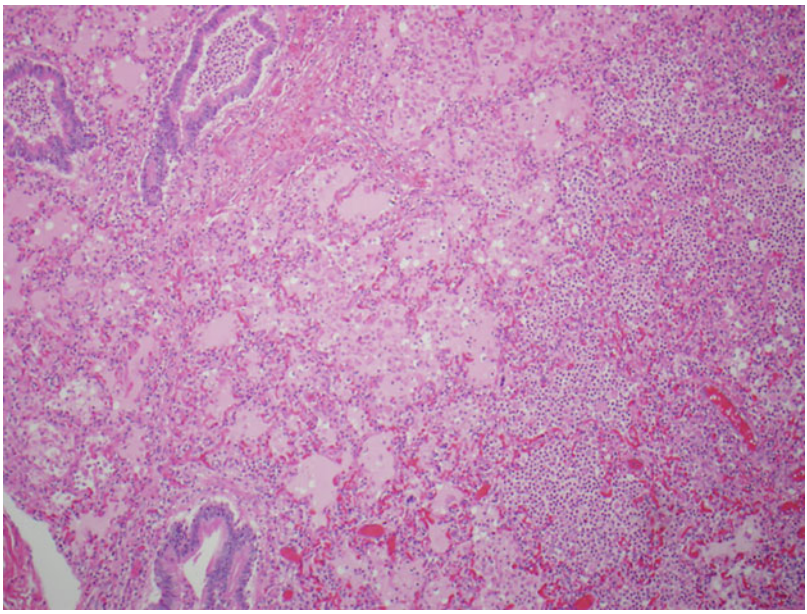

Fig. 30.7 Lungs with acute bacterial bronchopneumonia, medium-power H&E stain showing acute multifocal areas of acute inflammatory cells within the alveoli and bronchioles. There is also associated edema and congestion (Hematoxylin and Eosin, H&E ×10)

inclusions (e.g., cytomegalovirus, measles), or cytopathic effects (Chong et al. 2009). Infection with respiratory syncytial virus shows acute inflammation involving medium and small bronchioles and most cartilaginous airways. The lumens can be occluded by epithelial cellular debris, macrophages, fibrin, and mucin, and intrabronchiolar syncytia can be seen adjacent to the cellular debris (Johnson et al. 2007).

Cystic Fibrosis

Cystic fibrosis is a multisystem genetic disease caused by mutations in a gene that encodes the cystic fibrosis transmembrane-conductance regulator (CFTR) protein that functions mainly as a chloride channel. The sweat test is the most readily available way of establishing a diagnosis, although newborn screening is currently done by measuring immunoreactive trypsinogen (IRT) in blood spots. A high IRT is suggestive of pancreatic injury which may be indicative of cystic fibrosis. Cystic fibrosis affects fluid secretions in exocrine glands and the epithelial lining of the respiratory, gastrointestinal, and male reproductive tracts. Histologically, it does not affect the sweat glands. In this disease, there is abnormal viscid mucus secretion that obstructs passages in the lungs, pancreas, liver, intestines, and gonads.

Although survival has improved over time, at least 80 % of cystic fibrosis–related deaths are due to respiratory insufficiency (O'Sullivan and Freedman 2009). Cystic-fibrosis pulmonary disease is characterized by chronic pulmonary infection, progressive bronchiectasis, gas trapping, hypoxemia, and hypercarbia. At birth, the lungs in cystic fibrosis are normal; however, early on, the lungs become inflamed. Patients with cystic fibrosis commonly get *Pseudomonas aeruginosa* respiratory infections that initially grow as a non mucoid strain. Eventually the organism synthesizes biofilms and becomes difficult to eradicate with conventional antibiotics. These patients can also become infected with other microbes including *Burkholderia cepacia, Stenotrophomonas maltophilia*, methicillin-resistant *Staphylococcus aureus* (MRSA), and atypical mycobacteria. During the neonatal period other signs and symptoms of cystic fibrosis include meconium ileus, jaundice, intestinal atresia, abdominal or scrotal calcifications, and pancreatic insufficiency. Pancreatic insufficiency often leads to protein and fat malabsorption manifested by diarrhea, abdominal distention, poor weight gain, and significant failure to thrive. Malnutrition and dehydration can result in death. Meconium ileus is a common cause of death in neonates with cystic fibrosis (Oppenheimer 1981). During infancy, persistent infiltrates are commonly present on chest x-ray, and commonly these infants have *Staphylococcus aureus* or *Hemophilus influenza* pneumonia. In early infancy, acute respiratory infections commonly are the cause of death, and in late infancy into childhood, chronic pulmonary changes are usual, with or without superimposed acute pneumonia. In addition, infants may have abdominal distention, chronic diarrhea, cholestasis, and failure to thrive. During childhood into adolescence, chronic pansinusitis or nasal polyps, steatorrhea, rectal prolapse, intussusception or intestinal obstruction, pancreatitis, liver disease, bronchiectasis, hemoptysis, bronchopulmonary aspergillosis, and delayed puberty may be present (O'Sullivan and Freedman 2009). Sudden death can occur from a volvulus with intestinal ischemia in patients with cystic fibrosis. In addition, mucus plugging, duct dilation, and fibrosis affect the pancreas in up to 90 % of patients with cystic fibrosis. A significant proportion of patients with cystic fibrosis may also develop diabetes mellitus (most commonly type 2 diabetes) that is characterized by a progressive decline in pancreatic β-cell function and β-cell mass.

Postmortem Macroscopic and Microscopic Examination

In patients dying from the pulmonary complications of cystic fibrosis, the lungs typically contain extensive mucus plugging of the tracheobronchial tree and dilated, fusiform, vascular bronchi (bronchiectasis). There may be consolidation due to both secretions and pneumonia. A green discoloration is usually indicative of Pseudomonas infection. With pneumonia, abscesses are commonly present. Examination of the pancreas can show accumulation of mucus in the small ducts (mild cases) to complete mucus plugging of the ducts with atrophy of the exocrine glands and fibrosis. In neonates and infants, mucus plugs can also occur in the small intestine causing small-bowel obstruction, also known as meconium ileus. Rarely, infarcted

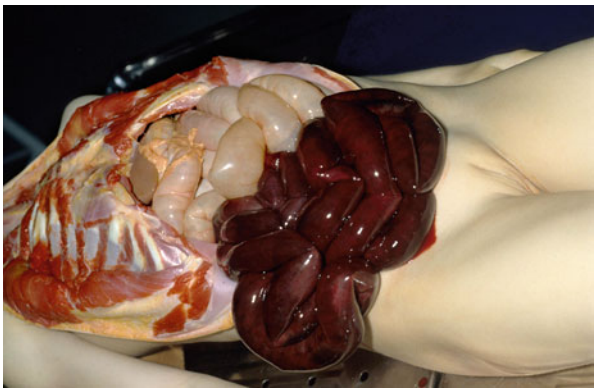

Fig. 30.8 Small intestines with necrosis due to intussusception in a case of cystic fibrosis

bowel may be seen associated with intussusception as a result of inspissated material in the bowel (Fig. 30.8). In approximately 5 % of cases, there is mucus plugging of the bile ducts that can result in biliary cirrhosis.

Early microscopic structural changes in the lungs that can be seen in neonates and infants with cystic fibrosis include hyperplasia and squamous metaplasia of the epithelium, hypertrophy, and hyperplasia of the bronchial submucosal mucus glands, thickening of the epithelial reticular basement membrane, and an increase in airway smooth muscle (Regamey et al. 2011). Chronic respiratory changes commonly seen in cystic fibrosis include atelectasis, mucus obstruction with distention of the bronchioles, acute and chronic inflammation, bronchiectasis, cyst formation, and fibrosis. Pulmonary hypertensive vascular changes are also common. Superimposed infection is common in both early and late stages with *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* (Hamutcu et al. 2002). Microscopic changes in the pancreas include mild-to-moderate dilation of the pancreatic ducts with mucus plugging and fibrosis of the exocrine pancreas with sparing of the islets. There may also be amyloidosis of the islets which can be a feature of diabetes in patients with cystic fibrosis.

Immune-Related Disease

Immune dysfunction affects approximately 25 % of children in some countries and is linked to asthma and allergies, type 1 diabetes mellitus, juvenile arthritis, otitis media, recurrent infections, celiac disease, Kawasaki disease, and childhood acute leukemia. Pediatric immune and inflammatory diseases associated with misdirected, exaggerated, or dysfunctional immune responses pose an increased risk of other conditions and diseases that impact health later in life (Dietert and Zelikoff 2010). In addition to increasing the risk of chronic disease, infections, asthma and allergies, diabetes, and acute leukemia also increase the risk of mortality in the pediatric population and are some of the diseases likely to be encountered at autopsy.

Asthma

Asthma is a chronic disease characterized by episodic wheezing, dyspnea, chest tightness, and cough due to inflammation of the airways causing bronchoconstriction and airflow limitation. Most asthmatics have a genetic predisposition to type I hypersensitivity (atopy) which begins during childhood. Wheezing episodes in asthmatics can be triggered by environmental antigens (although any antigen can be implicated) or triggered by respiratory infections. Although asthma is an uncommon cause of death, estimates reported in 2001 in the USA showed nearly 4,000 deaths occur annually (Centers for Disease Control and Prevention). Mortality data from 1999 to 2009 show that approximately 14 % of childhood deaths attributed to respiratory diseases were due to asthma. Viral respiratory infections appear to effect aspects of asthma. In infancy, viral infections, including RSV, rhinovirus, metapneumovirus, parainfluenza, and coronavirus, are associated with wheezing episodes, and certain viral infections, particularly RSV, are believed to be important in initiating the development of asthma. Respiratory viruses have also been shown to be associated with acute exacerbations in children with established asthma. In addition, allergy and viral infections appear to synergistically increase the risk of acute exacerbations of asthma by damaging airway epithelium (Busse et al. 2010). Asthma deaths have been reported in patients in association with food allergy, anaphylaxis (Shen et al. 2009), sickle-cell disease, illicit drug use (Greenberger et al. 1993), and in patients participating in sports activities (Becker et al. 2004).

Postmortem Macroscopic and Microscopic Examination

In situ examination shows hyperinflation of the lungs that appear to overfill the chest and obscure the heart. Further examination of the lungs typically shows both hyperinflation and areas of atelectasis. Examination of the airways shows thick tenacious mucus plugs within the bronchi and bronchioles.

On histology, there is typically thickening of the basement membrane of the bronchial epithelium, hypertrophy of the bronchial-wall muscle, enlarged submucosal glands, edema, and inflammation consisting of predominantly eosinophils and mast cells within the bronchial epithelium. Mucus plugs are not unusual (Fig. 30.9). Curschmann spirals and Charcot-Leyden crystals may be present.

Allergies and Anaphylaxis

Anaphylaxis is a serious allergic reaction with a rapid onset that involves both nonimmune activation and immune activation in previously sensitized individuals. Anaphylaxis commonly involves the synthesis of IgE in response to allergen exposure. The allergen becomes fixed to IgE high-affinity receptors on the surface membranes of mast cells and basophils and leads to the release of inflammatory mediators including histamine, tryptase, carboxypeptidase A, proteoglycans, leukotrienes, prostaglandins, cytokines (Il-6, IL-33, TNr-α), and platelet-activating

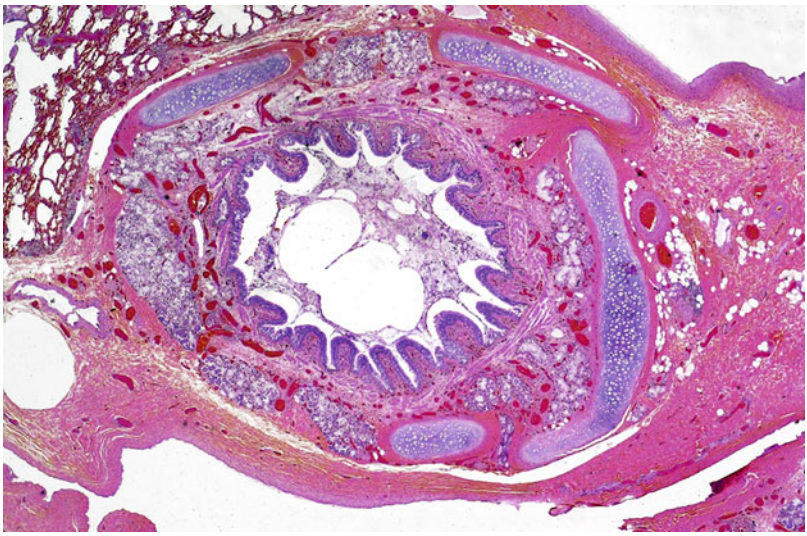

Fig. 30.9 Bronchus with mucus plugging in a patient with asthma, low-magnification H&E stain (Hematoxylin and Eosin, H&E ×10)

factors. Mainly mast-cell degranulation leads to systemic vasodilation that is associated with a sudden fall in blood pressure, bronchial mucosal edema, bronchoconstriction, and dyspnea (Unkrig et al. 2010). Triggers for anaphylaxis include certain types of food, medications, venoms, latex, occupational allergens, seminal fluid, and inhaled allergens. Food allergies are the most common trigger of anaphylaxis seen in hospital emergency room visits. Although most persons can be adequately treated, when death occurs, the symptom onset is most commonly within 0–30 min. Death occurs within the first hour of onset and is usually due to asphyxiation from laryngeal or oropharyngeal swelling, collapse from hypotensive shock, cardiac arrest, or acute severe bronchoconstriction causing respiratory failure and arrest (Greenberger et al. 2007). Peanut and tree-nut ingestions account for >85 % of all food-related anaphylactic deaths in the USA. Food allergy–induced anaphylaxis can occur without skin manifestations. Risk factors for fatal food allergy–induced anaphylaxis include asthma, failure to use epinephrine auto-injections promptly, a prior history of severe reactions, known food allergy, denial of symptoms, and adolescent or young-adult age (Greenberger and Ditto 2012). The relationship between asthma and severe anaphylactic reactions, in particularly food, is well established. A high percentage of fatal and near-fatal anaphylactic reactions have been reported in children, adolescents, and young adults with known asthma in which the mechanism of death was most commonly attributed to severe bronchospasm and respiratory arrest (Sampson et al. 1992). In examining deaths from possible anaphylaxis, it is important to elicit a history of known allergies and/or asthma, possible witnessed or documented exposures to

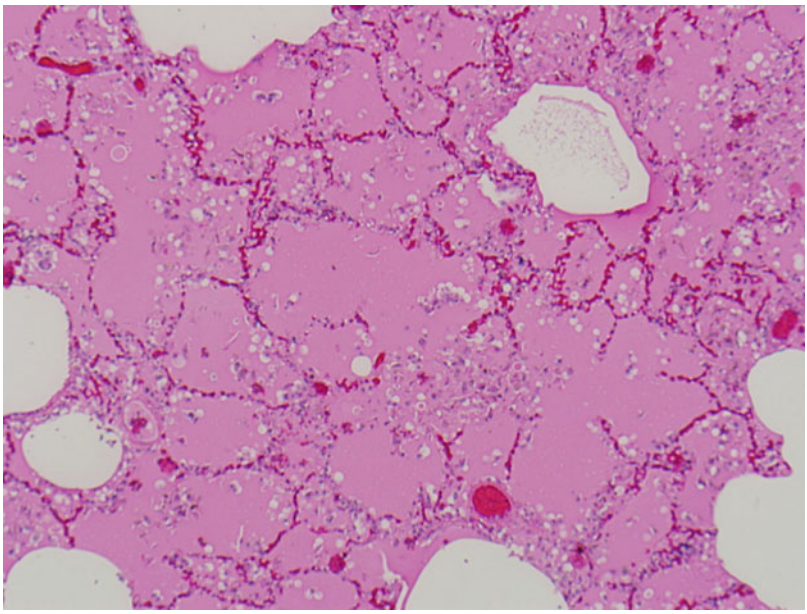

Fig. 30.10 Lungs with intense pulmonary edema in an anaphylactic reaction (Hematoxylin and Eosin, H&E ×10)

allergic triggers, as well as circumstances, timing, and symptoms prior to death. Consideration should be made in obtaining postmortem samples for toxicology, chemistry, and other ancillary tests prior to beginning the autopsy. In suspected anaphylactic deaths, measuring serum tryptase, histamine, diamine oxidase, and trigger-specific IgE antibody levels should be considered.

Postmortem Macroscopic and Microscopic Examination

Macroscopic findings may be nonspecific or absent. Pulmonary congestion with or without edema, intra-alveolar hemorrhage, increased tracheal and bronchial secretions, visceral congestion, or cutaneous edema may be present (Low and Stables 2006). There may also be mucus plugging, hyperinflated lungs, pharyngeal or laryngeal edema, and tracheal and vocal cord petechial hemorrhages (Greenberger et al. 2007; Pumphrey and Roberts 2000). In cases of venom-related anaphylaxis, there may be evidence of a sting present on the skin.

There may be increased numbers of mast cells present with degranulation seen microscopically in the tracheal or laryngeal mucosa. Mucus plugging may be seen in the bronchial airways as well as evidence of chronic asthmatic changes (see above). Pulmonary edema may also be seen in some cases (Fig. 30.10).

Ancillary Testing

Blood can be drawn from the iliac vein or inferior vena cava for serum tryptase levels. Tryptase levels in living patients can be used as a marker for mast cell number

(α-tryptase) and mast cell activation (β-tryptase). Tryptase is highly stable and can be assessed several days postmortem (Edston and van Hage-Hamsten 1998). Although there is variability in the interpretation of postmortem tryptase levels, several studies have shown that values above 11.4 μg/L (the upper normal limit in living subjects) are suggestive of anaphylactic deaths, though increased levels are not specific and have been shown to be elevated in other non anaphylactic deaths (Mayer et al. 2011). There have been mixed reports as to whether or not tryptase levels increase with increasing postmortem intervals. When the suspected allergen trigger is known, trigger-specific IgE antibody levels are also possible. Although elevated IgE antibody levels do not prove anaphylaxis, they can help determine the type of allergen responsible for the anaphylaxis (Prahlow and Barnard 1998).

Diabetes Mellitus

Diabetes affects an estimated 16 million people in the USA and 171 million worldwide (Wild et al. 2004). Although all forms of diabetes share the common feature of hyperglycemia, the pathogenic process resulting in hyperglycemia differs. Type 1 diabetes mellitus accounts for approximately 10 % of all diabetes cases. The incidence of type 1 diabetes in children increases with age and is highest among children 10–14 years old (Karvonen et al. 2000). In type 1 diabetes there is an absolute deficiency of insulin caused by destruction of the β-cells of the pancreas that is usually either immune-related or idiopathic. The onset of type 1 diabetes can occur at any age, but usually occurs in children beginning at around the age of 4 years, peaking in adolescence. Type 1 diabetes has genetic associations that have been mapped to at least 20 loci. By far, the most important linkage is to class-II MHC (HLA) genes with T-cell and humoral-mediated (TNF, IL1, NO) destruction of pancreatic β-cells resulting in absolute insulin deficiency. Type 2 diabetes is characterized by a peripheral resistance to insulin action and inadequate secretory response by the β-cells of the pancreas.

Diabetes is the leading cause of blindness and end-stage kidney disease in the Western hemisphere. Diabetes also contributes to the high incidence of cardiovascular disease. Diabetic children are also prone to infections. Within the first 10 years after a diagnosis of diabetes, acute complications are a leading cause of death (Secrest et al. 2010). Acute complications include diabetic ketoacidosis (DKA), hyperosmolar hyperglycemic state (HHS), hypoglycemia, and sudden death (including "dead in bed" syndrome). Diabetic ketoacidosis is predominantly seen in type 1 diabetics and is commonly the presenting symptom for the diagnosis of new-onset type 1 diabetes mellitus, particularly in children under the age of 4 years (Liu et al. 2010). Although most cases of DKA are adequately treated if diagnosed quickly, because it evolves within a short time frame, the mortality rate is around 2–5 %. In hospitalized children treated for DKA, death is often attributed to cerebral edema (Edge et al. 1999).

HHS is a hyperosmolar hyperglycemic state without significant ketosis or acidosis. HHS occurs most commonly in type 2 diabetics with other simultaneous

illnesses. In such cases, there is sufficient endogenous insulin release to suppress counter regulatory secretion of other hormones but inadequate insulin release to suppress hyperglycemia. Clinically, the onset of HHS can occur over several weeks, and hyperglycemia is more pronounced than in DKA which results in greater osmotic diuresis and dehydration. The mortality rate is approximately 15 %. The findings of a high glucose concentration with no significant ketone bodies are consistent with HHS (Hockenhull et al. 2012).

Type 1 diabetes mellitus increases the risk of sudden death in children. Multiple studies have reported sudden unexplained deaths in which the deceased was found dead in bed with no evidence of sweating or terminal struggle and no clear-cut cause of death found at autopsy, coined "dead in bed" syndrome. Since the first reports describing the characteristics of dead in bed syndrome, this syndrome has been reported in 22–45 % of all sudden unexplained death in young type 1 diabetics. These deaths have been theorized to result from hypoglycemia, malignant cardiac arrhythmias, cardiac autonomic neuropathy, hypoglycemia-associated autonomic failure, or a combination of these (Secrest et al. 2011). Current evidence suggests that those at risk for dead in bed syndrome may have reduced parasympathetic activity due to long-standing diabetes and early stages of cardiac autonomic neuropathy that result in ventricular arrhythmias or that hypoglycemia may result in abnormal cardiac repolarization as evidenced by long QT intervals and subsequent ventricular tachyarrhythmias (Secrest et al. 2011; Gill et al. 2009). As part of the investigation of deaths in diabetic children including sudden unexplained deaths, ancillary testing is important in ruling out other nonnatural causes. In particular, vitreous chemical analysis for determining electrolytes, glucose, and ketones may be the only positive finding. Consideration should also be made to obtain samples for possible molecular testing to help better determine the cause of death.

Postmortem Macroscopic and Microscopic Examination

In the absence of other natural disease (e.g., infection, malignancy), often there are no macroscopic abnormalities in the pancreas and other organs of diabetic children. In children with long-standing poorly controlled diabetes, there may be renal changes consisting of granular and thinned cortices or sequelae of macro- and microvascular disease.

On histological examination of the pancreas, leukocyte infiltration of the islets may be present, most commonly in recent-onset type 1 diabetes. In rapidly advancing disease, the islets may be small to inconspicuous. The kidneys typically show thickening of the basement membranes in the renal medullas and glomeruli, hyaline arteriosclerosis, diffuse mesangial sclerosis, and nodular glomerulosclerosis in long-standing disease. Acute pyelonephritis and necrotizing papillitis are also commonly seen in association with diabetes.

Ancillary Testing

Samples for microbiology studies are advised and in particular may be helpful when macroscopic examination reveals a potential source of infection. Postmortem blood

Table 30.3 Postmortem vitreous findings in diabetes, diabetic ketoacidosis, and hyperosmolar hyperglycemic state

	Glucose	Keto acids
Diabetes	++	–
DKA	+++	+
HHS	+++++	–

DKA - Diabetic ketoacidosis
HHS - Hyperosmoler hyperglycemic state

samples and tissue samples should be obtained and held for possible future molecular studies. Vitreous should be obtained and tested for electrolytes (see diarrheal infections, ancillary studies), glucose, and ketones. Acetone and β-hydroxy butyrate (βHB) levels can be determined from postmortem blood or vitreous samples. Blood βHB levels of >250 μg/mL and acetone levels >90 mg/L (9 mg/dL) are considered significant although as this may indicate an extrinsic source, it should not be used in isolation without vitreous glucose levels to diagnose ketoacidosis. Postmortem blood samples are not suitable for glucose levels due to rapid decrease (Palmiere and Mangin 2012). Vitreous glucose levels are generally lower than that in the blood (85 % of plasma levels) but are less affected by postmortem changes and are the preferred sample for testing glucose levels (Palmiere and Mangin 2012).

Table 30.3 shows typical vitreous-chemical findings in diabetes, diabetic ketoacidosis, and hyperosmolar hyperglycemic state.

Sudden Unexplained Death in Childhood and Seizure Disorders

Generalized seizures in children can be caused by a number of conditions including infections, metabolic or toxic disorders, vascular malformations, space-occupying lesions such as neoplasms, or structural central nervous system lesions. Lafora body disease and Unverricht-Lundborg disease are two well-defined autosomal recessive genetic disorders that cause progressive myoclonic epilepsy. The onset of seizures is earlier in Unverricht-Lundborg (6–13 years of age) than in Lafora body disease (15 years of age). In both diseases, there are intractable seizures, psychosis/emotional lability, and intellectual decline. Another cause of intractable seizures is Rasmussen encephalitis. This is an inflammatory disorder of possible immune etiology with features that are histologically consistent with chronic viral encephalitis. Although these types of cases are less likely to be encountered in forensic practice, specific histological changes seen in these conditions can help differentiate them from other causes of seizure disorders in children.

Sudden unexpected death in childhood (SUDC) is defined as death in a child older than 1 year of age in which the death remains unexplained following a thorough review of the history and circumstances of death and a complete autopsy with ancillary testing (Krous et al. 2005). Although rare, SUDC occurs most commonly between the ages of 1 and 4 years with an annual incidence of 1.2/100,000. Such cases are likely to be investigated by a forensic pathologist. SUDC most commonly is due to occult cardiac anomalies, intracranial hemorrhage,

or infections (Somers et al. 2006). In evaluation of SUDC cases from a registry, 24 % of children were found to have a history of febrile seizures that reportedly correlated with a fivefold increase in incidence compared to the general pediatric population (Kinney et al. 2009). An association has been shown between sudden death in children with a history of, or family history of, febrile seizures and hippocampal and temporal-lobe abnormalities. In these cases, the children were found dead in bed in a prone position, and the mechanism of death appeared analogous with that of sudden death in epilepsy. Febrile seizures involve the development of seizure activity that is associated with a febrile illness with no associated underlying central nervous system infection. These can either be simple seizures (e.g., tonic–clonic seizures lasting less than 10 min and occurring only once within 24 h) or complex seizure (e.g., prolonged focal or multiple seizures lasting greater than 10–15 min and with multiple seizures within a 24-h period). Most febrile seizures are simple and occur between 6 months and 36 months of age. In 30–50 % of cases, there is recurrence of the seizures, especially if the onset is before 1 year of age (Jones and Jacobsen 2007). The occurrence of an initial febrile seizure has been shown to be associated with a history of seizures in first- or second-degree relatives, day-care attendance, developmental delay, viral infections (e.g., influenza A, human herpesvirus 6, metapneumovirus), iron-deficiency anemia, and vaccinations (e.g., diphtheria-tetanus-whole cell pertussis [DTP] and measles, mumps and rubella [MMR] vaccines) (Jones and Jacobsen 2007).

Epilepsy is a chronic brain disorder characterized by recurrent seizures as a result of excessive discharge of neurons. In childhood, epilepsy can be symptomatic with a known cause, cryptogenic when an underlying condition is suggested, or idiopathic when there is no associated neurological condition or history of developmental delay (Donner et al. 2001). The mortality rate of individuals with epilepsy is two to three times higher than the general population. In children, the mortality rate may be 90 times higher than children without epilepsy, and while most cases of epilepsy can be explained by an underlying condition, there is a proportion of these cases in which the circumstances and autopsy fail to explain the death (Donner 2011). Such cases are classified as sudden unexpected death in epilepsy (SUDEP). Risk factors for SUDEP include early onset of seizures, refractory generalized tonic–clonic seizures, and polytherapy. A single mechanism is unlikely to explain all cases of SUDEP. Impaired brainstem function and heritable arrhythmogenic syndromes and channelopathies may help explain the mechanisms of SUDEP (Donner 2011). SUDEP refers to a witnessed or unwitnessed, nontraumatic, and non drowning death in a patient with epilepsy with or without evidence of a seizure, excluding documented status epilepticus, in which postmortem examination reveals no toxicological or anatomical cause of death (Nashef et al. 2012). It has been proposed that if investigation of the circumstances surrounding death indicates status epilepticus, for SUDEP to be excluded as the cause of death, the duration of the seizure activity should be more than 30 min (Nashef et al. 2012). Moreover, asphyxia or suffocation has been implicated as a cause of sudden death in persons with epilepsy particularly when the body position is such that the airway could be

obstructed. As a high percentage of SUDEP deaths occur at night with the decedent found dead prone in bed, asphyxia or suffocation may at least contribute to death. Ascribing SUDEP solely to asphyxia or suffocation may be simplistic as studies have shown that cerebral mechanisms also lead to respiratory compromise in the peri-ictal state. Additionally, when death occurs in water without circumstantial or autopsy evidence of submersion, a proposed classification is "possible SUDEP." These instances and further categorization of SUDEP cases have been proposed with examples of scenarios that may help in subclassifying cases (Nashef et al. 2012). In evaluating pediatric sudden deaths, it is imperative to investigate the circumstances surrounding the death, any known medical history including the character of the seizures (e.g., presence of intractable seizure and history of generalized tonic–clonic seizures) (Lathers et al. 2011), along with full postmortem examination and ancillary testing. Toxicology and other biochemical tests may prove to be useful at autopsy, but only a full investigation with negative results can permit a classification of SUDC or SUDEP.

Postmortem Macroscopic and Microscopic Examination

Fresh hemorrhage or bite marks on the lips, tongue, or buccal mucosa, evidence of urine incontinence, or signs of asphyxia (the latter are signs of venous engorgement and not asphyxia) may be indicative of a terminal seizure. Macroscopic examination in most instances of primary seizure disorders appears normal or may show only minimal changes in the brain. Changes may include asymmetry of the hippocampus. Neoplasms (mostly primary CNS) and vascular malformation have been described most commonly in the temporal lobes of patients who have undergone surgical biopsy or resections. With long-standing Rasmussen encephalitis, there may be extensive unilateral atrophy and dilated ventricles. Long-standing febrile seizures or prolonged status epilepticus can lead to post-convulsive hemiplegia in which unilateral hemispheric edema may be present. In chronic cases widespread atrophy can be seen.

Aside from neoplasms and vascular malformations, the most consistent histological finding is gliosis/sclerosis of Ammon's horn. In some cases, there may be focal accumulations of dysplastic neuroglial cells commonly with perinuclear halos of the glial cells (e.g., hamartoma) in the hippocampus or temporal lobes. With post convulsive hemiplegia, large areas of cystic cortex with subjacent gliotic white matter are often seen along with the typical Ammon's-horn sclerosis.

The typical finding seen in Lafora-body disease is round inclusion bodies with deep hematoxyphilic, PAS-positive central core. These are similar in appearance to corpora amylacea (Lafora bodies) in the cytoplasm of neurons and astrocytes in the cerebral cortex, basal ganglia, thalamus, substantia nigra, cerebellar cortex, and dentate nucleus. Swelling, vacuolation, and loss of Purkinje cells with Bergmann gliosis are the typical microscopic findings seen in Unverricht-Lundborg disease.

Ancillary Testing

Blood, urine, bile, vitreous, and gastric-content samples should be obtained to allow for quantification of antiepileptic-medication levels, alcohol, and drugs of abuse. These samples can prove particularly helpful in those cases where there are no significant postmortem findings.

Childhood Malignancies

Although cancer is a leading cause of death in childhood, most children are diagnosed and treated; those who die usually die within the hospital or in hospice care. Such cases are unlikely to come to the attention of the forensic pathologist. Table 30.4 depicts the most common types of childhood cancers by age groups.

Although mortality rates for all childhood cancers have decreased substantially for most cancers (with the exception of nervous-system cancers, which have risen from 17.8 % in 1975 to 25.7 % in 2006), leukemia (AML and ALL) remains the leading cause of cancer death in children followed by brain cancer and other nervous system tumors (Smith et al. 2010). In infants less than 1 year of age in the USA, death from malignancies falls markedly below other causes of death, ranking well below all other systemic diseases. Neuroblastoma is the most common non-CNS tumor diagnosed in infants and accounted for up to 12 % of all childhood cancer deaths in 2006 (Smith et al. 2010). Neuroblastomas most commonly arise in the adrenal medulla and typically are hemorrhagic.

In children from 1 to 19 years of age, malignancies are the leading cause of natural death in the USA (see Table 30.1). Although sudden unexpected death in children due to malignancies is exceedingly rare, it does occur, and those cases are likely to come to the attention of the forensic pathologist. In such cases, sudden death generally occurs due to direct involvement of vital structures including primary-cardiac or central nervous system tumors or sequelae such as hemorrhage secondary to leukemia or lymphoma (Somers et al. 2006). A number of case studies have been published documenting sudden death in children with undiagnosed brain tumors (primarily glioblastomas) (Matschke and Tsokos 2005; Manousaki et al. 2011; Sutton et al. 2010) and leukemia and lymphoma (Somers et al. 2006). Sudden deaths in children have also resulted from tumor emboli, pulmonary emboli, and hemorrhage due to underlying malignancies (Van den Heuval-Eibrink et al. 2008; Zakowski et al. 1990; Park and Prahlow 2011).

Childhood Tumors and Malignancies of the Nervous System

Cancer deaths due to brain and other nervous-system tumors have proportionally increased compared to other common childhood cancers (Smith et al. 2010). In the USA, the overall incidence from 2004 to 2008 for primary-brain and

Table 30.4 Most common childhood cancers among both genders and all races. Based on SEER Cancer Incidence Rates from 2005 to 2009

<1	1–4	5–9	10–14	15–19
Leukemias	Leukemias	CNS neoplasms	CNS neoplasms	Lymphomas
Neuroblastoma	CNS neoplasms	Leukemias	Leukemias	Malignant epithelial neoplasms and melanomas
CNS neoplasms	Neuroblastoma	Lymphomas	Lymphomas	CNS neoplasms
Retinoblastoma	Renal tumors	Soft tissue tumors	Malignant epithelial neoplasms and melanomas	Leukemias
Germ cell neoplasms	Soft tissue sarcomas	Malignant bone tumors	Malignant bone tumors	Germ cell and gonadal tumors
Soft tissue sarcomas	Lymphomas			Soft tissue sarcomas
Renal tumors	Retinoblastoma			Malignant bone tumors

CNS tumors in the 0–19 age group was 5.05 per 100,000, with a predominance of malignant tumors. Additionally, the incidence of malignancy was more prevalent infratentorially, among males and whites. CNS tumors in general had the highest incidence from infancy to 7 years of age and have the second highest rate of childhood cancer. Childhood brain tumors are associated with a number of genetic syndromes that include neurofibromatosis type I (associated with low-grade optic tract gliomas and other brain tumors) and type 2 (associated with acoustic neuromas), tuberous sclerosis (associated with CNS tubers and subependymal giant-cell astrocytomas), von Hippel-Lindau disease (associated with hemangioglioblastomas), and familial cancer predisposition syndromes (e.g., Li-Fraumeni syndrome associated with choroid plexus carcinomas) (Fleming and Chi 2012). Presenting symptoms in children with primary brain tumors include headaches, increased intracranial pressure, vomiting, and seizures. Most children with brain tumors who present with headaches also commonly experience vomiting and will have increased intracranial pressure and obstructive hydrocephalus (Fleming and Chi 2012). Low-grade tumors of the cerebral cortex may cause seizures, and as previously discussed, seizures can be a cause of sudden death in children.

Gliomas comprise approximately half of all primary CNS tumors occurring in children from 0 to 19 years of age (CBTRUS 2011). Gliomas encompass all tumors that arise from glial derivatives which include oligodendrogliomas, ependymomas, and astrocytomas, the latter of which accounts for 52 % of CNS malignancies in children under 20 years of age. Oligodendrogliomas typically do not present in childhood. Ependymomas generally present in young children with a mean age of

Table 30.5 WHO grading and characteristics of astrocytomas

WHO Grade	Tumor name	Histologic characteristics	Gross characteristics
I	Pilocytic astrocytoma	Hair-like processes, Rosenthal fibers	Well-circumscribed, cystic with mural nodule
II	Fibrillary astrocytoma	Increase in number of nuclei with atypia	Ill-defined, gray, firm or soft to gelatinous, possible cystic component
III	Anaplastic astrocytoma	Dense cellularity, greater nuclear pleomorphism, mitotically active	Ill-defined, soft to gelatinous, microcysts
IV	Glioblastoma	Pseudopalisades surrounding necrotic foci, vascular or endothelial cell proliferation	Diffusely infiltrating with distortion of anatomy; foci of firm to soft and necrotic, cystic components mixed with mucoid gray neoplastic tissue, possible hemorrhage; can appear well-defined with necrotic center (ring enhancing on CT)

4 years. Classic ependymomas generally occur as an intracranial neoplasm in children with 60 % occurring infratentorially and the other 40 % occurring supratentorially. Medulloblastoma (PNET) is one of the embryonal neuroepithelial tumors and is a common CNS tumor accounting for 20 % of all pediatric CNS tumors and comprising almost 40 % of all cerebellar tumors. The peak age for medulloblastoma is 4 years (CBTRUS 2011).

Astrocytomas

Low-grade astrocytomas (WHO grade I and II tumors) are the most common type of brain tumors in children and most often occur in the posterior fossa or optic pathway. Low-grade astrocytomas are amenable to treatment, and the prognosis is generally favorable with 5-year survival rates ranging from 84.7% to 96.6 % (CBTRUS 2011). High-grade astrocytomas (WHO grade III and IV tumors) are more common in adults but account for 10–20 % of pediatric tumors. In children with high-grade astrocytomas, the tumor generally grows quickly compressing or displacing surrounding structures with common presentations including seizures, cranial neuropathies, hemiparesis (Fleming and Chi 2012), and, less commonly, sudden death (Matschke and Tsokos 2005; Manousaki et al. 2011; Sutton et al. 2010). High-grade astrocytomas also have a tendency to recur.

Postmortem Macroscopic and Microscopic Examination

The gross and histological characteristics of astrocytomas are presented in Table 30.5.

Immunohistochemical stains show positive staining with GFAP in astrocytes, though high-grade tumors may not stain. Astrocytes may or may not stain with S-100. Labeling with MIB-1 (Ki-67) is used as an indicator of the proliferative index which correlates with survival.

Ancillary Testing

Sampling of tumor tissue and blood should be considered for possible cytogenetic and molecular studies. Malignant gliomas are associated with loss of heterozygosity on chromosomes 10 and 19q and deletion of chromosome 16p. Malignant gliomas are also associated with p53 gene mutations and EGFR gene amplifications on molecular analysis.

Childhood Leukemias

Leukemia is the most common childhood cancer with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) predominating. Although AML comprises only 15–20 % of childhood leukemias, it accounts for approximately 30 % of the deaths (Rubnitz et al. 2010). Age at diagnosis is inversely proportional to outcome, with a younger age at diagnosis associated with a better outcome (Rubnitz et al. 2010). Most cases of AML develop de novo although environmental exposures and inherited and acquired conditions (e.g., Down syndrome, Fanconi anemia, Shwachman-Diamond syndrome, neurofibromatosis type 1) are also associated with AML. From genetic analyses, t(9;11), t(8;21), and inv(16) mutations have been shown to be associated with a more favorable outcome, while -5, del(5q), -7, and abnormalities with 3q are associated with a poor outcome. New molecular markers (c-kit and FLT3) are also associated with a negative prognosis (Rubnitz et al. 2010). Children can present with pancytopenia, fever, fatigue, pallor, bleeding, bone pain, and infections. Disseminated intravascular coagulation (DIC) can occur with all AML subtypes but is most frequent in acute promyelocytic leukemia. In 15 % of cases, the CNS is involved and it can be mistaken for a primary CNS tumor. Children with AML may present with life-threatening complications including bleeding, leukostasis, tumor lysis syndrome, and infection.

Acute lymphoblastic leukemia is the most common malignancy in children and accounts for one-third of all pediatric cancers. The peak incidence is between 2 and 5 years of age. Acute lymphoblastic leukemia can be subdivided into precursor B-cell and precursor T-cell based on phenotype. B-cell precursor ALL is associated with a favorable outcome. ALL in infants is rare, and when it occurs it is usually of an immature B-cell phenotype (pro-B-ALL). Adolescents with ALL have a worse outcome compared to younger children. Children with Down syndrome have an increased risk of developing ALL (as well as AML). In T-cell ALL, translocations involving the T-cell receptor loci are present in approximately 35 % of cases, although T-ALL genetic studies have not been used to guide therapy (Harrison 2011).

Within the categories of follicular lymphomas and mantle-cell lymphomas, there are distinct variants that are exclusive to children and differ from those in adults. Pediatric follicular lymphoma presents with high-grade localized disease at both nodal (Waldeyer ring) and extranodal (e.g., testis, gastrointestinal tract) sites and does not express BCL-2 protein. Nodal mantle-zone lymphomas in children appear to have a low risk of progression and recurrence. They typically are associated with marked follicular hyperplasia and changes

Table 30.6 Basic immunohistochemistry findings in childhood acute leukemias

Marker	Interpretation	Comments
CD45	wk+	Indicates hematopoietic
TdT/CD34	+	Indicates blasts
CD117	+	Indicates myeloblasts
MPO	+	Indicates myeloid lineage
PAX-5/CD79a/CD22	+	Indicates B-cell lineage
CD3	+	Indicates T-cell lineage
HLA-DR	–	Indicates promyelocytic, erythroid, megakaryoblastic
CD68	+	Indicates monocytic
HgbA	+	Indicates erythroid
CD61	+	Indicates megakaryoblastic

resembling progressive transformation of germinal centers that are often difficult to differentiate from follicular lymphoma. Systemic Epstein Barr Virus (EBV) T-cell lymphoproliferative disease of childhood and hydroa vacciniforme-like lymphoma are two EBV-associated T-cell diseases that occur nearly exclusively in children of Asian and Central American descent. Systemic EBV T-cell lymphoproliferative disease is a highly aggressive disease with survival of only weeks to months and is usually associated with hemophagocytic syndrome. The diagnosis of leukemia or lymphoma is one based on presentation and sites of involvement (Jaffe 2009).

Postmortem Macroscopic and Microscopic Findings

On macroscopic examination there may be nonspecific findings. There may be evidence of blood within the gastrointestinal tract particularly in cases of AML with disseminated intravascular coagulation (DIC). Occasionally, when there is soft tissue extension (e.g., granulocytic/myeloid sarcoma, chloroma), there may be extramedullary spread seen in any organ including the skin, which may sometimes have a green hue. It is important to perform histological and immunohistochemical studies to confirm a suspected leukemia or lymphoma and to adequately profile them, especially since malignant pre-B- and pre-T-cell lymphoblasts appear morphologically similar. In addition, while precursor B-cell involvement is primarily that of leukemia, it can occasionally present with nodal and extranodal involvement. The same can be said of precursor T-cell leukemia. In terms of immunophenotype, lymphoblasts (B-ALL and T-ALL) may demonstrate considerable heterogeneity, aberrantly expressing opposite lymphoid lineage or myeloid markers. Table 30.6 illustrates an immunohistochemistry panel to help distinguish types of acute leukemias (Olsen et al. 2008).

Ancillary Testing

Peripheral blood and bone marrow smears can be obtained postmortem, but the yield can depend on the postmortem interval. The bone marrow sample can most easily be taken from a rib squeeze and smears made. The smears can be air-dried

and then stained with a Wrights stain. Postmortem blood clots can also serve as a sample. Although cytogenetic and flow-cytometry studies are critical in clinical leukemia diagnoses, they are generally not useful postmortem.

Pediatric Bone and Soft Tissue Tumors

Soft tissue tumors are primarily of primitive mesenchymal origin. During development, the mesenchyme matures into skeletal and smooth muscle, fat, fibrous tissue, bone, and cartilage. The malignant counterparts of muscle include leiomyosarcomas and rhabdomyosarcomas. Liposarcomas are the malignant tumors of fat, fibrosarcomas of fibrous tissue, osteosarcomas of bone, and chondrosarcomas of cartilage. Liposarcomas and leiomyosarcomas are more common in adults but do occur in children. Because such tumors are rare in children, the focus will be on bone and soft tissue malignancies that more commonly occur in children. Although bone and soft tissue tumors almost never cause sudden death in children, the forensic pathologist should be familiar with common types of tumors in children that may be encountered at autopsy.

Soft tissue sarcomas represent 7.4 % of all cancers in children and adolescents (Ries et al. 1975). Rhabdomyosarcomas are the most common soft tissue sarcoma in children below 15 years of age and make up half of all soft tissue sarcomas. The 5-year mortality for rhabdomyosarcoma is approximately 36 % (Ries et al. 1975). Older children, adolescents, and children with alveolar rhabdomyosarcoma have the worst prognosis. The most frequent site for rhabdomyosarcomas is the head and neck followed by the genitourinary tract, extremities, trunk, and retroperitoneum. A wide range of symptoms can occur based on the anatomical site of the tumor, although typically afflicted children do not present with bone pain in the absence of bone metastasis. Tumors of the orbit often produce proptosis, and tumors of the limbs often present as a painless mass. Bladder and prostate tumors may present as an abdominal mass or with obstructive symptoms or hematuria (Arndt and Crist 1999). The two most common subtypes are embryonal and alveolar rhabdomyosarcoma. Embryonal rhabdomyosarcomas account for more than half of the rhabdomyosarcomas in children and are most common before the age of 10 years. Embryonal rhabdomyosarcomas are associated with the cytogenetic abnormality t(8:11) or abnormalities of chromosome 11 (trisomy 11 or del 11). The alveolar subtype of rhabdomyosarcoma more frequently occurs in adolescents and accounts for the majority of rhabdomyosarcomas of the extremities and trunk. The cytogenetics of the alveolar subtype is associated with translocation of t(2;13)(q35:q14) or t(1;13) (p36;q14) chromosomal aberration (Jain et al. 2010).

Bone pain is a common presenting symptom in children with acute leukemia (acute lymphocytic leukemia), osteosarcoma, and Ewing sarcoma. The pain is often mistaken for other disorders including juvenile arthritis, trauma, tendonitis, or inflammation. Less commonly, children with bone tumors may also present with pathological fractures. Malignant bone tumors comprise approximately 6 % of

childhood cancers, of which 56 % are osteosarcomas and 34 % Ewing sarcomas. Deaths due to bone and joint malignancies represent 8.9 % of all childhood cancer deaths (Ottaviani and Jaffe 2009). Survival is greater in children with osteosarcoma. The peak incidence of bone cancers is at 15 years coinciding with pubertal bone growth (Ries et al. 1975). Osteosarcomas have a bimodal age distribution with the first peak in adolescence between 10 and 14 years of age and the second in older adulthood. Osteosarcoma most often occurs near the metaphyseal portion of the long bones. The most common sites are the distal femur, tibia, and humerus. Ewing sarcomas fall within the classification of small-cell neoplasms (e.g., Ewing sarcoma, primitive neuroectodermal tumor [PNET]) and typically arise from the diaphysis and occur in the extremities or the axial skeleton. Metastases commonly involve the lungs. Ewing sarcoma is also associated with t(11;22)(q24;q12) EWSR1-FL11 translocation (Potratz et al. 2012). MIC2 overexpression may be demonstrated by in situ hybridization.

Postmortem Macroscopic and Microscopic Examination

Embryonal rhabdomyosarcomas appear as a soft, gray, infiltrative mass most commonly in the nasal cavity, orbit, middle ear, prostate, or paratesticular region. The cut sections can appear fleshy with areas of cystic degeneration and necrosis. Histologically, the tumor is characterized by rhabdomyoblasts that are large round cells with abundant eosinophilic cytoplasm, eccentric nuclei, and fusiform outlines. The typical pattern is that of sheets of malignant round or spindled cells in a myxoid stroma with areas of loose and dense appearance and a subepithelial zone of condensation (e.g., cambium layer) (Parham et al. 2012). Alveolar rhabdomyosarcoma appears as a muscle mass usually in the deep musculature of the extremities in adolescent children. Histologically, the tumor resembles pulmonary alveolae with nests of small round cells, with peripheral condensation of nests of discohesive cells that line a network of fibrous septae. There may also be sheets of patternless small round cells with no intervening septae resembling lymphoma or Ewing sarcoma (Parham et al. 2012). Immunohistochemical stains show positive staining of the tumor cells with vimentin, muscle-specific actin, desmin, myogenin, and MyoD1 (Jain et al. 2010).

Osteosarcomas typically can be seen grossly as a mass within the intramedullary metaphysis with invasion through the bony cortex into soft tissue. It can appear heterogeneous depending on the extent of stromal component. Ossified and osteoblastic areas are generally hard and yellow to white and may be gritty, while chondroid areas are usually white-gray, translucent, and lobulated. Fibroblastic areas can be soft and fleshy. There may be areas of cystic change, necrosis, or hemorrhage. Histologically, there is usually tumor production of fibrillary, lace-like osteoid or woven bone between a spindle-shaped sarcomatous stroma that can be arranged in a "herring bone" or storiform pattern. Multinucleated giant cells can also be seen (Yaw 1999).

Ewing sarcoma macroscopically consists of a soft, glistening, gray-white intramedullary mass with areas of cystic change, hemorrhage, and areas resembling pus. Histologically, Ewing sarcoma consists of undifferentiated small round blue

cells with low mitotic activity arranged in broad sheets or rosettes with a lobular architecture composed of spindle cells, metaplastic bone, or cartilage. If the tumor contains greater than 20 % rosettes, then PNET should be considered. Previously treated cases may result in more pleomorphic tumor cells with large, folded, and multinucleated forms having prominent nucleoli. CD99 is positive in the tumor cells in over 90 % of cases, and tumor cells typically stain positive with periodic acid-Schiff (PAS). Vimentin and cytokeratin can show variable expression.

Cerebral Palsy

Cerebral palsy is one of the most common causes of severe physical disability in childhood. It is a nonprogressive neurological deficit characterized by spasticity, dystonia, ataxia, and paresis that occurs as a result of some type of insult to the developing brain. The specific etiology is, however, uncertain. The most common underlying cause of perinatal brain injury is premature birth, and of those infants that survive, 5–10 % will have spastic motor deficits (e.g., cerebral palsy). Full-term infants with congenital heart or respiratory disease are also susceptible to perinatal brain damage from hypoxic–ischemic insults to the developing brain. Other risk factors for cerebral palsy include birth asphyxia, multiple gestation, prematurity, low birth weight, maternal intrauterine infection, and fever. Thrombophilic disorders have also been identified as a risk factor for cerebral palsy (Gibson et al. 2003). Cerebral palsy is a chronic condition with complications that can affect multiple systems. Feeding and swallowing difficulties often lead to failure to thrive and increased susceptibility to aspiration pneumonia. Significant neurological sequelae include epilepsy and neurocognitive disorders.

Postmortem Macroscopic and Microscopic Examination

If the insult occurs during the first half of gestation, no glial repair occurs resulting in a smooth-walled defect with surrounding disorganization of the cerebral cortex that can be mistaken for a primary CNS malformation. Insults occurring in the last half of development and into the first year of life generally produce chronic multicystic lesions with a meshwork of thin gliovascular septa within the cerebral white matter and deep cortical layer. These chronic lesions can be posthemorrhagic (e.g., germinal matrix hemorrhages) forming periventricular cysts, post-white matter necrosis with unilocular or multilocular cysts, sclerotic atrophy or post–gray matter necrosis with microcephaly, cerebral atrophy producing mushroom-shaped gyri (e.g., ulegyria), scarring, and cysts. Posthemorrhagic lesions commonly involve the subependymal germinal matrix and ventricles and are often associated with other lesions including periventricular leukomalacia, brainstem necrosis, hydrocephalus, and cerebellar necrosis. White-matter lesions are most commonly periventricular and produce periventricular leukomalacia (e.g., focal necrosis,

axonal and glial injury, and diffuse white-matter gliosis). Gray-matter lesions generally involve the cortex, basal ganglia, thalamus, hippocampus, cerebellum, and brainstem and more often affect term infants (Folkerth 2005).

Sickle-Cell Disorders

Although sickle-cell disorders are not a leading cause of death in children, such deaths are likely to be encountered by the forensic pathologist particularly with cases of sudden death in sickle-cell trait (SCT) and sudden death in athletes. Sickle-cell disease (SCD) is one of the most common childhood single-gene disorders. Sickle-cell disease results from the presence of a mutation in the hemoglobin gene that causes substitution of valine for glutamic acid in the sixth position of the β-globin chain. Sickle-cell disease occurs when a person is homozygous for HbS, and the hallmark of the disease is vaso-occlusion and hemolysis which leads to sickle-cell crisis. Sickle-cell trait is the heterozygote form (HbAS) which occurs when a person has one normal Hb gene and one for HbS. Sickle-cell trait is most frequently found in areas where malaria is endemic (e.g., sub-Saharan Africa, parts of Sicily, Greece, Turkey, and India). It is the most common inherited hematologic disorder in the USA with approximately 1 in 12 African Americans having SCT. Under low-oxygen tension, sickling of red blood cells occurs. Clinical manifestations or complications associated with SCT include exercise-related sudden death, exertional rhabdomyolysis, renal failure, high anion gap, metabolic acidosis, and splenic sequestration and/or infarcts (Thogmartin et al. 2011; Goldsmith et al. 2012). Causes of death in sickle-cell disorders based on autopsy studies include infection, stroke, complications of therapy, pulmonary thromboemboli and fat/bone-marrow emboli, pulmonary hypertension, pulmonary edema, splenic sequestration, and chronic organ failure (Graham et al. 2007; Manci et al. 2003). Splenic-sequestration crisis is characterized by sudden enlargement of the spleen due to trapping of a significant volume of the blood and hypovolemia with a rapid drop in hematocrit and platelet count. Splenic-sequestration crisis is a leading cause of death in children with sickle-cell disease.

A number of deaths have been reported in NCAA Division I athletes in which the deaths occurred during conditioning (e.g., sprinting, speed drills, or weight lifting). It is postulated that during intense exercise a syndrome of rhabdomyolysis occurs as a result of exercise-induced sickling that triggers vaso-occlusion in muscles. This occurs particularly during intense exercise in suboptimally conditioned individuals, at high altitudes, or when an individual is dehydrated or hyperthermic (Key and Derebail 2010). The estimated risk of exertional death in African American Division I football athletes with sickle-cell trait is 37 times greater than athletes without SCT. Because of the increased risk, screening for SCT and simple precautions for college-level athletes have been advocated (NCAA 2010). For cases in which death was delayed long enough for athletes to receive medical intervention, it has been demonstrated that the athletes had exerted effort beyond their conditioning level, and all had evidence of metabolic acidosis, rhabdomyolysis, renal failure, and DIC

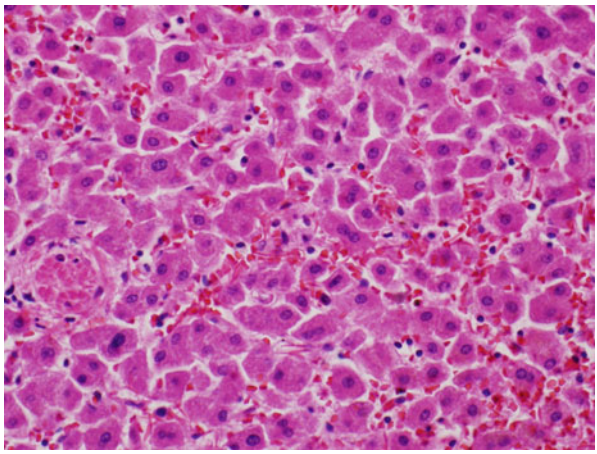

Fig. 30.11 Photomicrograph of liver, high-magnification H&E stain, in a sickle-cell disease adolescent showing sickle-shaped red blood cells within the liver sinusoids (Hematoxylin and Eosin, H&E ×40)

(Thogmartin et al. 2009). In athletes who experienced sudden death or in those who experienced cardiac arrest before medical intervention, postmortem examination should include sampling for toxicology, hemoglobin determination by electrophoresis or high-pressure liquid chromatography (HPLC) if sickle cell status has not previously been determined, microbial cultures, and fat staining.

Postmortem Macroscopic and Microscopic Examination

Macroscopic examination of the heart may reveal a benign increase in cardiac mass (so-called athlete's heart) characterized by mild to moderate eccentric or concentric left-ventricular hypertrophy, possible right-ventricular dilation, and biatrial enlargement. Right-ventricular hypertrophy may be evident in individuals dying with SCT particularly in association with pulmonary hypertension which has been demonstrated in children (Colombatti et al. 2010). Pulmonary edema and thromboemboli are common findings in individuals with SCT. There may be evidence of splenomegaly in cases of SCD, splenic sequestration, or evidence of splenic rupture. Alternatively in adolescents and young adults with SCD, the spleen may be small, scarred, and infarcted or consist only of fibrous tissue (e.g., autosplenectomy).

Typically, sickle-shaped (pointed or tapered ends) red blood cells can be seen in the microvasculature of multiple organs; however this is a common postmortem finding in sickle-cell disease (Fig. 30.11). Careful evaluation for fat or bone marrow emboli within the microvasculature should be undertaken as fat emboli can result from bone marrow infarction which is typical of pain crisis (Fig. 30.12). Fat emboli demonstrated in multiple organs (e.g., lungs, brain, and kidney) may indicate fat emboli syndrome which can be a cause of sudden death (Fig. 30.13a–c). Fibrin microthrombi may also be present within multiple organs. In children during the early phase of SCD, there may be congestion of the spleen with evidence of extramedullary hematopoiesis. Extramedullary hematopoiesis may also be present

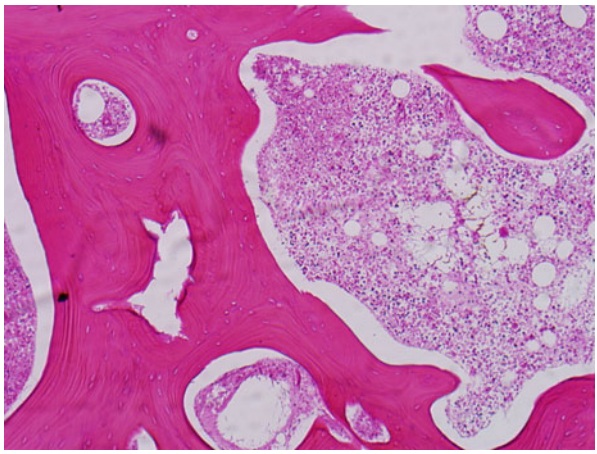

Fig. 30.12 Photomicrograph of bone marrow with infarction in a sickle-cell disease adolescent (Hematoxylin and Eosin, H&E ×4)

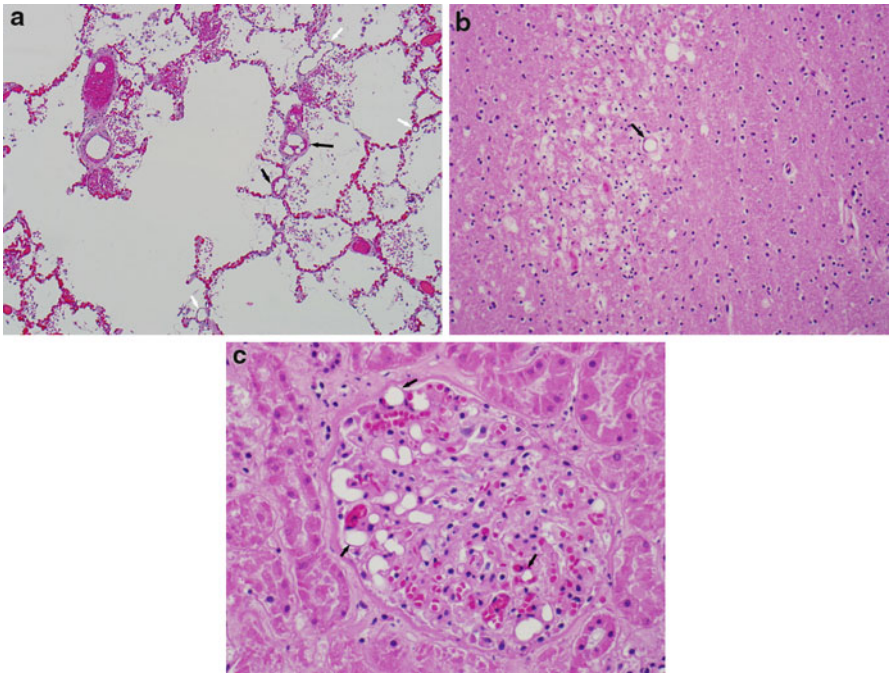

Fig. 30.13 Photomicrographs from an adolescent with sickle-cell disease beta thalassemia (**a**) lung, high-magnification H&E stain, showing multiple fat globules within the small arterioles (*black arrows*) and distention of the alveolar wall capillaries by fat globules (*white arrows*) (Hematoxylin and Eosin, H&E ×10) (**b**) brain, high-power H&E stain showing distention of a capillary with a single fat globule (*arrow*) and surrounding infarct with macrophage infiltration (Hematoxylin and Eosin, H&E ×10) (**c**) kidney, high-magnification H&E stain showing distention of the glomerular capillaries with fat globules (*arrows*) (Hematoxylin and Eosin, H&E ×20)

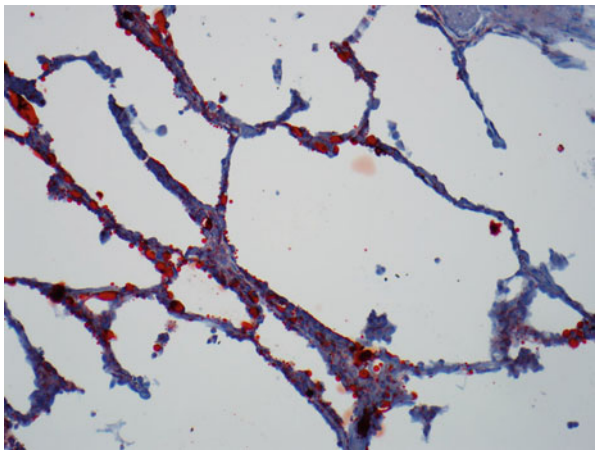

Fig. 30.14 Photomicrograph lung from an adolescent with sickle-cell disease beta thalassemia, high-magnification Oil Red O stain showing accentuation of fat globules within arterioles and alveolar capillaries (×20)

in the liver. The bone marrow in SCD is often hyperplastic due to compensatory expansion of normoblasts. New bone formation may occur due to resorption following compensatory expansion. In cases of sudden death or rhabdomyolysis, pigmented casts may be present in the distal tubules of the kidneys suggesting myoglobin. Immunohistochemistry stains using anti myoglobin antibody may help to confirm myoglobin casts in the distal tubules. Microscopic examination of skeletal muscle may reveal myocytolysis.

Ancillary Testing

Vitreous fluid should be obtained and tested for electrolytes in cases of suspected dehydration.

If fat emboli are suspected, Oil Red O stains can be performed on frozen-tissue sections (Fig. 30.14). Osmium stains can also be performed on formalin-fixed tissue before processing the tissue and counterstained with hematoxylin Masson trichrome. The fat will stain black.

Conclusion

As mentioned, the autopsy is important in the investigation of childhood deaths. In infants, commonly encountered conditions include sequelae from perinatal diseases, isolated malformations, trauma and child abuse, SIDS/SUDI, metabolic and genetic diseases, infections, and neoplasms. In older children, trauma is a leading cause of death with natural disease much less common. Although most naturally occurring childhood diseases are less likely to come to the attention of the forensic pathologist, such cases will be referred and therefore are important to consider. In children of all ages, infections and cancers are frequent causes of mortality. In cases of suspected infection, ancillary testing is particularly important

when the responsible agent is previously unknown. For malignancies, establishing the extent of tumor involvement as well as evaluating effects and complications of therapy is important. Likewise, the investigation of sudden unexpected death in childhood warrants careful consideration. In all cases, the clinical information, circumstances surrounding the death, and postmortem findings (including ancillary testing) will help to accurately determine the cause and manner of death.

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Cardiac Channelopathies and the Molecular Autopsy

31

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Contents

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Abstract

This chapter reviews clinical and molecular observations for three potentially lethal arrhythmia syndromes: long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome. It summarizes the role of cardiac channelopathies in sudden infant death syndrome and sudden and unexpected infant deaths; illustrates the role of cardiological assessment of surviving family members and the role of a molecular autopsy in the evaluation of sudden unexplained death and unexplained drowning in the young; and discusses some of the important issues in performing a molecular autopsy, including the benefits of genetic testing, indications for molecular autopsy, the biological material to be used in a molecular autopsy, interpretation of genetic test results, and the legal and societal implications of the molecular autopsy.

Introduction

In the United States (USA), sudden cardiac death (SCD) is one of the most common causes of death as an estimated 300,000–400,000 individuals die suddenly each year with the vast majority involving the elderly and secondary to coronary artery disease (Virmani et al. 2001). In comparison, sudden death in children, adolescents, and young adults is relatively uncommon with an incidence between 1.3 and 8.5 per 100,000 patient-years (Liberthson 1996). However, tragically, thousands of individuals under the age of 35 years die suddenly each year. Sudden death under 1 year of age can be attributed to infection, cardiovascular anomalies, child abuse/neglect, homicide, accidents, or metabolic/genetic disorders. However, 70–80 % of these sudden and unexpected infant deaths (SUID) have no substantiated cause of death following a death-scene investigation and complete autopsy and are labeled as sudden infant death syndrome (SIDS) (Arnestad et al. 2002; Cote et al. 1999; Kinney and Thach 2009).

Fortunately for those deaths occurring beyond the first year of life, the cause and manner of death is often explained for many cases following a comprehensive medicolegal investigation that includes an autopsy (Chugh et al. 2000; Maron et al. 1996). Because the sudden death often occurs as the sentinel event for nearly half of young victims from 1 to 35 years of age without any apparent warning signs (Liberthson 1996), the medicolegal investigation and autopsy are vital to determine the cause and manner of death. A postmortem examination may detect a noncardiac cause such as asthma, epilepsy, or pulmonary embolism. However, SCD is the most common cause of sudden death in the young, and often structural cardiovascular abnormalities, identifiable at autopsy, including hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), congenital coronary artery anomalies, and myocarditis, provide a cogent explanation for the death (Corrado et al. 2001; Maron et al. 1996). Yet, approximately one-third of sudden deaths, involving previously healthy young individuals with structurally

normal hearts, have no obvious attributable cause that can be determined at autopsy and remain unexplained, and the SCD is labeled as autopsy-negative *s*udden *u*nexplained *d*eath (SUD) (Behr et al. 2003; Chugh et al. 2000; Maron et al. 1996; Morentin et al. 2003; Puranik et al. 2005).

While SCD is the most common natural cause of death in the young, drowning is one of the leading causes of injury-related deaths in this group. Drowning claims the lives of approximately 150,000 individuals worldwide annually. From 1999 to 2007, more than 10,000 individuals younger than 20 years drowned in the USA, with the majority of these deaths occurring inadvertently and unrelated to boating (Brenner et al. 2003). It is estimated that for every child who dies from drowning, another four children suffer a serious nonfatal near-drowning event that leaves many with a permanent disability including long-term neurological deficits (Kemp and Sibert 1992).

Cardiac channelopathies including long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and Brugada syndrome (BrS) are potentially lethal and inheritable cardiac arrhythmia disorders associated with structurally normal hearts that leave no trace of their presence at a comprehensive medicolegal autopsy. In fact, the absence of any material evidence at autopsy should prompt coroners, medical examiners, and forensic pathologists to consider the possibility of a cardiac channelopathy–triggered lethal arrhythmia (Ackerman 2004, 2005a; Chugh et al. 2000; Goldenberg et al. 2005; Tester and Ackerman 2006; Wever and Robles de Medina 2004). Accordingly, this reasonable suspicion should invoke either a first-degree relative cardiological evaluation or the performance of postmortem cardiac-channel genetic testing (i.e., "molecular autopsy") in order to potentially elucidate the pathogenic mechanism and establish the probable cause and manner of SUD (Ackerman et al. 2001a, b; Chugh et al. 2004; Priori et al. 2000).

In this chapter, the clinical and molecular observations for three potentially lethal arrhythmia syndromes, LQTS, CPVT, and BrS, will be reviewed, and then the role of cardiac channelopathies in SIDS/SUID will be summarized. Next, the role of cardiological assessment of surviving family members and the role of a molecular autopsy in the evaluation of SUD and unexplained drowning in the young will be illustrated. Finally, the important issues in performing a molecular autopsy, including the benefits of genetic testing, indications for molecular autopsy, the biological material to be used in a molecular autopsy, interpretation of genetic test results, and the legal and societal implications of the molecular autopsy will be addressed.

Cardiac Channelopathies Associated with "Structurally Normal Heart" Sudden Death

The cardiac channelopathies comprising heritable and potentially lethal arrhythmia syndromes including congenital LQTS, CPVT, and BrS involve electrical

instability with the propensity to produce fatal arrhythmias in the setting of a structurally normal heart. These often unremarkable electrical abnormalities have the ability to cause the heart of an unsuspecting individual to spiral out of control into a potentially lethal arrhythmia, resulting in the sudden and early death of an otherwise healthy individual (Tester and Ackerman 2006). Often these inheritable cardiac channelopathies are associated with reduced penetrance and variable expressivity that create a significant challenge for the appropriate diagnosis and pedigree interpretation of the disorder. For example, a LQTS-susceptibility gene mutation with an ascribed penetrance of 25 % means that 25 % of patients within the family pedigree who possess that particular gene mutation will exhibit a measurable, diagnostic feature indicative of its presence such as electrocardiographic evidence of QT prolongation in LQTS. The expressivity of these disorders is highly variable, ranging from lifelong asymptomatic individuals to SCD during the first year of life. Patients may have a substantial history of relatively benign cardiac events, such as syncope, or these disorders may manifest for the first time as sudden death. Through molecular advances in cardiovascular genetics, the underlying genetic basis responsible for many inherited cardiac arrhythmia syndromes has been discovered.

Long QT Syndrome

Clinical Presentation

Long QT syndrome (LQTS) consists of a diverse group of cardiac channelopathies characterized by delayed repolarization of the myocardium, QT prolongation (QTc > 480 ms), and increased risk of syncope, seizures, and SCD (Fig. 31.1). The incidence of LQTS may exceed 1 in 2,500 persons (Schwartz et al. 2009). Owing to reduced penetrance, individuals with LQTS may or may not present with QT prolongation on a resting 12-lead surface electrocardiogram (ECG). In fact, about 40–50 % of mutation-positive LQTS patients have a normal resting QTc. This electrical glitch of delayed repolarization is almost always without consequence. However, rarely, triggers such as exertion, swimming, emotion, auditory stimuli such as an alarm clock, or the postpartum period can cause the heart to become electrically unstable and culminate in a potentially life-threatening and sometimes lethal arrhythmia of torsade de pointes (TdP). Though most often this abnormal cardiac rhythm spontaneously returns to normal, resulting in only an episode of syncope, 5 % of untreated and unsuspecting LQTS individuals succumb to a fatal arrhythmia as their first event. Yet, it is estimated that nearly half of the individuals experiencing SCD, resulting from this very treatable arrhythmogenic disorder, may have demonstrated previous cardiac events or "warning signs" consistent with LQTS (i.e., exertional syncope, family history of premature sudden death) that went unrecognized (Tester and Ackerman 2007). Approximately 20 % of autopsy-negative sudden unexplained deaths in the young and 10 % of sudden infant death syndrome (Arnestad et al. 2007; Tester and Ackerman 2007) may be explained by LQTS.

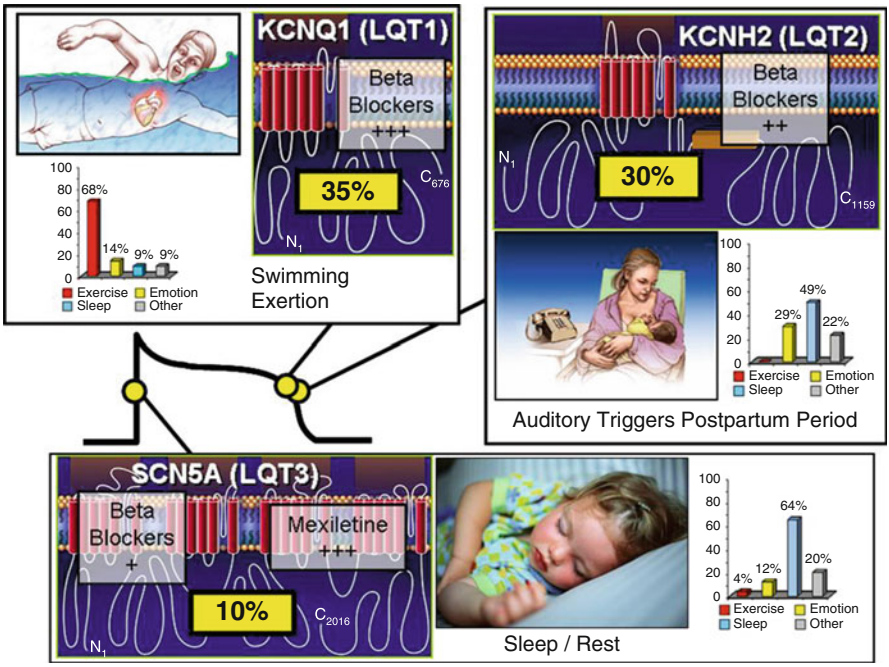


Fig. 31.1 Genotype-phenotype correlations in long QT syndrome. Seventy-five percent of clinically strong LQTS is due to mutations in three genes (35 % *KCNQ1*, 30 % *KCNH2*, and 10 % in *SCN5A*) encoding for ion channels that are critically responsible for the orchestration of the cardiac action potential. Genotype-phenotype correlations have been observed, including swimming/exertion and LQT1, auditory triggers/postpartum period and LQT2, and sleep/rest and LQT3. The bar graphs represent genotype-phenotype data from (Schwartz et al. 2001). Also illustrated is the relative gene-specific effectiveness in β blocker therapy where β blockers are extremely protective in LQT1 patients, moderately protective in LQT2, and may not provide sufficient protection for those with LQT3. The sodium channel blocker mexiletine may be protective in LQT3

Genetic Basis for Long QT Syndrome

A genetically heterogeneous disorder, LQTS is inherited typically in an autosomal dominant pattern, previously known as Romano-Ward syndrome (Ackerman 2004). LQTS is rarely inherited as the recessive trait characterized by a severe cardiac phenotype and sensorineural hearing loss, first described by Jervell and Lange-Nielsen. Nearly 5–10 % of LQTS is accounted for by spontaneous or sporadic germline mutations. To date, hundreds of mutations have been identified in 13 LQTS-susceptibility genes (Table 31.1). Approximately 75 % of LQTS can be elucidated genetically with either gain-of-function or loss-of-function pathogenic mutations identifiable in the three major LQTS-causative genes that encode ion-channel subunits that orchestrate the action potential of the heart (Keating and Sanguinetti 2001): *KCNQ1*-encoded I_{Ks} (Kv7.1) potassium channel (LQT1, ~35 %)

Table 31.1 Summary of heritable arrhythmia syndrome susceptibility

Gene	Locus	Protein
Long QT syndrome		
Major LQTS genes		
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, KV7.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, KV11.1)
SCN5A (LQT3)	3p21-p24	Cardiac sodium channel alpha subunit (NaV1.5)
Minor LQTS genes (listed alphabetically)		
AKAP9 (LQT11)	7q21-q22	Yotiao
ANKB (LQT4)	4q25-q27	Ankyrin B
CACNA1C (LQT8/TS1)	12p13.3	Voltage gated L-type calcium channel (CaV1.2)
CAV3 (LQT9)	3p25	Caveolin-3
KCNE1 (LQT5)	21q22.1	Potassium channel beta subunit (MinK)
KCNE2 (LQT6)	21q22.1	Potassium channel beta subunit (MiRP1)
KCNJ2 (LQT7/ATS1)	17q23	I_{K1} potassium channel (Kir2.1)
KCNJ5 (LQT13)	11q24.3	K_{ATP} potassium channel (Kir3.4)
SCN4B (LQT10)	11q23.3	Sodium channel beta 4 subunit
SNTA1 (LQT12)	20q11.2	Syntrophin-alpha 1
Brugada syndrome		
SCN5A (BrS1)	3p21-p24	Cardiac sodium channel alpha subunit (NaV1.5)
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1-like
CACNA1C	2p13.3	Voltage gated L-type calcium channel (CaV1.2)
CACNB2	10p12	Voltage gated L-type calcium channel beta 2 subunit
CACNA2D1	7q21.11	Voltage gated L-type calcium channel delta 2 subunit
SCN1B	19q13	Sodium channel beta 1
SCN3B	11q24.1	Sodium channel beta 3
KCNE3	11q13.4	Potassium channel beta subunit (MiRP2)
KCND3	1p13.2	I_{to} potassium channel (Kir4.3)
KCNJ8	12p12.1	Inward rectifying potassium channel (Kir6.1)
RANGRF	17p13.1	RAN guanine nucleotide release factor (MOG1)
Catecholaminergic polymorphic ventricular tachycardia		
RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
CASQ2 (CPVT2)	1p13.3	Calsequestrin 2
Sudden infant death syndrome (listed alphabetically)		
CAV3	3p25	Caveolin-3
GPD1L	3p22.3	Glycerol-3-phosphate dehydrogenase 1-like
KCNJ8	12p12.1	Inward rectifying potassium channel (Kir6.1)
KCNH2 (LQT2)	7q35-36	I_{Kr} potassium channel alpha subunit (HERG, KV11.1)
KCNQ1 (LQT1)	11p15.5	I_{Ks} potassium channel alpha subunit (KVLQT1, KV7.1)

(*continued*)

Table 31.1 (continued)

Gene	Locus	Protein
RYR2 (CPVT1)	1q42.1-q43	Ryanodine receptor 2
SCN3B	11q24.1	Sodium channel beta 3
SCN4B	11q23.3	Sodium channel beta 4 subunit
SCN5A (LQT3, BrS1)	3p21-p24	Cardiac sodium channel alpha subunit (NaV1.5)
SNTA1	20q11.2	Syntrophin-alpha 1

(Wang et al. 1996), *KCNH2*-encoded I_{Kr} (Kv11.1) potassium channel (LQT2, ~30 %, loss-of-function) (Curran et al. 1995), and *SCN5A*-encoded I_{Na} (Nav1.5) sodium channel (LQT3, ~10 %, gain-of-function) (Wang et al. 1995). Approximately 5–10 % of patients have multiple mutations in these genes, and patients with multiple mutation LQTS present at a younger age and with greater expressivity (Tester et al. 2005b). The vast majority of mutations are coding-region single-nucleotide substitutions resulting in non synonymous missense (an amino acid substitution for another amino acid), nonsense (amino acid substitution for a termination codon), splice-site alterations (resulting in exon skipping or intron inclusion), or small insertions/deletions leading to frameshift mutations (altered amino acid coding resulting in an early termination) (Napolitano et al. 2005; Splawski et al. 2000; Tester et al. 2005b). However, more recently a few large gene rearrangements involving the deletion or duplication of hundreds to thousands of nucleotides resulting in single or multiple whole-exon deletions/duplications have been described (Eddy et al. 2008; Koopmann et al. 2006; Tester et al. 2010).

Compared to rare, pathogenic LQTS-associated channel mutations present in an estimated 0.04 % (1 in 2,500) of persons and 75 % of clinically strong diagnosed LQTS cases, comprehensive genetic testing of the major LQTS genes, *KCNQ1*, *KCNH2*, and *SCN5A*, for over 1,300 ostensibly healthy volunteers has illustrated that about 4 % of Caucasians and up to 8 % among non-Caucasians host rare non synonymous genetic variants (<0.5 % allelic frequency) in these specific cardiac channel genes. In fact, a total of 79 distinct channel variants were detected among these healthy subjects including 14 genetic missense variants in *KCNQ1*, 28 in *KCNH2*, and 37 in *SCN5A* (Ackerman et al. 2004, 2003). Whether any of these 79 variants are either functionally or clinically relevant requires further examination.

In addition to this background rate (4–8 %) of rare genetic variants, 15 distinct common polymorphisms (allelic frequency >0.5 % in at least 1 ethnic group) have been identified in the 4 potassium-channel subunit genes (Ackerman et al. 2003), and 8 common polymorphisms in the sodium channel have been discovered (Ackerman et al. 2004). Several studies suggest that some of these common polymorphisms may be clinically informative and relevant to the identification of those at risk of cardiac arrhythmias, specifically in the setting of QT-prolonging drugs or other environmental factors. The quintessential example is S1103Y-SCN5A (originally annotated as the Y1102 variant), the most prominent common

amino acid–altering genetic variant (non synonymous polymorphism) to confer arrhythmia susceptibility in an ethnic–specific manner (Splawski et al. 2002). Importantly, most individuals hosting this polymorphism never have an arrhythmia; however, data suggest that potential lethal arrhythmias associated with this variant may occur in the setting of common endogenous factors including exposure to QT-prolonging drugs, hypokalemia, structural heart disease, and conditions of acidosis (Plant et al. 2006; Splawski et al. 2002). S1103Y, seen in 13 % of African Americans, but not observed in any Caucasian or Asian controls (>1,000 subjects), has been shown to be overrepresented in arrhythmia cases (Splawski et al. 2002), among African American adolescent and adult cases of autopsy-negative sudden unexplained death (SUD) (Burke et al. 2005; Tester et al. 2012), and sudden infant death syndrome (SIDS) (Plant et al. 2006; Van Norstrand et al. 2008b). This common genetic variant, S1103Y, has very subtle alterations in channel kinetics in heterologous-expression studies when studied under normal conditions (Splawski et al. 2002). However, functional and modeling studies supported the potential for QT prolongation and arrhythmias particularly in the setting of concomitant exposure to HERG (I_{kr} potassium channel)-blocking drugs (Splawski et al. 2002). Further, under conditions mimicking cellular acidosis, Y1103-SCN5A channels exhibited significant persistent late sodium current, a hallmark phenotype of LQT3 (Plant et al. 2006).

Specific genotype/phenotype associations in LQTS have materialized, signifying relatively gene-specific triggers, ECG patterns, and response to therapy (Fig. 31.1) (Ackerman 2005; Schwartz et al. 2001). For example, while swimming- and exertion-induced cardiac events are strongly associated with mutations in *KCNQ1* (LQT1), auditory triggers and postpartum-period episodes most often occur in LQT2 patients. Events occurring during periods of sleep/rest are most common in LQT3. These phenotype–genotype associations may be used to facilitate phenotype-directed genetic testing for LQTS. Not only does genetic testing in LQTS offer diagnostic value but it also has prognostic and therapeutic implications in LQTS. To illustrate, the underlying genetic basis has a substantial influence on the response to standard LQTS pharmacotherapy, where β-blockers are extremely protective in LQT1 patients and moderately protective in LQT2, but may offer insufficient protection in those patients with LQT3 (Villain et al. 2004; Vincent et al. 2009). However, patients with LQT3 may benefit from late sodium current–blocking agents like mexiletine, flecainide, ranolazine, or propranolol as gene-specific therapeutic options for LQT3 (Moss et al. 2005, 2008).

Additionally, intra genotype risk stratification has emerged for LQT1 and LQT2 based on the mutation type, mutation location, and cellular function (Jons et al. 2009; Migdalovich et al. 2011; Moss et al. 2007, 2002; Nagaoka et al. 2008; Shimizu et al. 2004, 2009). For example, LQT1 patients with KCNQ1 transmembrane-localizing missense mutations have a twofold greater risk of a LQT1-triggered cardiac event than LQT1 patients with C-terminal-localizing KCNQ1 mutations. Moreover, LQT1 patients with KCNQ1 mutations resulting in a greater degree of potassium ion-channel loss-of-function at the cellular in vitro level (i.e., dominant negative) have a twofold greater risk than those

mutations that less severely hamper the biological function of the channel (i.e., haploinsufficiency). Likewise, patients with LQT2-associated KCNH2 mutations residing in the PORE region of the ion channel have a longer QTc, a more severe clinical manifestation of the disorder, and significantly more arrhythmia-related cardiac events occurring at a younger age than those with non pore mutations (Moss et al. 2002). Additionally, those LQT2 patients with mutations in the PORE region of the channel had the greatest risk of cardiac events, those with frameshift or nonsense mutations in any region of the channel had a moderate risk, and those with missense mutations in the C-terminus had the lowest risk of cardiac events (Shimizu et al. 2009).

The remaining minor LQTS-susceptibility genes collectively explain perhaps 5 % of LQTS. These genes encode for either important cardiac-channel interacting proteins that regulate the native ion-channel current (I_{Ks}, I_{Kr}, or I_{Na}) or structural-membrane scaffolding proteins that function in proper localization of the major LQTS-associated ion channels to the plasma membrane. The latest LQTS-susceptibility gene, identified in 2010 in a single large Chinese pedigree with concomitant prolonged QTc and persistent atrial fibrillation, stems from mutations in the *KCNJ5*-encoded Kir3.4 potassium channel (Yang et al. 2010).

Importantly, there are no particular mutational "hot spots" within these genes, as the vast majority of unrelated families have their own unique "private" mutation. In 2012, it is imperative to note that nearly 20–25 % of clinical definite cases of LQTS remain genetically elusive.

Catecholaminergic Polymorphic Ventricular Tachycardia

Clinical Description

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a heritable arrhythmia syndrome that typically presents with exercise-induced syncope or sudden death and is predominately expressed in the young (Fig. 31.2) (Priori et al. 2002). However, while once thought to present only during childhood, more recent studies have suggested that the age of first manifestation can vary from during infancy to 40 years of age. Unlike LQTS, CPVT is associated with a completely normal resting electrocardiogram (ECG) and is electrocardiographically suspected following either exercise or catecholamine stress testing that demonstrates significant exercise-induced ventricular ectopy although CPVT's pathognomonic arrhythmia of bidirectional VT is expressed infrequently (Horner and Ackerman 2008). Like LQT1, swimming is a particularly arrhythmogenic trigger in CPVT. In fact, both LQT1 and CPVT have been implicated as the underlying basis in cases of unexplained drowning or near-drowning in the otherwise young healthy swimmer (Choi et al. 2004; Tester et al. 2011a, 2005a).

The lethality of CPVT is demonstrated by mortality rates of 30–50 % by age 35 years and the incidence of a positive family history of young (<40 years) SCD for greater than a third of CPVT individuals and in as much as 60 % of families hosting RyR2 mutations (Liu et al. 2008). Furthermore, approximately 15 % of

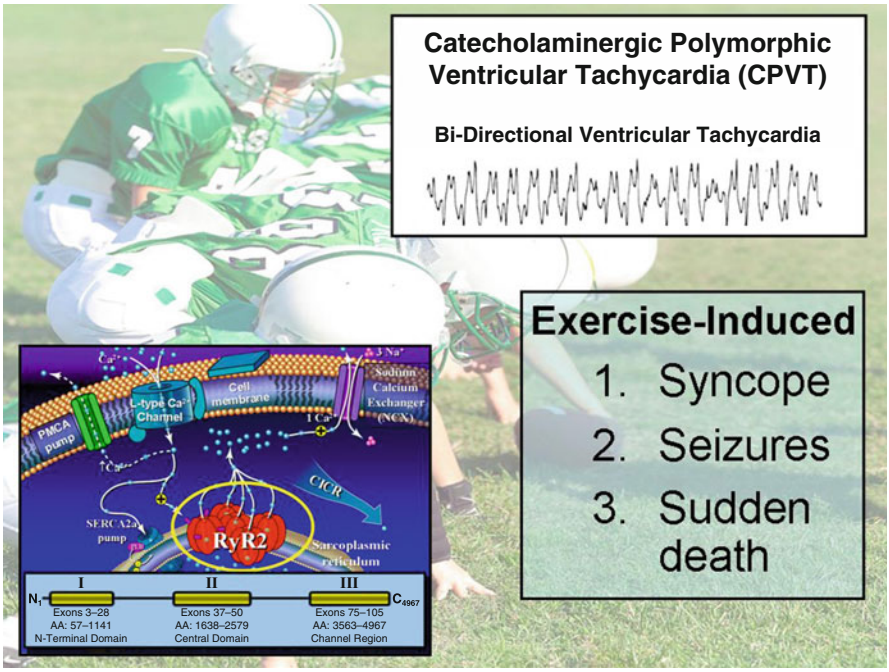


Fig. 31.2 Catecholaminergic polymorphic ventricular tachycardia: a disorder of intracellular calcium handling. Catecholaminergic polymorphic ventricular tachycardia (*CPVT*) often manifests as exercise-induced syncope, seizures, or sudden death in the setting of a structurally normal heart. While the ECG is normal at rest, the signature ECG pattern of bidirectional ventricular tachycardia may be observed during exercise treadmill testing. Perturbations in key components of the calcium-induced calcium release (*CICR*) mechanism responsible for cardiac excitation-contraction coupling are the pathogenic basis for CPVT. At the center of this mechanism is the *RYR2*-encoded cardiac ryanodine receptor/calcium release channel located in sarcoplasmic reticulum membrane. Mutations in RyR2 are clustered and distributed in three "hot spot" regions of this 4,967 amino acid (*AA*) protein; Domain I or N-terminal Domain (*AA 57–1141*), Domain II or the Central Domain (*AA 1638–2579*), and Domain III or Channel Region (*AA 3563–4967*)

autopsy-negative SUD in the young and some cases of SIDS/SUID have been attributed to CPVT (Tester and Ackerman 2006; Tester et al. 2007).

Genetic Basis for Catecholaminergic Polymorphic Ventricular Tachycardia

Alterations in the key biological machinery that governs intracellular calcium–induced calcium release from the sarcoplasmic reticulum serve as the pathogenic basis for CPVT (Fig. 31.2). Inherited in an autosomal dominant fashion, 60 % of robust clinically diagnosed cases of CPVT stem from mutations in the

RYR2-encoded cardiac ryanodine receptor/calcium release channel as is annotated as type 1 CPVT (CPVT1, Table 31.1). Gain-of-function mutations in RyR2 produce "leaky" calcium release channels that result in excessive diastolic calcium release, specifically during sympathetic stimulation that can precipitate calcium overload, delayed after depolarizations (DADs), and ventricular arrhythmias (Liu et al. 2008). Like LQTS, the vast majority of unrelated CPVT families are identified with their own unique *RYR2* mutation, and about 5 % of unrelated mutation-positive individuals host multiple putative pathogenic mutations (Medeiros-Domingo et al. 2009). One of the largest genes in the human genome, *RYR2*, contains 105 exons that transcribe/translate one of the largest cardiac ion-channel proteins comprising 4,967 amino acids. While there are no specific mutation "hot spots," there are three regional "hot spots" or "domains" where unique mutations localize (Medeiros-Domingo et al. 2009). This observation has allowed for targeted genetic testing of *RYR2* (~61 exons) rather than a comprehensive 105-exon analysis. Mutations in CASQ2-encoded calsequestrin are responsible for the extremely rare recessive form of CPVT annotated as type 2 CPVT (CPVT2, Table 31.1).

Brugada Syndrome

Clinical Description and Manifestations of Brugada Syndrome

Brugada syndrome (BrS) is a heritable arrhythmia syndrome characterized by an ECG pattern consisting of coved-type ST-segment elevation ($\geq$2 mm) followed by a negative T wave in the right precordial leads V_1 through V_3 (often referred to as type 1 Brugada ECG pattern) and an increased risk of sudden death resulting from episodes of polymorphic ventricular tachyarrhythmias (Fig. 31.3) (Brugada et al. 2009; Chen and Priori 2008). BrS is generally considered a disorder involving young male adults, perhaps greatest among Southeast Asian males, with arrhythmogenic manifestation first occurring at an average age of 40 years with sudden death typically occurring during sleep (Ruan et al. 2009; Shimizu 2008). In fact, sudden unexplained nocturnal death (SUND) in young males is endemic to Southeast Asia and is now considered phenotypically, genetically, and functionally the same disorder as BrS (Brugada et al. 2009). However, BrS has been demonstrated in children and infants (Probst et al. 2007). In a 2007 population study of 30 children (<16 years of age) affected by BrS from 26 families, fever represented the most common precipitating factor for arrhythmic cardiac events, including syncope and SCD (Probst et al. 2007). Mutations in genes associated with BrS have been described in both cases of autopsy-negative SUD and SIDS/SUID.

Genetic Basis for Brugada Syndrome

BrS is inherited as an autosomal-dominant trait, yet over half of BrS may be sporadic in nature. While gain-of-function mutations in *SCN5A*-encoded cardiac sodium channel account for about 5–10 % of LQTS, approximately 20–30 % of BrS

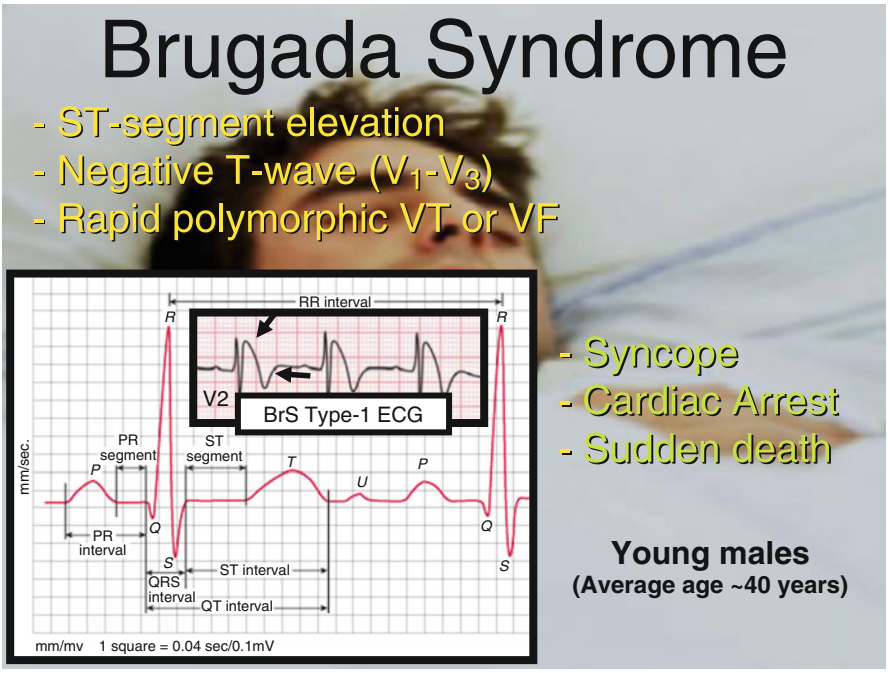


Fig. 31.3 Clinical presentation of Brugada syndrome. Brugada syndrome (*BrS*) is a heritable arrhythmia syndrome characterized by an ECG pattern consisting of coved type ST-segment elevation (≥2 mm) followed by a negative T wave in the right precordial leads V_1 through V_3 (often referred to as type 1 Brugada ECG pattern) and an increased risk for syncope, cardiac arrest, and sudden death. BrS is generally considered a disorder involving young male adults with arrhythmogenic manifestation first occurring at an average age of 40 years with sudden death typically occurring during sleep

results from loss-of-function mutations in *SCN5A* and is annotated as Brugada syndrome type 1 (BrS1, Table 31.1). In 2009, an international compendium of *SCN5A* mutations derived from over 2,000 patients referred for BrS genetic testing reported nearly 300 distinct mutations in 438 of 2,111 (21 %) unrelated patients, and the mutation detection yield ranged from 11 % to 28 % across nine centers (Kapplinger et al. 2010). Familial forms of BrS may have a significantly higher yield of mutation detection than among sporadic cases. For example, Schulze-Bahr and colleagues identified *SCN5A* mutations in 38 % of their familial BrS cases compared to none in 27 sporadic cases ($p = 0.001$). Approximately 3 % of the genotype-positive patients have multiple putative pathogenic *SCN5A* mutations, and akin to the genotype–phenotype observations in LQTS (Tester et al. 2005b), patients hosting multiple *SCN5A* mutations are usually younger at diagnosis (29.7 ± 16 years) than those hosting a single mutation (39.2 ± 14.4 years) (Kapplinger et al. 2010). Again, like LQTS and CPVT there is no specific mutational "hot spot" as nearly 80 % of the BrS-associated *SCN5A* mutations occur as "private" single-family mutations.

In addition to mutations of the sodium channel, mutations in genes (GPD1L (London et al. 2007), SCN1B (Watanabe et al. 2008), SCN3B (Hu et al. 2009), and MOG1 (Kattygnarath et al. 2011), Table 31.1) that regulate the sodium-channel function are suggested to cause BrS. Besides sodium-channel dysfunction, mutations involving the L-type calcium-channel alpha, beta, and delta subunits encoded by the *CACNA1C*, *CACNB2b*, and *CACNA2D1* genes, respectively, may cause approximately 10 % of BrS cases with concomitant short QT intervals (Table 31.1) (Antzelevitch et al. 2007; Burashnikov et al. 2010). Other minor causes of BrS include mutations in the alpha subunit and a putative beta subunit of the transient outward potassium channel (Ito) encoded by *KCND3* (Giudicessi et al. 2011) and *KCNE3* (Delpon et al. 2008), respectively, and mutations in the *KCNJ8*-encoded Kir6.1 K_{ATP} potassium channel (Medeiros-Domingo et al. 2010) (Table 31.1). However, these minor genes represent rare causes of BrS. Mechanistically, either decreases in the inward sodium or calcium currents or increases in the outward Kv4.3 potassium current produce the BrS phenotype through perturbations of either the respective-channel alpha subunits or channel-interacting proteins (Shimizu 2008). While to date there have been 11 BrS-susceptibility genes discovered, the genetic cause of 70–80 % of clinically diagnosed BrS remains elusive, suggesting a high degree of genetic heterogeneity for this disorder.

Cardiac Channelopathies and Sudden Infant Death Syndrome/ Sudden and Unexpected Infant Death

SIDS is a sudden and unexpected infant death (SUID) occurring prior to 1 year of age, with the onset of fatal arrhythmia apparently occurring during sleep, which remains unexplained following a death scene and medicolegal investigation including a complete autopsy, review of the circumstances of the death, and clinical history review (Willinger et al. 1991; Krous et al. 2004). These perplexing tragedies remain a leading cause of infant mortality and the third leading cause of infant death in the USA with an estimated incidence of 0.57 per 1,000 live births (Dwyer et al. 1995; Kinney and Thach 2009). In fact, in the USA over 2,500 ostensibly healthy infants will fail to reach their first birthday due to SIDS/SUID (Guyer et al. 1999). SIDS/SUID remains obscure in its causes and overwhelming in the consequences rendered. Over the past few decades, a triple-risk hypothesis for SIDS/SUID has materialized suggesting a convergence involving the triad of the vulnerable infant in the setting of exogenous stressors that occurs during a critical development period, and it is the convergence of these three factors that is thought to result in SIDS. Accordingly, SIDS/SUID does not occur in normal infants, but rather only those vulnerable infants with an underlying abnormality (Kinney and Thach 2009). Since the emergence of this triple-risk hypothesis, investigators worldwide have proposed several predisposing risk factors for SIDS/SUID. Although many pathophysiological theories, mostly implicating failed defense mechanisms, have been postulated for SIDS/SUID,

including cardiorespiratory instability, maladaptive sympathetic bias, and coronary artery spasm, decisive pathogenic mechanisms triggering an infant's sudden demise remain unclear (Guntheroth 1989; Kanda and Endo 1997; Valdes-Dapena 1973; Yun and Lee 2004). However, genetic factors representing possible underlying vulnerabilities in SIDS/SUID victims have been identified in genes involved in neurotransmission, energy metabolism, autonomic response to infection, and cardiac potential duration (Kinney and Thach 2009).

In 1976, Schwartz and Maron first proposed a hypothesis implicating the heart and the autonomic system in the involvement of SIDS/SUID, specifically abnormal cardiac repolarization, and LQTS (Maron et al. 1976; Schwartz 1976). Two decades later, Schwartz and colleagues provided significant evidence to support the QT hypothesis in the pathogenesis of SIDS/SUID by conducting a monumental 19-year prospective collection of day 3 or 4 of life-screening 12-lead electrocardiograms on 34,442 neonates born in nine maternity hospitals (Schwartz et al. 1998). This study convincingly demonstrated QTc as a significant risk factor for SIDS/SUID with a day 3/day 4 of life QTc $>$ 440 ms having a 41.3 odds ratio for SIDS/SUID, an odds ratio far greater than other recognized risk factors for SIDS/SUID such as environmental exposure to secondhand smoke and prone sleep position.

Following the study by Schwartz, several case reports provided proof of principle that LQTS-associated primary cardiac-channel mutations may underlie the pathogenic basis for some cases of SIDS/SUID (Schwartz et al. 2000). While these anecdotal case reports provide the molecular proof of concept that cardiac channelopathies could cause SIDS/SUID, large population-based studies were needed to assess the incidence of cardiac channelopathic mutations in SIDS/SUID. The Ackerman group provided the first such genetic epidemiological study to determine the spectrum and prevalence of congenital LQTS in the pathogenesis of SIDS/SUID. Initial discoveries involving a comprehensive open reading frame/splice-site mutational analysis of *SCN5A* in a population-based collection of 93 unexplained infant deaths revealed that 2 of 58 white infants (3.4 %) hosted "classic" LQT3-like "gain-of-function" SCN5A missense mutations (Ackerman et al. 2001a). Both mutations were absent in nearly 600 reference alleles from healthy white controls (Ackerman et al. 2004). Since this first study, the Ackerman group has now identified putative LQTS-causing mutations in 3 of 58 (5.2 %, 2 SCN5A and 1 KCNH2) white SIDS/SUID cases and 1 of 34 (2.9 %, 1 KCNQ1) black SIDS/SUID cases (Table 31.1) (Ackerman et al. 2001a; Tester and Ackerman 2005). In addition, they have identified SIDS/SUID-associated mutations in some of the more recently discovered "minor" LQTS- and BrS-susceptibility genes (*CAV3* (Cronk et al. 2007), *GPD1L* (Van Norstrand et al. 2007), *SNTA1* (Van Norstrand et al. 2008), *SCN3B* (Tan et al. 2010), and *SCN4B* (Tan et al. 2010, Table 31.1). The group has also extended the compendium of SIDS/SUID-associated mutations beyond LQTS and BrS with the identification of functionally significant CPVT1-like *RYR2* mutations in 1 of 50 (2 %) black SIDS/SUID and 1 of 84 (1 %) white SIDS/SUID cases (Tester et al. 2007). Most recently loss-of-function *KCNJ8* (Kir6.1 K_{ATP} potassium channel, Table 31.1) mutations

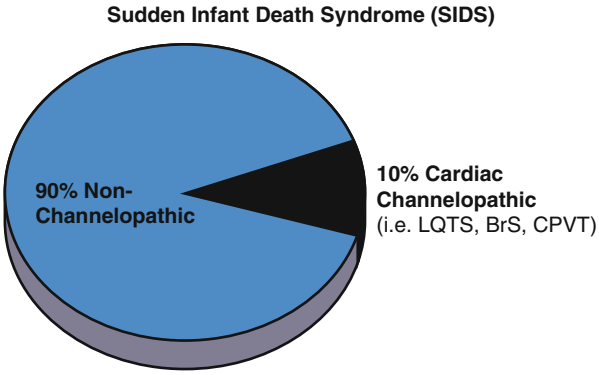


Fig. 31.4 The prevalence of cardiac channelopathy in sudden infant death syndrome (***SIDS***). Depicted is a pie chart illustrating that approximately 10 % of sudden infant death may be due to cardiac channelopathy sudden death-related disorders including LQTS, BrS, and CPVT

were identified in 2 out of 292 unrelated SIDS/SUID victims, as a novel pathogenic basis for SIDS/SUID, possibly by predisposition to maladaptive cardiac response to systemic infection akin to mouse models of KCNJ8 deficiency (Tester et al. 2011a). Importantly, in all of these studies, only those variants that were deemed primary pathogenic mutations (not seen in controls) were reported rather than rare polymorphisms seen both in cases and controls that may or may not represent a significant underlying risk of sudden death during infancy. Collectively, this analysis has illustrated that approximately 10 % of SIDS/SUID may be due to underlying cardiac channelopathies, namely, LQTS, BrS, and CPVT (Fig. 31.4).

It is well known that 90 % of SIDS/SUID occurs before 6 months of age, and that is reflected in this cohort where only 9 % died suddenly and unexpected at or beyond 6 months. Interestingly, although the numbers are small, the Ackerman group has observed that one-third of the "older" SIDS/SUID cases (>6 months) were LQTS/CPVT mutation-positive compared to 4 % of the infants who died before 6 months of age ($p < 0.004$), suggesting that perhaps the prevalence of cardiac channelopathies will be higher among older SIDS/SUID cases.

In 2007, Schwartz and colleagues independently demonstrated a 9.5 % prevalence of functionally significant genetic variants in LQTS-associated genes among 201 Norwegian SIDS/SUID victims (Arnestad et al. 2007). In this study, they performed comprehensive mutational analysis of the three most common LQTS-associated genes (*KCNQ1*, *KCNH2*, and *SCN5A*) as well as four other less common LQTS genes (*KCNE1*, *KCNE2*, *KCNJ2*, and *CAV3*). After excluding known rare variants, they identified putative pathogenic primary disease-causing mutations presumably capable of precipitating a lethal arrhythmia by themselves (absent in controls and functionally significant) in 8 of 201 (4 %, 4 SCN5A, 2 KCNQ1, and 2 KCNH2) SIDS/SUID cases (Ackerman et al. 2003, 2004). However, they also provided compelling functional evidence to suggest that a significant number of rare non synonymous amino acid–altering variants (rare polymorphisms seen in SIDS/SUID and in health), particularly those identified in the cardiac sodium channel, behave differently from normal wild-type channels and consistent with an LQT3-like molecular phenotype. Perhaps it is the

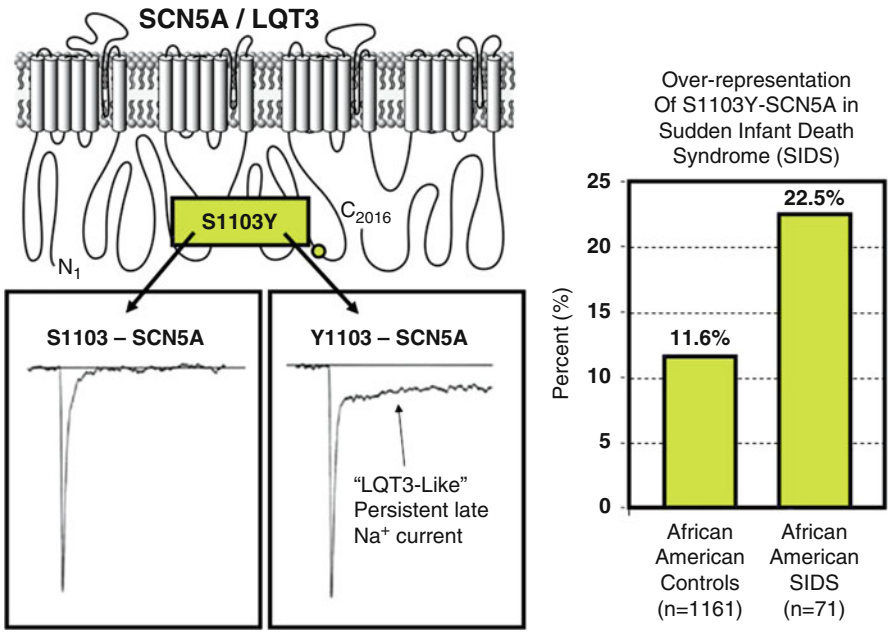


Fig. 31.5 Overrepresentation of the proarrhythmic sodium channel common polymorphism S1103Y in SIDS. Illustrated is the topological representation of the LQT3- and BrS1-associated *SCN5A*-encoded cardiac sodium channel with localization of the common proarrhythmic, "LQT3-like" sudden death-associated *SCN5A* polymorphism S1103Y, which has been shown to be overrepresented among African American SIDS cases compared to healthy African American controls (Plant et al. 2006; Van Norstrand et al. 2008)

infant hosting such a functionally significant channel polymorphism, that is, the vulnerable infant, that may succumb to SIDS/SUID in the setting of exogenous stressors that increase cardiac electrical instability during the critical development period of the first year of life (Arnestad et al. 2007). In fact, it stands to reason that this may be the case for some SIDS/SUID victims, given the mounting evidence that the common proarrhythmic, "LQT3-like" sudden death–associated *SCN5A* polymorphism S1103Y has been shown to be overrepresented among SIDS/SUID cases compared to healthy controls (Fig. 31.5) (Splawski et al. 2002; Van Norstrand et al. 2008). Interestingly, in the Schwartz study, the median age was 5 months for the mutation-positive cases compared to 3.5 months for the negative cases, but this did not reach statistical significance (Arnestad et al. 2007). However, this parallels our previous observation that older SIDS/SUID victims may have a higher prevalence of cardiac channelopathic mutations.

Collectively, these population-based studies indicate that the incidence of either primary cardiac-channel mutations or rare genetic variants that may impair proper channel function and subsequent disease formation leading to early death in the setting of endogenous stressors during the first year of life is approximately 10 %.

Accordingly, it appears prudent to inform parents of a SIDS/SUID victim, especially an "older" infant, (1) that an estimated 10 % of SIDS/SUID may be due to underlying cardiac channelopathy such as LQTS, BrS, or CPVT; (2) that perhaps as much as one-third of SIDS/SUID infants older than 6 months of age may be LQTS/CPVT mutation-positive; and (3) that postmortem cardiac-channel genetic testing is available. It remains unknown the extent to which LQTS/BrS/CPVT-precipitated SIDS/SUID is sporadic versus familial. As such, a recommendation for LQTS, BrS, and CPVT clinical screening for surviving family members of SIDS/SUID infants may be appropriate, but it should be acknowledged that compelling evidence for such clinical evaluations is lacking.

Evaluation of Sudden Unexplained Death in the Young

Given their lethal and unsuspected nature, LQTS, CPVT, and BrS represent ideal arrhythmogenic assassins able to escape suspicion, detection, and apprehension by a standard medicolegal autopsy (Behr et al. 2003; Lee and Ackerman 2003). Because of the potentially devastating impact that these inheritable genetic disorders can have on living family members, the proper and thorough evaluation of a sudden unexplained death is paramount.

SCD may be the first manifestation of these inherited arrhythmia syndromes and the autopsy, and death-scene investigation may represent the first opportunity to make a proper diagnosis of a potentially lethal congenital disorder (Crotti 2011). These tragic unforeseen deaths in the young leave an overwhelming psychological toll on living family members. While an autopsy may indicate underlying pathology to give a reason for the sudden death (i.e., Hypertrophic cardiomyopathy (HCM), Arrhythmogenic right-ventricular dysplasia (ARVD), pulmonary embolism), a negative autopsy leaves the family without proper closure wondering what might have led to their loved one's sudden demise and whether other living family members are "next in line." In cases of autopsy-negative SUD, continued investigation through the use of either a cardiological and genetic evaluation of first- or second-degree relatives and/or a molecular autopsy may elucidate the underlying mechanisms contributing to the sudden death and allow for the identification of living family members with the pathogenic substrate that leaves them with an increased risk of cardiac events including syncope, cardiac arrest, or SCD.

While there is global consensus on the necessity to perform an evaluation of a sudden unexplained death in the young, there is extreme variability and currently a lack of guidance and standardization in the approach to such evaluations. However, specific guidelines for autopsy investigation of sudden unexpected death in the young are beginning to emerge. In 2008, Basso and colleagues on behalf of the Association for European Cardiovascular Pathology (Basso et al. 2008) and members of the Trans-Tasman Response Against Sudden Death in the Young (TRAGADY) endorsed by the Royal College of Pathologists of Australasia (TRAGADY 2008) have recently put forward guidelines to ensure standardization of autopsy practice in young sudden unexpected deaths, ancillary testing, and

Table 31.2 Key principles of postmortem investigations of sudden unexpected death in the young

1. All cases of sudden unexpected or unexplained death in the young (age group of 0–40 years) should have an autopsy
2. A full postmortem examination should be completed
3. The investigation, ideally lead by a pathologist, should involve a team approach:
a. A person designated to liaise with the family
b. Specialist cardiology involvement with the family when noncardiac causes are excluded
c. Laboratories with molecular genetics, toxicology, and metabolic expertise
4. A detailed antecedent clinical history must be obtained:
a. Circumstances of the death – detailed review of the date, time, place, and activity surrounding the death (i.e., at home, work, or on the athletic field, at rest or during exercise or emotional excitement). Was the death witnessed? Document any associated seizures, prodromal symptoms
b. Past medical history – document the general health status, including previous significant illness or events such as syncope, seizures, epilepsy, palpitations, and respiratory or neurological disease. Retrieve results of any prior investigations (e.g., ECG, EEG, CT, or MRI)
c. Previous surgical procedures or interventions – document details of current medications, in particular those that are known to be proarrhythmic (see www.qtdrugs.org)
5. A detailed and relevant family history must be obtained
a. Family history – document any family history of premature death (explained or unexplained death, SIDS, unexplained drowning, or unusual motor vehicle accidents), seizures, or syncope. Be sure to include a detailed description of the date, time, place, and activity surrounding such events, if available
b. Diagnosed disorders – document any family history of clinical diagnosis of potentially arrhythmic disorders, including LQTS, CPVT, BrS, familial cardiomyopathy, or other cardiac conditions
6. Skilled macroscopic and microscopic examination of the organs is required, particularly of the heart (especially right ventricular muscle) and the brain. This may require some specimens to be examined by other specialists
7. Adequate histological material be obtained for review or if necessary, referral
8. Tissue or blood suitable for DNA extraction must be obtained (see Fig. 31.16)
9. Results, including photography, must be clearly documented
10. Results must be described and annotated in a standard fashion which will allow epidemiological data gathering

Adapted from TRAGADY (2008)

retention of appropriate material for genetic testing. See Table 31.2 for a summary of the key principles for autopsy investigation of SUD. A key message of the TRAGADY best practices guideline is that skilled postmortem evaluation is critical after such deaths, even when there is pressure from the family to avoid an autopsy and simply ascribe the sudden death as a "heart attack," especially in light of some previous chest pain in the decedent, for example (Skinner et al. 2008). Unfortunately, many families have suffered the tragic loss of several family members due to incomplete investigations (Skinner et al. 2008).

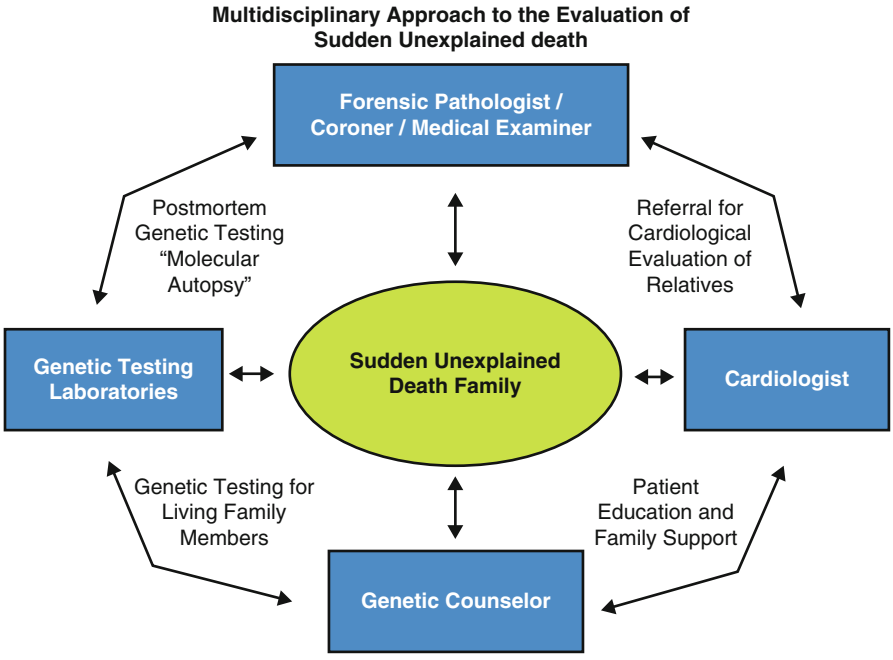


Fig. 31.6 Multidisciplinary approach to the evaluation of sudden unexplained death. The evaluation of an SUD should be an interdisciplinary collaboration between expert pathologist/medical examiner, cardiologist, and colleagues equipped with expertise in genetic counseling

The evaluation of an SUD should be an interdisciplinary collaboration between expert pathologist/medical examiner, cardiologist, and colleagues equipped with expertise in genetic counseling (Fig. 31.6) (Ingles and Semsarian 2007; Michaud et al. 2009; Semsarian and Hamilton 2011). Multidisciplinary centralized teams guiding postmortem cardiac genetic analysis will help to minimize the risk of misinterpretation of pathology findings, genetic testing results, and borderline cardiac clinical test results (Skinner et al. 2011). Collaborative efforts with a board-certified genetic counselor with specific training in cardiovascular genetics may provide valuable assistance in the evaluation of an SUD. An appropriately trained genetic counselor may be instrumental in collecting a detailed personal and family history comprising at least three to four generations and explaining the benefits, limitations, risk, availability, costs, and potential outcomes of clinical cardiological assessments, genetic testing for living relatives, and molecular autopsy for the decedent. A genetic counselor may be influential in providing information as to the clinical manifestations of specific sudden death–related disorders, their various modes of inheritance, risk stratification, and implications in family planning. The genetic counselor will also be invaluable in discussing the possible psychosocial impact of these potentially lethal disorders with the living relatives of the young SUD victim (Charron 2006; Hershberger et al. 2009; Ingles et al. 2011).

Table 31.3 Recommendations for postmortem genetic testing in sudden unexpected death cases (SUDS/SIDS)

HRS/EHRA expert consensus recommendations
1. For all SUD and SIDS cases, collection of "DNA-friendly" biological material **is recommended** for subsequent DNA analysis/genetic testing
2. In the setting of autopsy-negative SUD, comprehensive or targeted ion channel (*RYR2*, *KCNQ1*, *KCNH2*, and *SCN5A*) genetic testing **may be considered** in attempt to establish a probable cause and manner of death and to facilitate the identification of potentially at-risk relatives and **is recommended** if the circumstantial evidence points toward a clinical diagnosis of LQTS or CPVT specifically (such as emotional stress, acoustic trigger, drowning as the trigger of death)
3. Mutation-specific genetic testing **is recommended** for family members following the identification of a SUDS-causative mutation in the decedent

Table was adopted from Ackerman et al. (2011)

While there is not yet a clear consensus statement on the clinical evaluation of surviving family members, it seems reasonable to advise that first-degree relatives of the decedent undergo at least a limited cardiovascular evaluation that includes an extensive personal and family historical clinical review, physical examination, a 12-lead electrocardiogram, treadmill stress test, and echocardiogram. These tests might be viewed as the "minimal SUD screen" for all first-degree relatives. Additional tests may be required depending on the clinical suspicion of specific disorders. For example, if BrS is suspected, then a flecainide/procainamide/ajmaline challenge may further assist in the diagnosis (Semsarian and Hamilton 2011).

Alternatively or even simultaneously, postmortem genetic testing (aka, a molecular autopsy) involving the major genes associated with LQTS, CPVT, and BrS should be considered a part of the "standard operating procedure" in the evaluation of autopsy-negative SUD, especially for such deaths <40 years of age (Tester and Ackerman 2006). A much-needed HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies has been published recently, and it provides initial consensus-based guidelines and recommendations for postmortem genetic testing in sudden unexpected death cases (SUDS/SIDS/SUID) (Ackerman et al. 2011). See Table 31.3 for detailed HRS/EHRA recommendations.

A Cardiological Assessment of Living Family Members

To give perspective on the overall worth and the diagnostic yield of clinical assessment of first- and/or second-degree relatives, we highlight some recent cardiovascular evaluation series of families faced with an SUD. In 2003, Behr and colleagues performed a detailed cardiovascular evaluation of 109 first-degree relatives of 32 SUD cases and illustrated that 22 % of these families had evidence of inherited cardiac disease with the majority having clinical sequela suggestive of LQTS (Behr et al. 2003). Similarly, in 2005, Tan and colleagues found that 28 %

of families had an identifiable cardiac channelopathy including CPVT and LQTS following a rigorous clinical assessment of first-degree relatives of young SUD victims (Tan et al. 2005). In a 2008 follow-up study by Behr and colleagues, a diagnosis of inheritable heart disease was rendered in 53 % of first-degree relatives of SUD victims following a more comprehensive clinical evaluation, with 70 % being diagnosed with either LQTS (53 %) or BrS (17 %) (Behr et al. 2008). Strikingly, 30 % of the families evaluated reported a family history of additional unexplained premature sudden deaths under the age of 45 years, and nearly 20 % of the decedents had a prior history of syncope.

In 2010, van der Werf and colleagues identified a certain or probable diagnosis in 47 (33 %) of 140 families of SUD victims (aged 1–50 years) following a cardiological clinical assessment, with 96 % of the families diagnosed with an inherited cardiac disease (21 % LQTS, 17 % CPVT, 15 % BrS, and 15 % ARVC) (van der Werf et al. 2010). The diagnostic yield among families depended significantly on the age of the decedent ranging from a high of 70 % when the decedent was between ages 1 and 10 years to a low of 21 % when the decedent was between 41 and 49 years of age. Akin to the observations by Behr, many of these sudden-death victims had antecedent warning signs prior to their demise, including syncope in 15 % and a family history of young sudden death in 29 %, yet there was no prior clinical diagnosis of an inherited cardiac disease for either the decedent or any other family member.

Incomplete penetrance and variable expressivity are hallmarks of the various cardiac channelopathies which consequently lead to "concealed" forms of these disorders (Fig. 31.7) (Priori et al. 1999). LQTS has an overall penetrance of less than 40 % among families, and traditional clinical diagnostic criteria only had 38 % sensitivity in correctly identifying carriers of the familial genetic defect (Priori et al. 1999). Further, 17 % of *RyR2* mutation-positive subjects from CPVT families displayed no phenotype, and 75 % of genetically affected parents that transmitted the disorder were asymptomatic (Priori et al. 2002). Therefore, clinical assessment of surviving family members of SUD victims may not be enough to detect LQTS, CPVT, or BrS in unsuspecting individuals. A molecular autopsy involving postmortem cardiac-channel genetic testing may provide the much-needed utility for the forensic pathologist/medical examiner/coroner to provide the answer to many unexplained deaths in the young and subsequently benefit their family members left behind (Tester and Ackerman 2006).

Molecular Autopsy of Sudden Unexplained Death in the Young

In August of 1999, a young decedent's mother brought her 13-year-old son to the Mayo Clinic for an evaluation and asked: "Does my 13-year-old son have what killed my 17-year-old son 5 months ago?"(Ackerman et al. 2001b; Tester and Ackerman 2006). The 17-year-old had been found dead in bed. The results of autopsy and toxicology were negative. The results of a standard clinical assessment of the decedent's immediate family were negative for LQTS, with family members having normal ECGs.

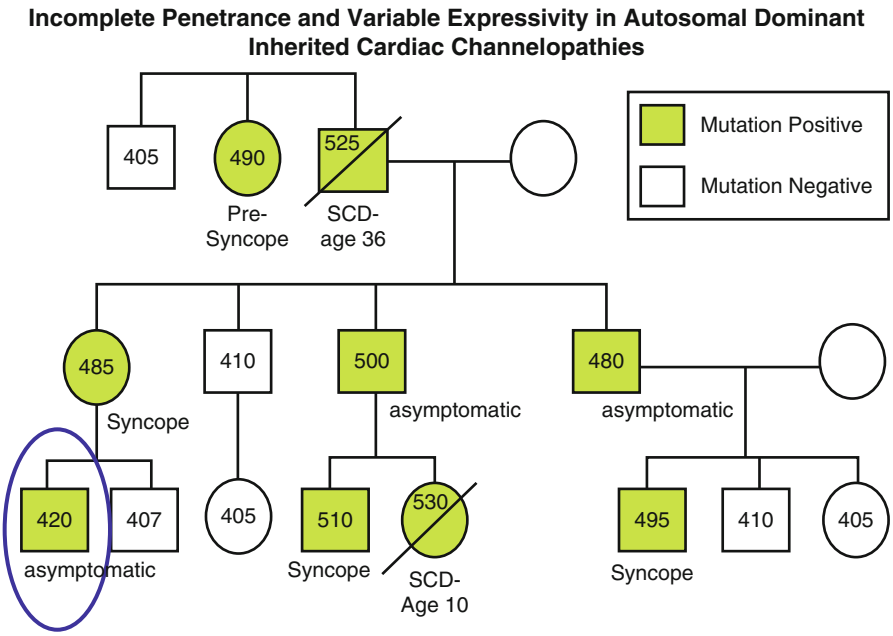


Fig. 31.7 Incomplete penetrance and variable expressivity in autosomal dominant genetic disorders. Depicted is a hypothetical long QT syndrome pedigree demonstrating incomplete or reduced penetrance (mutation-positive host with absence of disease's clinical marker; asymptomatic with a nondiagnostic QTc – *blue oval*) and variable expressivity (expression of the disorder ranging from symptom free to sudden cardiac death (*SCD*) at a young age). The numbers provided represent the QTc as measured in milliseconds (ms) (Modified from Tester and Ackerman 2008)

However, a molecular autopsy provided the answer to the mother's query. Genetic testing of properly procured autopsy material identified a familial 5- bp deletion in *KCNQ1*, which provided a definitive affirmative to the mother's question. Besides her 13-year-old son, expansion of genetic testing to remaining family members illustrated that the mutation was present in the mother's sibling and could be traced back to the decedent's maternal grandmother. Pedigree expansion also allowed the identification of those family members who did not host the specific underlying pathogenic substrate and therefore were free from the heightened risk of SCD that "comes with the territory" of hosting an LQTS-associated mutation. This particular case illustrates the role of the molecular autopsy, especially when the clinical assessment of first-degree relatives fails to reveal an underlying etiology for the sudden death.

Since this preliminary case report of molecular autopsy, investigators have sought to determine the spectrum and prevalence of pathogenic cardiac ion-channel mutations in several small series of SUD cases. To date, 10 molecular autopsy series involving the major LQTS and CPVT genes have been reported (Table 31.4) (Chugh et al. 2004; Creighton et al. 2006; Di Paolo et al. 2004;

Table 31.4 Summary of molecular autopsy series in autopsy-negative sudden unexplained death (arranged from the smallest to largest case series published)

Reference	Year published	Number of cases	Age range (years)	Males/ females	Gene analyzed	Number of mutations (% yield)	DNA source	Mutation analysis technique
Creighton	2008	9	1–43	5M/4F	*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *RYR2* (target)	1 KCNQ1, 2 RYR2 (33 %)	Frozen tissue	direct DNA sequencing
Di Paolo	2004	10	13–29	5M/5F	LQTS genes	2 KCNQ1 (20 %)	FF-PET	SSCP
Chug	2004	12	N/A	N/A	*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*	2 KCNH2 (17 %)	FF-PET	SSCP/direct DNA sequencing
Nishio	2009	17	12–42	13 M// 4 F	*KCNQ1*, *KCNH2*, *SCN5A*, *RYR2* (target)	1 KCNQ1, 3 RYR2 (24 %)	Autopsy blood	High-resolution melt
Gladding	2010	18	2–39	11M/7F	*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*	2 KCNQ1, 2 KCNH2 (22 %)	Guthrie (blood spot) card	DHPLC
Skinner	2011	33	1–40	24M/9F	*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*	1 KCNQ1, 1 KCNH2, 1 SCN5A, 2 KCNE1 (15 %)	Frozen tissue or autopsy blood	DHPLC
Doolan	2008	59	1–35	38M/ 21F	*KCNQ1*, *SCN5A* (target)	0 (0 %)	FF-PET	DHPLC
Tester	2004, 2007, 2012	173	1–43	106M/ 67F	*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, *KCNE2*, *RYR2* (target)	11 KCNQ1, 6 KCNH2, 6 SCN5A, 2 KCNE2, 20 RYR2 (26 %)	Frozen tissue or autopsy blood	DHPLC

N/A not available, *M* male, *F* female, *FF-PET* formalin-fixed paraffin-embedded tissue, *SSCP* single-stranded confirmation polymorphism, *DHPLC* denaturing high performance liquid chromatography

Doolan et al. 2004; Gladding et al. 2010; Nishio et al. 2006; Skinner et al. 2011; Tester et al. 2004, 2012; Tester and Ackerman 2007).

In 2004, Chugh and colleagues identified 12 cases of SUD following a comprehensive postmortem analysis of a consecutive series of 270 adult (age $\geq$ 20 years) cases of SCD occurring over a 13-year period (Chugh et al. 2004). Postmortem genetic analysis of the LQTS-susceptibility genes revealed the identical *KCNH2* mutation in 2 of 12 (17 %) cases of autopsy-negative SUD. Similarly, Di Paolo and colleagues performed LQTS postmortem genetic testing on 10 cases of juvenile (ages 13–29 years) SUD and identified *KCNQ1* mutations in 2 individuals (Di Paolo et al. 2004). In 2008, Creighton et al. identified putative mutations in three of nine SUD cases (Creighton et al. 2006). In 2009, Nishio identified channel mutations in 24 % of their 17-SUD case cohort (Nishio et al. 2006), and in 2010, Gladding, using DNA isolated from Guthrie (newborn blood spot) cards, identified LQTS-associated mutations in 4 of 18 (22 %) cases of SUD, aged 2–39 years (Gladding et al. 2010).

Skinner and colleagues, in 2011, published on a prospective, population-based long-QT molecular-autopsy study of postmortem-negative sudden death in 1–40-year-olds (Skinner et al. 2011). Over a 26-month period (2006–2008), DNA was collected at autopsy for 52 cases of sudden unexpected death, 33 of which remained negative following a comprehensive autopsy investigation and underwent postmortem LQTS genetic testing. Five of the 33 (15 %) were identified as having rare, possible LQTS-predisposing missense variants.

Doolan and colleagues completed a molecular autopsy series of 59 Australian cases of SUD (age range 1–35 years, 38 males, 21 females) and did not identify any putative disease-causing mutations following a mutational analysis of *KCNQ1* and a targeted (exons 10–28) analysis of *SCN5A* using genomic DNA isolated from formalin-fixed paraffin-embedded tissue (FF-PET) (Doolan et al. 2004). Individuals died while in bed, asleep, or at rest in 57 % of their cohort, while 12 % died during or after exercise and 31 % during an unknown (unwitnessed) circumstance. Based on their observations, the authors conclude that the "hit rate" of the molecular autopsy in young unexplained deaths is low. However, given the limited mutational analysis and the use of a largely unreliable source (FF-PET) of high-quality DNA for comprehensive mutation analysis, it is not too surprising that the yield of mutation detection was low. Important to note, in order to successfully perform postmortem genetic testing, coroners, medical examiners, and forensic pathologists must secure "DNA-friendly" blood or tissue samples at autopsy as will be discussed in more detail in a later section on biological material to use for molecular autopsy.

In 2007, we completed one of the largest molecular autopsy series of SUD to date (Tester and Ackerman 2007). Comprehensive mutational analysis of all 60 translated exons in the LQTS-associated genes, *KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, and *KCNE2*, along with targeted analysis of the CPVT1-associated, *RYR2*-encoded cardiac ryanodine receptor, was performed in a series of 49 medical examiner–referred cases of SUD (Tester et al. 2004). Since then, we have extended this cohort to now include over 170 cases of SUD to provide a more extensive

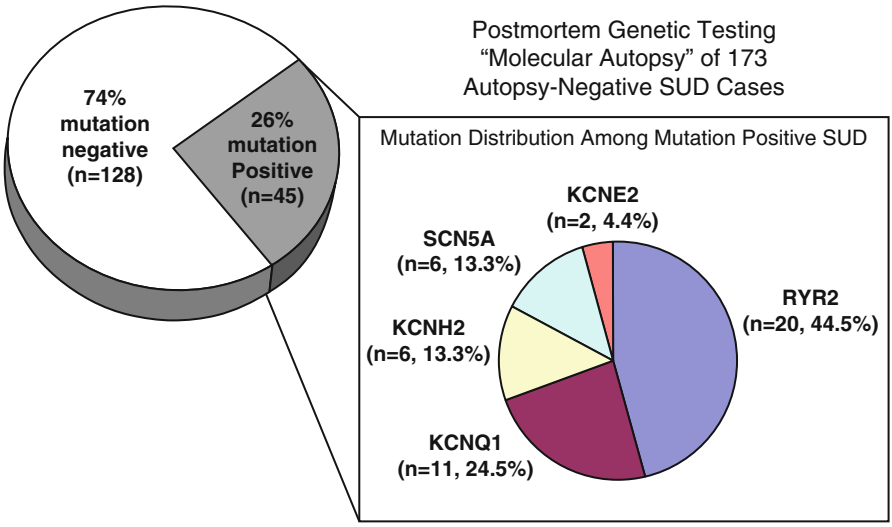


Fig. 31.8 Postmortem genetic testing yield and genotype distribution among mutation-positive sudden unexplained death cases. Shown are pie charts illustrating the overall cardiac channel molecular autopsy mutation detection yield and the specific genotype distribution among the mutation-positive cohort ($n = 45$) (Tester et al. 2012)

analysis to better define the expected yield of mutation detection and offer possible genotype/phenotype correlations that may assist in guiding phenotype-directed mutation-detection efforts in future cases of SUD (Tester et al. 2012). In this expanded molecular analysis of 173 SUD cases (106 males and 67 females, average age 18.4 ± 12.9 years), over a fourth (26 %) of these SUD cases host putative pathogenic mutations in critical ion-channel genes associated with the potentially lethal arrhythmia syndromes LQTS and CPVT, with overall 14.5 % having mutations in the LQTS-associated genes (6.5 % in *KCNQ1*, 3.5 % in *KCNH2*, 3.5 % in *SCN5A*, and 1 % in *KCNE2*) and 11.5 % with mutations in the CPVT-associated *RYR2* gene (Fig. 31.8). When specified, most of the deaths occurred during sleep (40 %), followed by a nonspecific event (30 %), or with exertion (27 %). Sudden death was the sentinel event in 30 of the 45 mutation-positive SUD cases in this series. Tragically however, despite no premortem diagnosis of a suspected cardiac channelopathy in the decedent or family member, there was a personal or family history of cardiac events or warning signs (syncope, seizures, survived cardiac arrest, near-drowning, drowning, or SCD) indicative of an underlying potentially lethal arrhythmia syndrome in nearly 60 % of the mutation-positive SUD cases that went unheeded prior to the unfortunate early demise of the decedent.

Importantly, this cohort has provided several interesting genotype/phenotype observations that may provide insight into the expected yields of postmortem genetic testing for SUD and assist in selecting cases with the greatest potential for mutation discovery and directing genetic testing efforts (Figs. 31.9–31.13) (Tester et al. 2012). For example, the yield was greatest for those with an

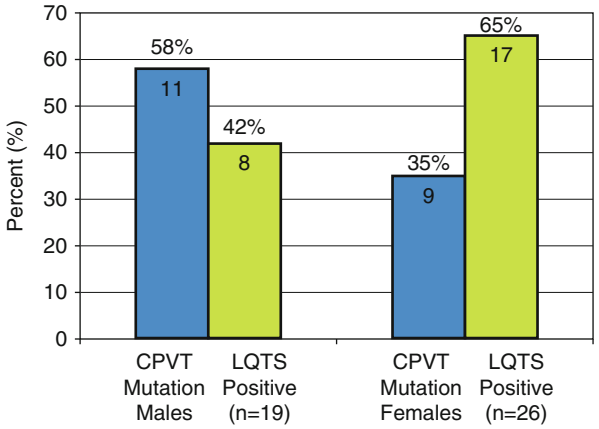


Fig. 31. 9 Summary of sex-specific genotype distribution. Bar graph comparing the percent distribution of mutations identified in the CPVT-associated *RYR2* gene to mutations identified in LQTS-associated genes for the mutation-positive males ($n = 19$) and females ($n = 26$). The number in the bar represents the number of cases with a mutation. For example, 11 of 19 (58 %) mutation-positive males had a CPVT-associated RYR2 mutation compared to 8 (42 %) that had a mutation in a LQTS-associated gene (*KCNQ1*, *KCNH2*, *SCN5A*, *KCNE1*, or *KCNE2*) (Tester et al. 2012)

exercise-induced death or positive personal/family history of syncope or sudden death. Females had a significantly higher yield than males especially if the SUD was during adolescence. Females were more likely to have LQTS-associated mutations, while males were more likely to have CPVT1-associated mutations. Among SUD victims with exercise-induced death, the yield was much higher among the 1–10-year-olds compared to the 11–20-year-olds. However, for those with death during a period of sleep, the 11–20-year-olds had a much higher yield than the 1–10-year-old group (Tester et al. 2012).

Molecular Autopsy of Unexplained Drowning

Drowning is often attributed to lack of adult supervision, poor swimming ability, drug or alcohol abuse, or seizures. However, a considerable number of these drownings are insufficiently explained by a postmortem investigation including autopsy and may in fact be secondary to a cardiac channelopathy such as LQTS or CPVT (Ackerman et al. 1999), where swimming is a relatively common arrhythmogenic trigger in these disorders. In fact, up to 15 % of children and young adults with symptomatic LQTS and a significant number of those with CPVT have cardiac events occurring during swimming-related activity (Fig. 31.14). Compared to LQT2 (*KCNH2*) and LQT3 (*SCN5A*), swimming is a relatively gene-specific trigger for LQT1 (*KCNQ1*). Choi and colleagues demonstrated that in a large cohort of 43 LQTS referral cases with a personal or family history of swimming-triggered events, 91 % had a putative arrhythmia syndrome–causing mutation (Choi et al. 2004). Among the 33 with high clinical probability for

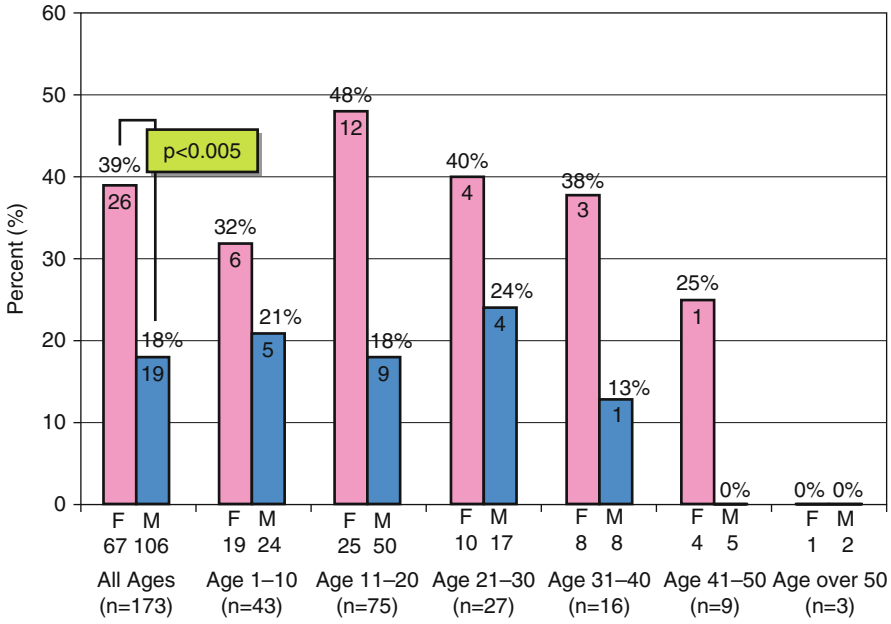


Fig. 31.10 Age and sex-specific effect on the molecular autopsy mutation detection yield. Bar graph showing the yield of mutation detection for different age groups in 10 year intervals (1–10, 11–20, 21–30, 31–40, 41–50, and over 50 years) for both males (*M*) and females (*F*). The number in parenthesis ($n = x$) represents the total number of cases and the number below F or M represents the number of females or males in the respective category. The number in the bar represents the number of cases with a mutation with the percent yield of mutation detection highlighted above the bar (Tester et al. 2012)

LQTS, 85 % were genotyped as LQT1. Furthermore, for all 16 LQT1-positive index cases with a personal symptomatic history, the near-drowning or drowning represented the sentinel event. For those LQTS referrals with a swimming-triggered event but a low diagnostic score for LQTS, 90 % had mutations in *RYR2*: the gene causative for the LQTS-mimicking disorder, CPVT (Choi et al. 2004). Given the highly arrhythmogenic nature of swimming among these potentially lethal inheritable channelopathies where drowning often represents the sentinel cardiac event in many unsuspecting LQTS or CPVT families, the performance of a molecular autopsy in cases of unexplained drowning appears warranted.

In fact, the first ever report of a postmortem molecular diagnosis of an arrhythmia disorder through the use of a molecular autopsy occurred in 1999 when we reported the diagnosis of inherited LQTS in a 19-year-old woman who died after a near-drowning (Ackerman et al. 1999). This postmortem analysis identified a novel inherited *KCNQ1* (LQT1) mutation in a previously asymptomatic, otherwise healthy and vibrant youth who was discovered face down at the bottom of the pool where she had been swimming laps following her routine weight-lifting regime. The family history was unremarkable for syncope, seizures, palpitations,

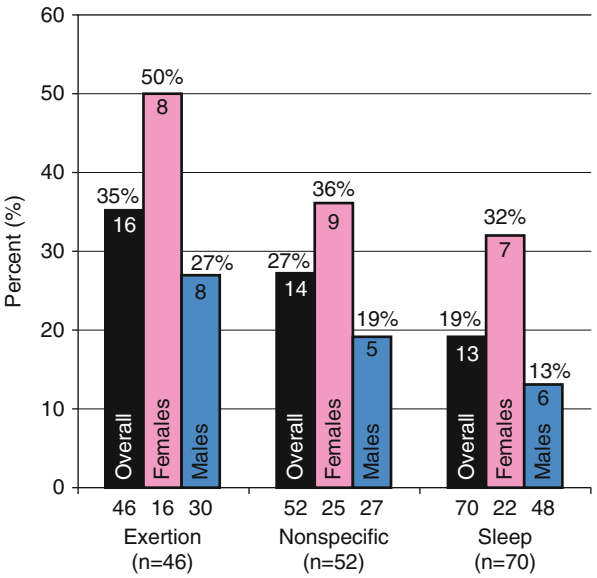


Fig. 31.11 Effect of sudden death-associated trigger/event on the yield of molecular autopsy. Bar graph illustrating the different yield of mutation detection between three main categories of sudden death-associated triggers/events (exertion, nonspecific, and sleep) for the overall cohort, females, and males at all ages. The number in the bar represents the number of cases with a mutation with the percent yield of mutation detection highlighted above the bar (Tester et al. 2012)

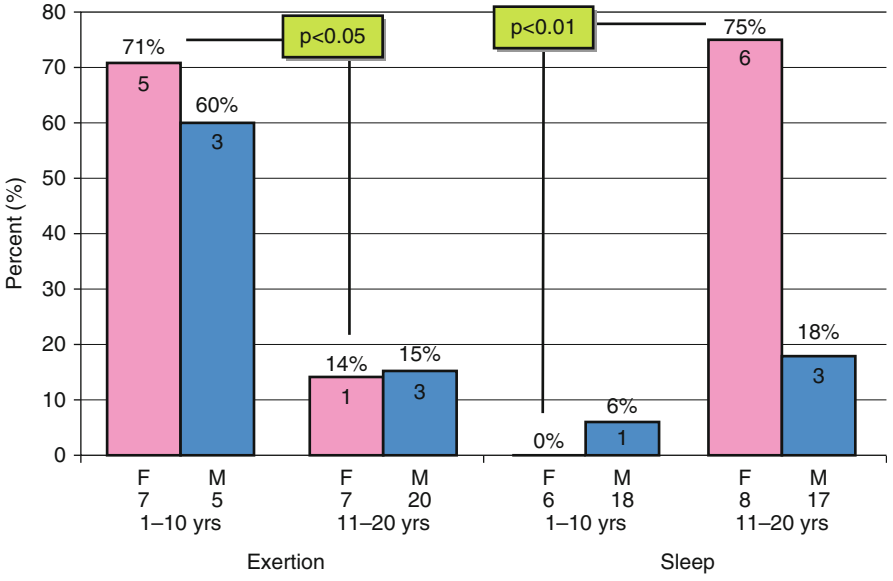


Fig. 31.12 Effect of age, sex, and trigger/event on the molecular autopsy yield. Bar graph illustrating the difference in mutation detection between children ages 1–10 and adolescence ages 11–20, among both male and female SUD victims with either exertion- or sleep-associated sudden death. The number in the bar represents the number of cases with a mutation with the percent yield of mutation detection highlighted above the bar (Tester et al. 2012)

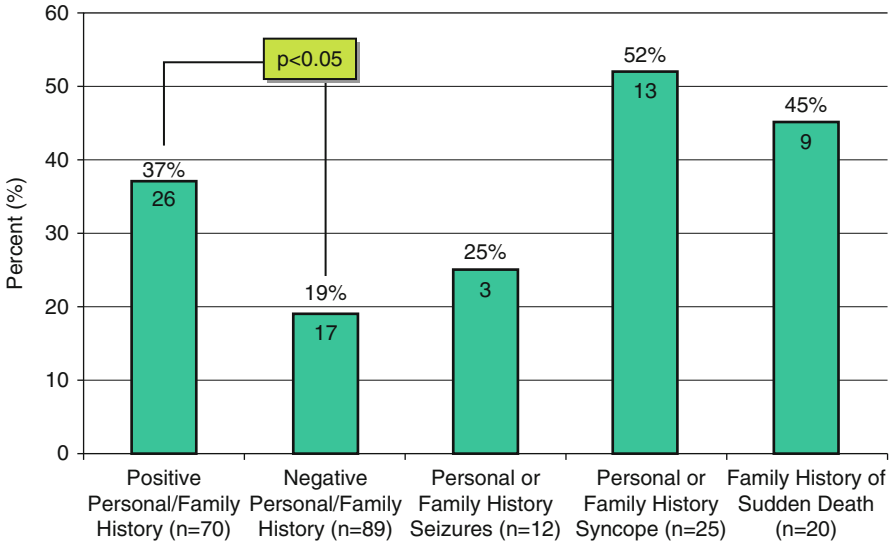


Fig. 31.13 Effect of a positive previous personal or family history of cardiac events on the yield of postmortem cardiac channel genetic testing. Bar graph showing the difference in mutation detection yield between those SUD victims with either a negative ($n = 89$) or positive ($n = 70$) documented personal or family history of cardiac events or other "warning" signs including, seizures ($n = 12$), syncope ($n = 25$), or sudden cardiac death ($n = 20$). The number in the bar represents the number of cases with a mutation with the percent yield of mutation detection highlighted above the bar (Tester et al. 2012)

or sudden death. Tragically, her sudden death was the sentinel manifestation of the familial LQTS in this family. Particularly important for this family, the elucidation of the disease-causing mutation, which was traced back to the woman's maternal grandfather, provided the means for definitive genetic analysis of at least 60 extended relatives and the initiation of prophylactic and potentially life-saving medical therapy for those with the familial mutation. In 2005, the Ackerman group provided proof of principle that some cases of unexplained drownings harbor mutations in the cardiac ryanodine receptor associated with CPVT1 following a cardiac-channel molecular autopsy in two young medical examiner–referred cases (Tester et al. 2005a). A familial mutation was identified in a 16-year-old female who drowned during swim team practice, and a sporadic de novo mutation was identified in a 9-year-old apparently healthy boy who failed to surface while diving into a lake with friends at a summer camp. Since these initial case reports, two molecular autopsy studies have sought to determine the prevalence of pathogenic cardiac ion-channel mutations in unique series of unexplained drowning cases.

In 2003, Lunetta and colleagues performed a postmortem genetic analysis identifying only a single LQT2 mutation in 1 out of 165 consecutive bodies (mean age of 49.1 years, range 1–89 years) found in water in Finland, a bathtub death of a 44-year-old female initially ruled as a suicidal drowning (Lunetta et al. 2003). This study concluded that the minimum prevalence of LQTS in drownings was only 0.61 % and

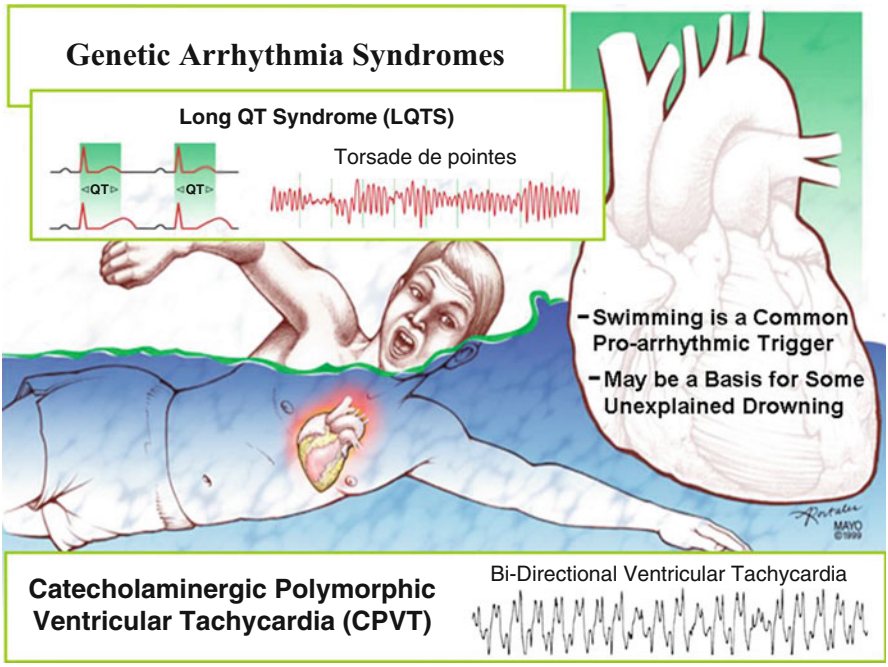
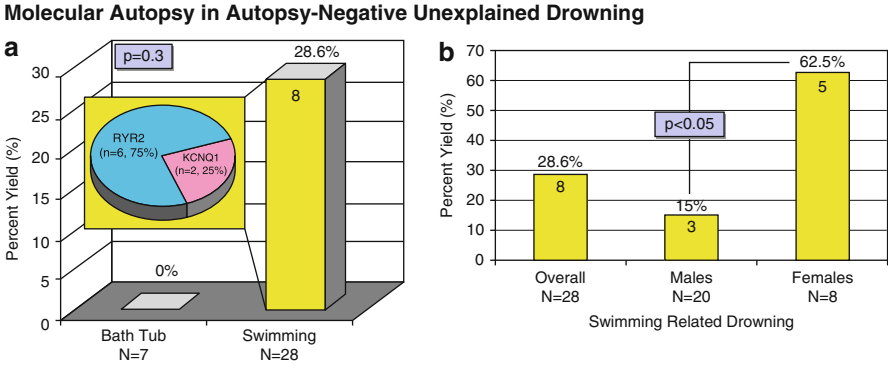


Fig. 31.14 Cardiac arrhythmia syndromes and swimming-triggered cardiac events. A significant number of drowning remain unexplained by a postmortem investigation including autopsy and may in fact be secondary to a cardiac channelopathy, like LQTS or CPVT, where swimming is a relatively common arrhythmogenic trigger for these potentially lethal disorders

provided a point estimate of 1–2 % overall. However, this very limited mutational analysis only sought to identify two specific LQTS Finnish founder mutations in this cohort: G589D-KCNQ1 (LQT1) and L522S-KCNH2 (LQT2), which encompass about 35 % of familial LQTS in Finland. This retrospective 165-person study consisted of mostly accidental (65 %) or suicidal (22.5 %) deaths. Only 9 % of the cohort represented "undetermined intent."

In 2011, the Ackerman group performed a molecular autopsy, including postmortem genetic testing involving the three major LQTS genes (*KCNQ1*, *KCNH2*, and *SCN5A*) and the major CPVT gene (*RYR2*), on 35 medical examiner/coroner–referred cases of unexplained drowning; 7 represented bathtub submersions and 28 were swimming-related drownings (Tester et al. 2011a). While none of the seven bathtub drowning victims was mutation-positive, 28 % of swimming-related drowning cases hosted putative pathogenic mutations in the critical LQTS/CPVT-associated ion-channel genes (Fig. 31.15). Of the 28 swimming-related drowning cases, 7 % had an LQTS-associated *KCNQ1* mutation and 21 % had a CPVT-associated *RYR2* mutation, with the majority of mutations being identified as familial. Interestingly, the yield of mutation detection for the postmortem genetic test in the swimming-related drowning cohort was higher significantly in females



C Cardiac Channelopathy Mutations Identified in Swimming Related Drowning Victims

Age (years)	Race	Mutation	Familial or sporadic	Personal or family history
19	White	**AAPde171-73-KCNQ1, V524G-KCNQ1**	Familial	Documented prolonged QTc - family member
12	White	**L273F-KCNQ1**	N/A	Unexplained drowning - family member
16	White	**R414C-RYR2‡**	Familial	No
13	White	**I419F-RYR2**	Familial	Unexplained drowning - 2 family members
19	White	**R1013Q-RYR2**	N/A	No
14	White	**V2321A-RYR2**	Familial	No
8	White	**R2401H-RYR2**	Sporadic	Exercise-induced cardiac arrest -self
9	White	**V2475F-RYR2**	Sporadic	No

Fig. 31.15 Molecular autopsy in autopsy-negative unexplained drowning. (**a**) Bar graph comparing the percent yield in mutation identification between those victims of a bathtub submersion ($n = 7$) and those victims suffering a swimming-related unexplained drowning ($n = 28$). The number within the bar represents the number of cases identified with a mutation. The pie chart inset illustrates the distribution of genotypes for the eight cases hosting putative pathogenic mutations. (**b**) Bar graph showing the significant ($p < 0.05$) difference in mutation detection yield between male ($n = 20$) and female ($n = 8$) drowning victims. The number within the bar represents the number of mutation-positive individuals. Shown in (**c**) is a summary table of cardiac channel mutations identified in swimming-related drowning victims (Tester et al. 2011a)

(62.5 %) compared to males (15 %). While 35 % (eight cases) of the drowning victims 20 years or younger ($n = 23$) were found to be mutation-positive, no mutations were identified in the five drowning victims who were over the age of 20 years. The yield of mutation detection among those swimming-related drowning victims with either a positive personal or family history was 50 % (4/8) compared to only 24 % (4/17) for those decedents with a negative history (Tester et al. 2011a).

This data also suggests that many cases of unexplained drowning may be preventable. Although the unexplained drowning was the sentinel event in the majority of the cases, half of the eight drowning victims with a cardiac-channel mutation exhibited potential warning signs, either personally or in the family, yet no premortem diagnosis of LQTS or CPVT had been established. It is critical that such warning signs be heeded and thoroughly investigated. Given the efficacy of LQTS- and CPVT-related therapies, it is expected that a premortem diagnosis of these conditions might have thwarted the sudden death. A molecular autopsy

can have a profound influence on surviving family members and should be considered in all cases of unexplained drowning. The elucidation of a channelopathy–susceptibility mutation in a postmortem sample may provide molecular confirmation as to cause and manner of death and a prospective life-saving clue for the evaluation and management of living relatives. These data also support the recommendation of a comprehensive cardiological evaluation for surviving first-degree relatives (Tan et al. 2005).

Postmortem Genetic Testing: The Molecular Autopsy

Benefits of Genetic Testing for Potentially Lethal Cardiac Channelopathies

Genetic testing for cardiac channelopathies in SUD may assist in establishing a definitive molecular diagnosis of a likely cardiac channelopathy in the decedent by elucidating the exact molecular underpinnings contributing to the sudden and unexpected early demise. Establishing the exact molecular cause may provide a gold standard molecular marker which can be used to confirm or exclude the presence of a disease-causing mutation in presymptomatic family members and allow for rapid and accurate identification of those family members who would benefit from further clinical assessment and guide the commencement of preemptive strategies targeted toward the prevention of another tragedy among living family members (Behr et al. 2003). Additionally, the identification of an underlying cause of death may bring some much-needed closure to grieving family members as to why their child, spouse, or other loved one died suddenly.

Considering that autopsy-negative SUD accounts for a significant number of sudden deaths in the young and that inherited cardiac channelopathies may underlie many of these deaths, the clinical cardiological assessment of surviving family members and a cardiac-channel molecular autopsy should be viewed as the standard of care for the postmortem evaluation of SUD. Accordingly, the issue should no longer be whether relatives should be evaluated following an autopsy-negative SUD or whether a molecular autopsy should be performed on an autopsy-negative SUD victim. Instead, the issue now must shift to focus on three key questions: (i) What type of SUD/SIDS/SUID victims should undergo a molecular autopsy, (ii) what type of biological materials are necessary to harvest at autopsy for the use of a molecular autopsy, and (iii) how should one interpret and report genetic test results?

Indications for Molecular Autopsy

Recently, an HRS/EHRA expert consensus statement on the state of postmortem genetic testing has recommended the collection of “DNA-friendly” biological

material to be collected on all sudden-unexplained-death and SIDS/SUID cases and has recommended postmortem cardiac-channel genetic testing, especially in cases where circumstantial evidence suggests that a cardiac channelopathy like LQTS or CPVT may be the underlying mechanism of the early and sudden demise (Ackerman et al. 2011). See Table 31.3 for detailed HRS/EHRA recommendations.

Unfortunately, it has been extremely difficult for some medical examiners, coroners, or forensic pathologists to provide this level of care for several reasons. Most importantly, insurance companies or other third-party payers largely do not accept responsibility for providing coverage for the molecular autopsy of a deceased person, regardless of the implications to surviving relatives. This severely limits the postmortem genetic analysis to those families who can afford the out-of-pocket expense for commercially available genetic testing or leaving the medical examiner, coroner, or forensic pathologist with the option of enrolling the deceased's sample into non-fee research-based genetic testing where the process can be painfully slow (Ackerman 2009). Unfortunately, given the expensive and time-consuming nature of postmortem genetic testing, it is currently necessary for the medical examiner, coroner, or forensic pathologist to be case-selective (Oliva et al. 2011).

Through a recent molecular-autopsy investigation on now more than 170 medical examiner–referred and/or coroner-referred cases of autopsy-negative SUD cases, some interesting genotype/phenotype correlations that may assist in selecting a priori cases with the greatest potential for mutation discovery and directing genetic testing efforts have been gleaned (Tester et al. 2012). To summarize, while males represented two-thirds of the SUD cohort, females (39 % yield overall) were significantly ($p < 0.005$) more likely to host a channel mutation than males (18 % yield overall), especially if the SUD was during adolescence (48 % yield females vs. 18 % in males, aged 11–20 years). In general this higher yield in females was consistent across all ages. For those cases that were identified as mutation-positive, females were most likely to host mutations in LQTS-susceptibility genes, while males most often had mutations in the CPVT-associated RYR2 gene. When considering the event/circumstance surrounding the death, those decedents with a death associated with exercise (35 % overall, 50 % in females, 27 % in males) had a higher detection rate than those with a nonspecific trigger/circumstance (27 % overall, 36 % in females, 19 % in males) and those who died during a period of sleep (19 % overall, 32 % in females, 13 % in males). Interestingly, when comparing events at death (exertion vs. sleep) combined with age at death (1- to 10-year-olds vs. 11–20-year-olds), for those decedents who were between the ages of 1 and 10 years with an exercise-associated death, the mutation detection yield was 71 % for females and 60 % for males, with mutations most often associated with CPVT1 or LQT1. However, the yield dropped significantly to around 15 % for both male and female decedents aged 11–20 years with an exercise-associated death. Conversely, for those who died during sleep, those aged 11–20 years had a much higher yield (75 % in females and 18 % in males) than when the sleep-associated death occurred in a victim aged 1–10 years (0 % in females and 6 % in males). As expected, SUD cases with a positive personal or

family history of cardiac events had a significantly higher mutation-detection yield (40 %) than those with no personal or family history (19 %) of cardiac events, with mutations identified in 45 % of SUD victims with a family history of a prior sudden death. Interestingly, the mutation-detection yield was two times higher in those SUD victims with a personal or family history of syncope compared to a history of seizures (52 % vs. 25 %). While not as common as syncope, some patients with LQTS or CPVT do experience seizure-like symptoms. This data suggests that sudden unexplained death of an individual with a personal or family history of seizure activity may in fact be a result of a neurological disorder, akin to sudden unexplained death in epilepsy (SUDEP) rather than as a result of a primarily cardiac channelopathy, like LQTS or CPVT (Tester et al. 2012).

Accordingly, one might a priori expect a higher yield of LQTS-associated mutation detection in an adolescent or young adult female compared to a higher expected yield of CPVT-associated mutations among male children. Since young male and female children with exercise-associated death and adolescent females with death during a period of sleep have the highest mutation-detection rate ranging from 60 % to 75 %, these types of SUD cases should undergo molecular autopsy (Tester et al. 2012).

Knowing the effect of sex, age, death circumstance (i.e., sleep or exertion), and/or personal/family history of cardiac events on the overall yield of mutation detection may help in guiding both the clinical evaluation of surviving relatives and the molecular autopsy for cases of SUD, thereby creating a more cost-effective approach to the evaluation of SUD.

Biological Material Used in a Molecular Autopsy

Unfortunately, due to its ease of storage and transportation, archived formalin-fixed paraffin-embedded tissue is often the only source available for DNA procurement (Basso et al. 2010). However, DNA from paraffin-embedded tissue is error-prone and should be considered largely unreliable for the molecular autopsy (Carturan et al. 2006). In contrast, at least 5–10 ml of whole blood collected in EDTA (purple-top tube) and/or 5 g of fresh heart, liver, or spleen tissue provides the greatest source of intact DNA, permitting the successful performance of postmortem genetic testing and should be obtained at autopsy (Fig. 31.16) (TRAGADY 2008; Ackerman et al. 2001b, 2011; Basso et al. 2010). The tissue should be stored at −80 °C, until DNA can be extracted. Alternatively, 50–100 μl of whole blood on filter paper may be used for a molecular autopsy. However, this tends to provide a very limited amount of DNA and, while a viable option, should be considered as a suboptimal source due to the limited amount of genetic analysis that can be done. It is of extreme importance that guidelines central to the procurement of DNA-friendly sources be added to the standard of care for the postmortem analysis of a SUD.

Acceptable DNA Source – High Quality and "DNA Friendly"

- 5 to 10 ml of whole blood in EDTA (purple top) tube
- 5 grams of tissue (heart, spleen, or liver) stored frozen at -80 c

Acceptable DNA Source with Limited Capability due to Low DNA Yield

- 100 to 200ul of blood spot on filter card
  (a 50ul drop ~ size of an American Quarter)

Unacceptable DNA Source – Do Not Use

- Formalin fixed tissue
- Formalin fixed paraffin embedded tissue

Fig. 31.16 Biological material for molecular autopsy. Depicted is a summary of acceptable (*green heading*) and unacceptable (*red heading*) DNA sources for the performance of a molecular autopsy

Interpretation of Genetic Testing Results

Given the severe consequences surrounding the misdiagnosis and mismanagement of patients with these potentially lethal cardiac disorders, the clinical evaluation and management of a patient and family suspected of having genetic heart disease should be performed under the supervision of a pediatric or adult cardiologist with experience and expertise in heritable cardiac channelopathies (Tester and Ackerman 2008). Because of the issues associated with incomplete penetrance and variable expressivity, the genetic test result must be interpreted cautiously and incorporated into the overall diagnostic evaluation for these disorders. In fact, even when a genetic variant has been published previously as a putative pathogenic mutation, assignment of a specific genetic variant as a true disease-causing mutation still requires vigilant scrutiny.

To demonstrate this necessity, recently a comprehensive analysis of the spectrum and prevalence of rare non synonymous single-nucleotide "mutations" (amino acid–altering variants) in the major LQTS-associated cardiac ion-channel genes (*KCNQ1*, *KCNH2*, and *SCN5A*) in over 1,300 apparently healthy subjects showed that approximately 4 % of Caucasians and up to 8 % of healthy non-Caucasians hosted rare amino acid–altering missense variants (Ackerman et al. 2004, 2003). While some of the variants identified in this healthy population may represent subclinical disease modifiers, most probably represent benign background "genetic noise." Of course, this observation of background nonpathogenic missense variants is not confined to the LQTS genes, but may extend to virtually any gene in the human genome. For LQTS, this "signal-to-noise" observation has enabled case/control mutational analysis of the properties and localization of case-associated mutations compared to the compendium of presumably innocuous rare variants seen in controls. Algorithms based on mutation location, species conservation, and

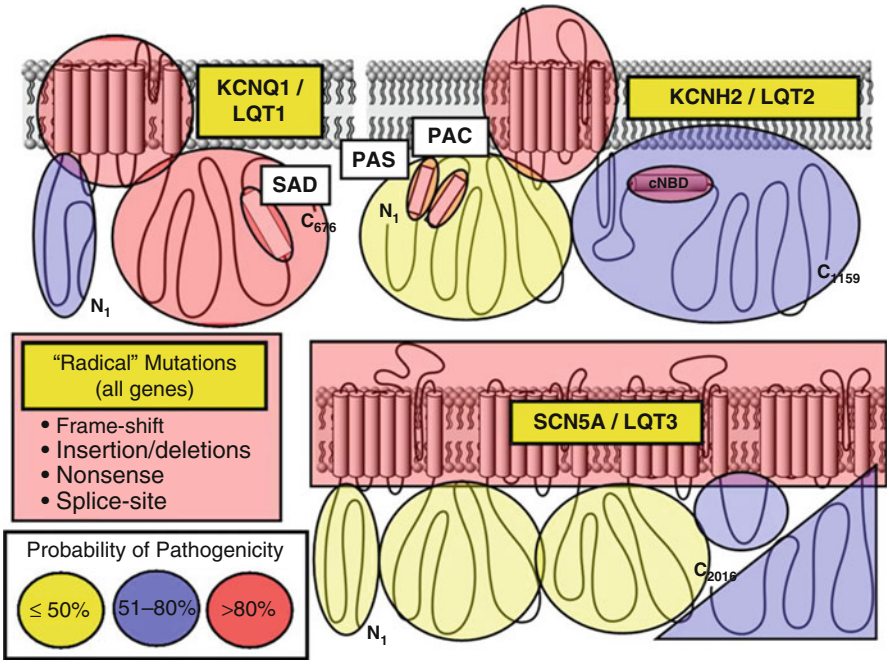


Fig. 31.17 Probabilistic nature of LQTS genetic testing. Three major ion channels causative for LQTS with areas of probability of pathogenicity shown for mutations localizing to these respective areas. While "radical" mutations have a greater than 90 % probability of being a true pathogenic mutation, the level of probability for missense mutations varies depending on their location for each channel protein. Missense mutations residing in red shaded areas have a high probability (>80 %) of being pathogenic, those in blue are possibly (51–80 %) pathogenic, and those in yellow shaded areas truly represent variants of uncertain significance (VUS, ≤5.0 % probability) clinically (Kapa et al. 2009) (Adopted from Tester and Ackerman 2012)

the biophysical nature of the amino acid substitution may assist in distinguishing pathogenic mutations from otherwise rare variants of uncertain significance (VUS) and perhaps allow for the assignment of estimated predictive values for the probability of pathogenicity of each novel mutation identified within a specific gene (Fig. 31.17) (Kapa et al. 2009).

Legal and Societal Implications of the Molecular Autopsy

While benefits of postmortem genetic testing such as (i) identifying the underlying cause for the SUD, (ii) providing a diagnostic "gold standard" for living family members, and (iii) guiding risk stratification and the use of prophylactic therapies, genetic testing may also contribute to risk of depression, anxiety, guilt, stigmatization, discrimination, family conflict, and unnecessary or inappropriate use of risk-reducing strategies (Van Riper 2005). Therefore, it is crucial that family members are well informed on postmortem genetic testing implications and must not be coerced

into providing a sample of their own for genetic analysis. Full disclosure must be given as to the research or clinical intent of the genetic test, the results of the analysis, and who will have access to the results (Tester and Ackerman 2008).

Genetic information must be considered private and personal information with the potential for mishandling (Lea et al. 2005; Thomas 2004). Confidential information disclosure to third parties, including insurance companies or employers, can have genetic discriminatory consequences to the patient. However, in May 2009, the Genetic Information Nondiscrimination Act (GINA) was signed into federal law in the USA preventing employers and health insurers from denying employment or insurance to a healthy individual based on genetic test results (Abiola 2008). Despite this welcomed advance, the law failed to extend discriminatory protection over either life insurance or disability insurance.

Genetic testing should be considered both a family and individual experience (Van Riper 2005). While the molecular autopsy is performed on the decedent's genetic material, the test results may have substantial implications for living family members. However, under current practice, only the legal guardian or "next of kin" (i.e., spouse or parent) may be informed of the decedent's genetic test results. The decision or responsibility to inform unsuspecting relatives of the potential for genetic predisposition for sudden cardiac death resides exclusively on that informed relative (Tester and Ackerman 2008). To what degree moral or even legal obligation should be placed on the informed family member to be responsible for disclosing potentially life-saving/life-ending genetic information to uninformed and unaware relatives who may be at risk of a potentially lethal cardiac event is debatable. For example, should an individual with a family history of sudden cardiac death be held accountable, if he or she has been informed of the identification of their family's cardiac-channelopathy mutation yet fails to inform a family member who subsequently experiences sudden cardiac death?

Given these extremely important family matters involving both legal and societal implications of genetic testing, it is well advised whenever possible to have an appropriately masters-trained board-certified genetic counselor, preferably with specialized training in cardiovascular genetics, as a part of the molecular-autopsy team to be involved in the communication process with the family regarding the implications of postmortem genetic testing and genetic test results. At a minimum, these key concepts/issues must be detailed with the family.

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Other Pediatric Cardiac Conditions

32

Dylan V. Miller

Contents

Abstract

An awareness of the cardiac conditions encountered at autopsy in the pediatric population is important for pathologists in their investigation of death and efforts to help improve life for surviving family members. This chapter discusses

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several cardiac conditions, including those specific to this age group as well as those occurring at any age, with emphasis on the unique aspects of their manifestations during infancy and childhood. These conditions include typically adult-onset diseases, inflammatory diseases, genetic conditions, congenital malformations, and cardiomyopathies of uncertain etiology.

Introduction

Just as in adults, the vital role of the cardiovascular system is emphasized through the consequences of its disease and dysfunction in infants and children. Unlike adults, sudden cardiac death in this age-group is much less frequent and reflects, with few exceptions, an entirely different spectrum of pathology. Genetic and malformative conditions, as well as intrinsic defects in the contractile apparatus and action potential propagation, manifest early in life and are primarily the realm of pediatric medicine. Acquired conditions accelerated by unique aspects of the developing immune system or influenced by systemic metabolic defects also come to attention early in life and show relatively little overlap with adult-onset cardiac disease.

Inherited arrhythmia syndromes linked to ion-channel defects are covered in ► Chap. 31, "Cardiac Channelopathies and the Molecular Autopsy." An awareness of the "other" cardiac conditions encountered at autopsy in the pediatric population is also important for pathologists in their investigation of death and efforts to help improve life for surviving family members. This chapter reviews several such conditions, including those specific to this age group as well as those occurring at any age, with emphasis on the unique aspects of their manifestations during infancy and childhood.

Typically Adult-Onset Diseases Occurring in Pediatric Patients

Coronary Atherosclerosis in Adolescents and Familial Hypercholesterolemia

Atherosclerosis is recognized to have early events traceable to childhood and to progress through adolescence. Among young men aged 15–19 yrs with high-risk modifiable behaviors (hyperlipidemia, hyperglycemia, hypertension, smoking, and obesity), there is an estimated 6 % chance of detecting a raised plaque in the left anterior descending (LAD) coronary artery with potential for rupture and/or thrombosis and a 70 % chance of finding any type of plaque in the same vessel (McMahan et al. 2006).

While deaths from usual ischemic coronary heart disease in adolescents are extremely rare, they do occur. Familial hypercholesterolemia significantly accelerates the rate of atherosclerotic progression, and there are several reports of

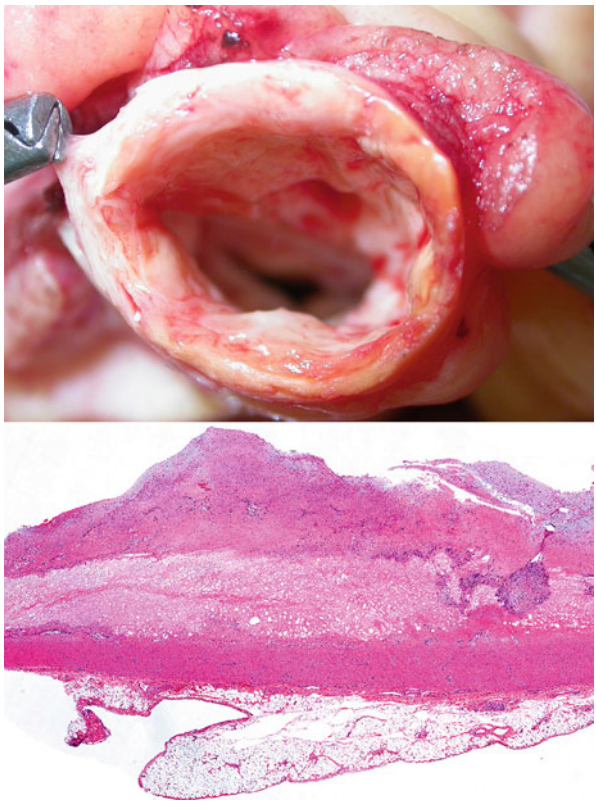

Fig. 32.1 Aortic atherosclerosis in familial hypercholesterolemia. Ascending aorta in cross section from the explanted heart of a 13-year-old boy with familial hypercholesterolemia showing marked wall thickening (*upper panel*) and a corresponding photomicrograph showing extensive atherosclerotic plaque (*lower panel*, (Hematoxylin and Eosin, H&E × 10)

affected patients dying during childhood from complications of coronary heart disease (Moorjani et al. 1989; Williams 1989; Widhalm et al. 2011). The histopathology does not differ significantly from those seen in adults, aside from the vessel caliber and degree of outward remodeling, which is usually less impressive due to the shortened interval of plaque evolution. The plaques are essentially indistinguishable from those seen in adults, though the lipid and necrotic-core material in plaques may be less prominent. They are usually prominent in the aorta (Fig. 32.1) as well as coronary and other medium-size muscular arteries (Fig. 32.2). Cutaneous xanthomas are also common in familial hypercholesterolemia and can be an important clue from the external examination.

Non-atherosclerotic Coronary Obstructions

As with adults, obstructions to coronary flow not related to atherosclerosis can occur in children with similar downstream effects on the myocardium. These include septic

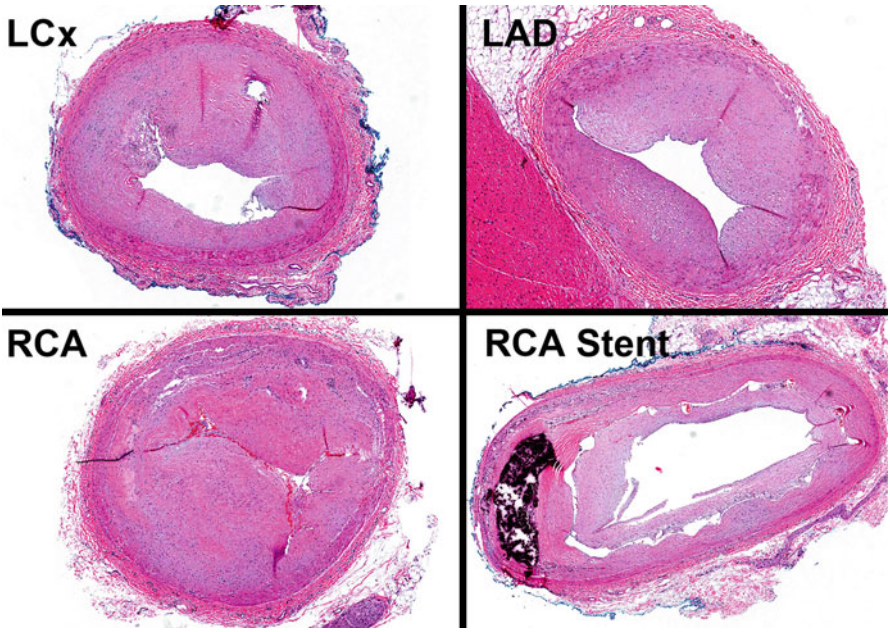

Fig. 32.2 Coronary atherosclerosis in familial hypercholesterolemia. Photomicrographs from the coronary arteries of the same patient shown in Fig. 32.1. There is >75 % occlusion in all vessels. The plaques are mostly fibrous and with intimal smooth muscle infiltration rather than cholesterol clefts and necrotic debris. There is also comparatively little outward vessel remodeling in response to the luminal stenosis compared to what is seen in adults (Hematoxylin and Eosin, H&E ×10)

embolization from endocarditis, thromboembolism from intracardiac clots, and dissection as a complication of angiography or surgical interventions.

Inflammatory

Kawasaki Disease

An important complication of the mucocutaneous lymph node syndrome, or Kawasaki disease, is vasculitis affecting muscular arteries (including the coronaries) and resulting in weakening of the wall with pseudoaneurysm formation (Fig. 32.3). The pseudoaneurysms are prone to rupture acutely and thrombotic occlusion chronically. Thrombosis may also lead to distal embolic complications and subsequent myocardial infarction. Death from these complications is estimated at 0.3 % (Newburger and Burns 1999).

Kawasaki disease affects primarily young children (50 % <2 years and 80 % <4 years) and presents as cervical lymphadenopathy, fever, conjunctivitis, oral mucosal erythema, "strawberry tongue," and diffuse rash with characteristic involvement of the palms and soles. Vasculitis is seen in affected organs (including skin).

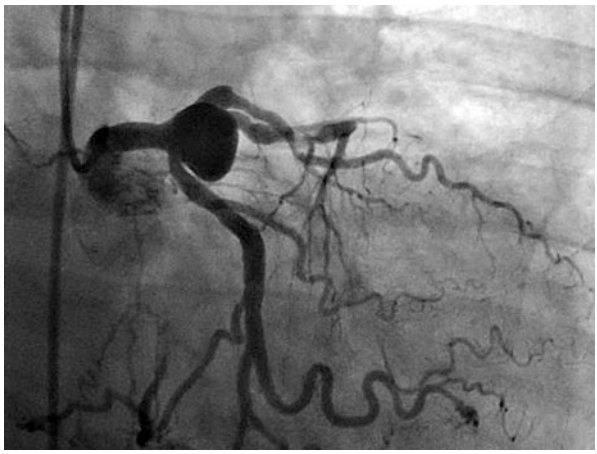

Fig. 32.3 Coronary pseudoaneurysm in Kawasaki disease. Coronary angiogram showing a large pseudoaneurysm at the bifurcation of the left anterior descending and left circumflex (LCx) coronary arteries from a patient with Kawasaki disease as a child

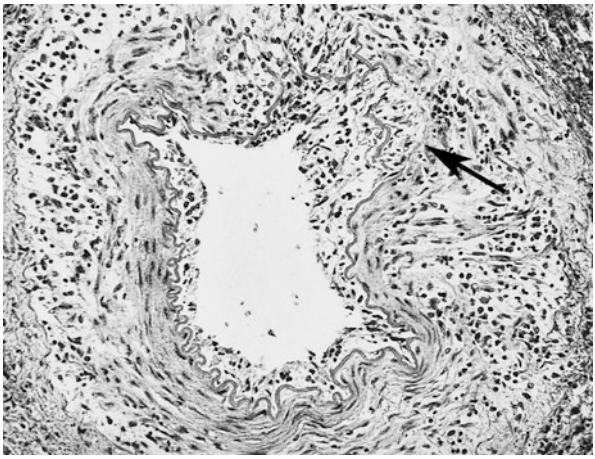

Fig. 32.4 Histopathology of active Kawasaki disease. Photomicrograph of a coronary artery involved by active-phase Kawasaki disease. There is transmural inflammation, rich in neutrophils, and disruption of the internal elastic lamina (*arrow*). Softening of the wall due to necrosis leads to contained rupture and later pseudoaneurysm formation (Used with permission, adapted from Fig. 18-8 in Kawasaki Disease in Churg & Churg eds. *Systemic Vasculitides*. p264. Copyright IGAKU-SHOIN (1991))

Cardiac manifestations include myocarditis, pericarditis, endocarditis, valvulitis, and coronary arteritis (Quam et al. 1986). Coronary pseudoaneurysms develop between 1 and 8 weeks after the acute phase and persist into adulthood.

In the acute phase, the coronary vasculitis appears acute and necrotizing (Fig. 32.4). There is transmural inflammation with abundant neutrophils and fibrinoid necrosis. Contained rupture may be seen as well, and such is the basis for later pseudoaneurysms. Fresh thrombus may also be seen acutely. As the vasculitis

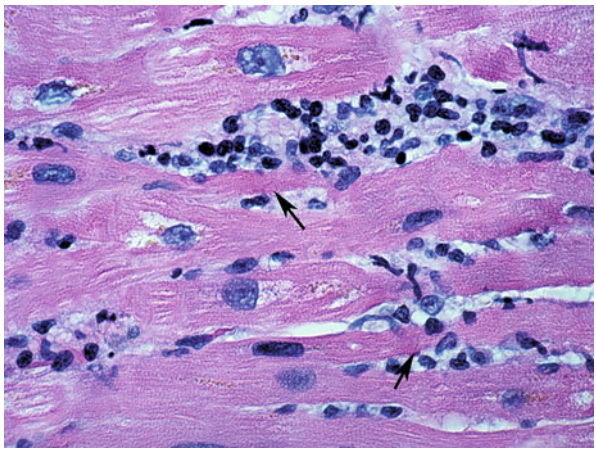

Fig. 32.5 Histopathology of myocarditis. Photomicrograph showing unequivocal myocarditis. There is both interstitial lymphocytic inflammation and associated myocyte damage (*arrows*) (Hematoxylin and Eosin, H&E ×400)

heals, evidence of transmural wall damage persists as disruption of the internal elastic lamina and replacement-type fibrosis. Pseudoaneurysms can be confirmed (and distinguished from true aneurysms) by elastic staining as well, demonstrating disruption of the internal elastic lamina at the neck of the aneurysm.

The histological features in the chronic phase are not readily distinguishable from other forms of vasculitis (including polyarteritis nodosa and mycotic aneurysm due to septic embolism). Implicating Kawasaki disease as a cause of coronary artery aneurysm without a convincing history of classic symptoms can be difficult. This condition is often raised in the differential and favored given its predilection for coronary arteries (Bartoloni et al. 2002).

Myocarditis

Myocarditis is a common finding among patients dying suddenly and in the absence of grossly apparent pathological findings at autopsy. It affects patients of all ages, but since the majority of cases are related to sequelae of viral infection, it is common in children.

The diagnosis of myocarditis rests on demonstrating interstitial and perivascular inflammation within the myocardium along with evidence of injury to myocytes in the vicinity. These requisite findings were formalized in the so-called Dallas criteria in 1987 (Aretz et al. 1987), which specify that both inflammation and myocyte damage are required for unequivocal myocarditis (Fig. 32.5). Inflammation without myocyte injury is termed borderline for myocarditis according to these criteria. This is important because a study of 100 normal hearts at autopsy showed that up to five lymphocytes per high-power field may be seen in random samples (Foley and Edwards 1988). It should be emphasized, however, that these criteria were developed to look for myocarditis in biopsy samples from living patients. The obvious limitations of sampling in the biopsy setting (taking only small pieces

from a localized area of the right ventricle) do not apply to autopsy pathology. Consequently, there is the natural expectation that myocarditis would be more widespread and impressive at autopsy since full-thickness sections from any area of the heart can be examined. Still, because myocarditis may be a focal phenomenon that is grossly inapparent, it is important to thoroughly examine and sample the ventricular myocardium (10 full-thickness pieces from different segments are recommended). Even if only a single convincing focus of myocarditis is found, there is the real possibility it could have served as a focus of electrical excitability leading to ventricular arrhythmia. Correlating this with the clinical history is important in this setting. Focal myocarditis would be a more compelling cause of death in a patient with an out-of-hospital arrest and no immediate resuscitation efforts than it would in a hospitalized patient with serial echocardiography showing chamber dilatation and global dysfunction despite inotropic support for several days before death, for example.

Myocarditis can be subclassified according to etiology or by its histopathological appearance. Causes include direct infection (viral, bacterial, fungal, protozoal) and post-infectious sequelae (especially post-viral) as well as drug-related (toxic and hypersensitivity) and autoimmune disease. Cases in which none of these can be identified are considered idiopathic, although most regard these as undiagnosed virally mediated cases. The most commonly implicated viruses are in the enterovirus group (particularly Coxsackie B) though several others including adenovirus, cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus (EBV), parvovirus, respiratory syncytial virus (RSV), and influenza A virus are also reported (Bowles et al. 2003). This has generated interest in viral-detection strategies as an adjunct to myocarditis diagnosis, both clinically and at autopsy. Several commercial and academic laboratories offer screening for these. The clinical utility of such testing in living patients has been called into question since antiviral therapy has not proven effective in myocarditis, and neither the supportive treatment nor the prognosis of patients differs based on results of these tests. The utility of viral testing in the autopsy diagnosis of myocarditis is also questionable. Frequency of detection is generally low and the presence of viral genome does not establish causality, particularly for EBV, CMV, parvovirus, and other fairly ubiquitous viruses. As such, viral testing in myocarditis remains largely an academic exercise.

Grossly, myocarditis may be completely inapparent, requiring an index of suspicion and generous sampling of the myocardium. As the myocardial involvement progresses, an acute reversible dilatation phenotype may develop. This typically involves the left ventricle, but all four chambers can be involved. Cases of healed myocarditis may resolve with normal cardiac morphology or may lead to persistent dilated cardiomyopathy.

The histopathological patterns of myocarditis include lymphocytic, eosinophilic, mixed, and giant cell types. Lymphocytic is the most common of these and is typically seen in virus-associated and idiopathic myocarditis, though it may also be seen in drug-related and autoimmune cases. It is important to note that while lymphocytes predominate within the inflammatory infiltrate in these cases, there may also be occasional eosinophils and neutrophils, especially early in the course.

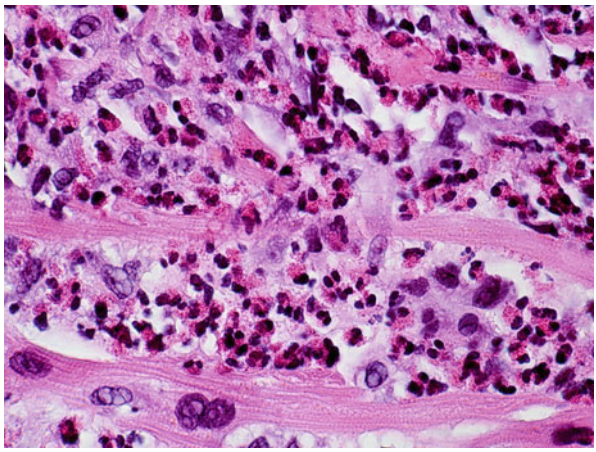

Fig. 32.6 Eosinophilic myocarditis. Photomicrograph showing eosinophilic myocarditis. There are very prominent eosinophils with degranulation and associated myocyte damage (Hematoxylin and Eosin, H&E ×400)

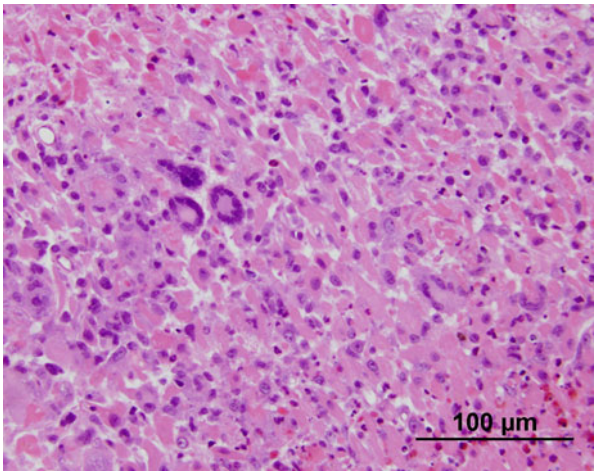

Fig. 32.7 Giant cell myocarditis. Photomicrograph showing giant cell myocarditis, characterized by diffuse hemorrhage and myocyte injury with widespread inflammation and focal multinucleated giant cells (Hematoxylin and Eosin, H&E ×100)

As the disease progresses, there is also an influx of macrophages that may be prominent in this pattern. Eosinophilic myocarditis (Fig. 32.6) is rare and associated with hypersensitivity, protozoal infection, eosinophilic endomyocarditis (with eosinophil-rich mural thrombus), and chronic systemic hypereosinophilic syndrome. The mixed-type myocarditis pattern has high interobserver variability but is generally reserved for cases falling on the spectrum between lymphocytic and eosinophilic types. Giant-cell myocarditis is a distinct entity with a particularly aggressive course. In addition to the presence of multinucleated giant cells, the pattern is diffuse and destructive and often shows substantial numbers of eosinophils in the background (Fig. 32.7). Giant-cell myocarditis has not been described in children, but does occur in adolescents (Cooper 2007).

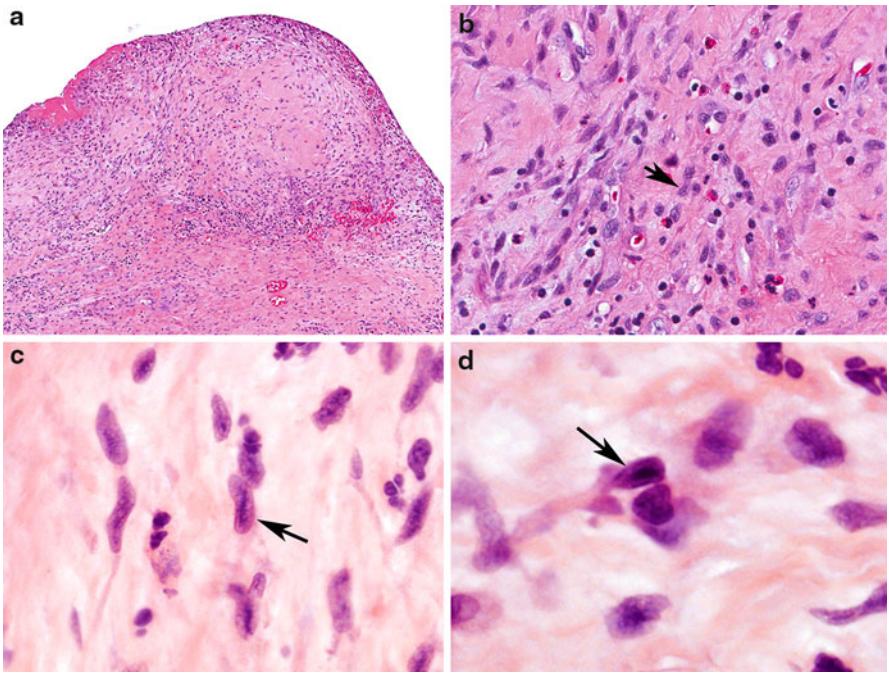

Fig. 32.8 Rheumatic carditis with Aschoff nodules and Anitschkow cells. Photomicrographs from the mitral valve of a 13-year-old boy with acute rheumatic valvulitis. (**a**) Aschoff nodule with central hyalinizing necrosis (Hematoxylin and Eosin, H&E ×20), (**b**) higher magnification at the periphery of the Aschoff nodule showing mixed inflammation with occasional cells showing central clumped chromatin (*arrow*) (Hematoxylin and Eosin, H&E ×200), (**c**) high magnification of an Anitschkow cell with a "caterpillar"-type inclusion (*arrow*) (Hematoxylin and Eosin, H&E ×1000), and (**d**) high magnification of an Anitschkow cell with an "owl-eye"-type inclusion (*arrow*) (Hematoxylin and Eosin, H&E ×1,000)

Rheumatic Carditis

One of the major Jones criteria for acute rheumatic fever is the so-called pancarditis or inflammation affecting any combination of endocardium (typically valves), myocardium, or epicardium. Myocardial involvement in particular has the potential for arrhythmic sudden death (Josselson et al. 1984). Acute rheumatic fever has become rare in recent decades with improved recognition and treatment of Streptococcal infections, at least in developed countries. The histopathological appearance of myocardial lesions is quite distinctive, having a vaguely granulomatous or necrobiotic pattern at low magnification with clusters of histiocytic cells termed Aschoff nodules or bodies. At higher power, cells with a central dense bar of compacted chromatin in the nuclei (Anitschkow cells) can be seen in association with the Aschoff nodules (Fig. 32.8). When viewed longitudinally, these chromatic structures resemble caterpillars, and in cross section, they are said to have the appearance of "owl eyes." Finding Aschoff nodules and Anitschkow cells should

prompt review of the clinical history for others of the major Jones criteria (migratory polyarthritis, erythema marginatum, subcutaneous nodules, and Sydenham chorea) as well as fever, arthralgia, and elevated acute-phase reactants. Serum antistreptolysin O or anti-DNAse B titers may also be informative.

Genetic Conditions

Desmin Cardiomyopathy

Desmin cardiomyopathy is another rare form of cardiomyopathy in children, characterized by large, typically perinuclear, eosinophilic inclusions in cardiomyocytes as well as skeletal muscle (Stoeckel et al. 1981). Clinically, patients typically present with heart failure and muscle weakness with moderate creatine kinase (CK) elevation and cardiac-conduction abnormalities. The cardiomyopathy phenotype is most often dilated or restrictive, but hypertrophic and arrhythmogenic features have also been described (Gudkova et al. 2012). There may also be evolution from one form to another over time. Milder forms may not be recognized until adulthood (Abraham et al. 1998).

The characteristic sarcoplasmic inclusions show positive immunohistochemical staining for desmin (but not actin or vimentin) as well as the expected ultrastructural features of desmin fibers (electron-dense and comprised of aggregated 7–10 nm fibers). Histochemical stains show bright-red staining of the inclusions on trichrome with negative staining for PAS (Fig. 32.9).

Mitochondrial Myopathy

Mitochondrial cardiomyopathy is a form of primary cardiomyopathy caused by mutations affecting oxidative phosphorylation and mitochondrial function. Those mutations can occur in the extrachromosomal mitochondrial DNA (mtDNA) or chromosomal DNA. Mitochondrial DNA includes genes for 22 transfer RNAs, 2 ribosomal RNAs, and 13 protein subunits of the enzymatic system responsible for oxidative phosphorylation (complexes I–V). Disease-causing mutations can involve any of these. The mutated chromosomal genes causing mitochondrial cardiomyopathy encode other components of this enzyme cascade. mtDNA mutations are inherited in an exclusively maternal pattern (genes are passed to all offspring of affected women but no offspring of affected men), whereas chromosomal genes are inherited in a classical Mendelian fashion. The genetics of these disorders is complex, and diagnostic screening is challenging (Zaragoza et al. 2011).

Phenotypically, mitochondrial myopathies most often manifest as congenital dilated cardiomyopathy, but hypertrophic and other forms of cardiomyopathy have also been described (Ozawa 1994). As expected given defects in oxidative phosphorylation, lactic acidosis is common. There is also phenotypic overlap with related heritable disorders affecting the mitochondria including combined

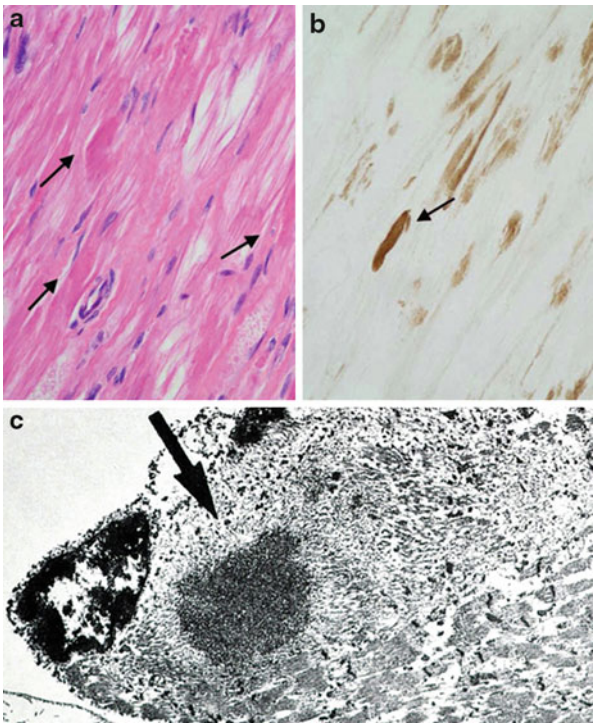

Fig. 32.9 Desmin cardiomyopathy. Photomicrographs of desmin cardiomyopathy. (**a**) Homogeneous eosinophilic intra-sarcoplasmic inclusions (*arrows*) (Hematoxylin and Eosin, H&E ×200), (**b**) immunoperoxidase staining for desmin highlights these inclusions (*arrows*) (×200), and (**c**) ultrastructural appearance of the inclusions (Used with permission, **a** & **b** adapted from Fig. 32.8 in Adv Exp Med Biol. Vol. 642 Goldfarb LG, Olive M, Vicart P, Goebel HH. Intermediate filament diseases: Desminopathy. p163. Copyright Springer (2008) **c** adapted from Hum Pathol. Vol. 29 Iss. 8 Abraham SC, DeNofrio D, Loh E, et al. Desmin myopathy involving cardiac, skeletal, and vascular smooth muscle: report of a case with immunoelectron microscopy. p880. Copyright Elsevier (1998)]

respiratory-chain deficiencies (Müller-Höcker et al. 1991) and "mitochondrial myopathy, encephalopathy with lactic acidosis, and stroke-like episodes (MELAS)" (Marin-Garcia and Goldenthal 1997).

Histologically, mitochondrial cardiomyopathy causes myocyte clearing with loss of normal contractile sarcoplasmic elements, as well as the appearance of "ragged-red" fibers. These reflect accumulation and increased numbers of abnormal mitochondria in the sarcoplasm. Ultrastructurally, the sarcoplasm is replete with aggregates of abnormal (swollen, elongated, and distorted) mitochondria (Fig. 32.10) with abnormal cristae (often in concentric whorls) and electron-dense inclusion bodies (Ozawa 1994). The conduction-system myocytes are also involved (Kajihara et al. 1986).

The onset is usually gradual, and most childhood cases come to attention because of heart failure rather than sudden death. Still, mitochondrial

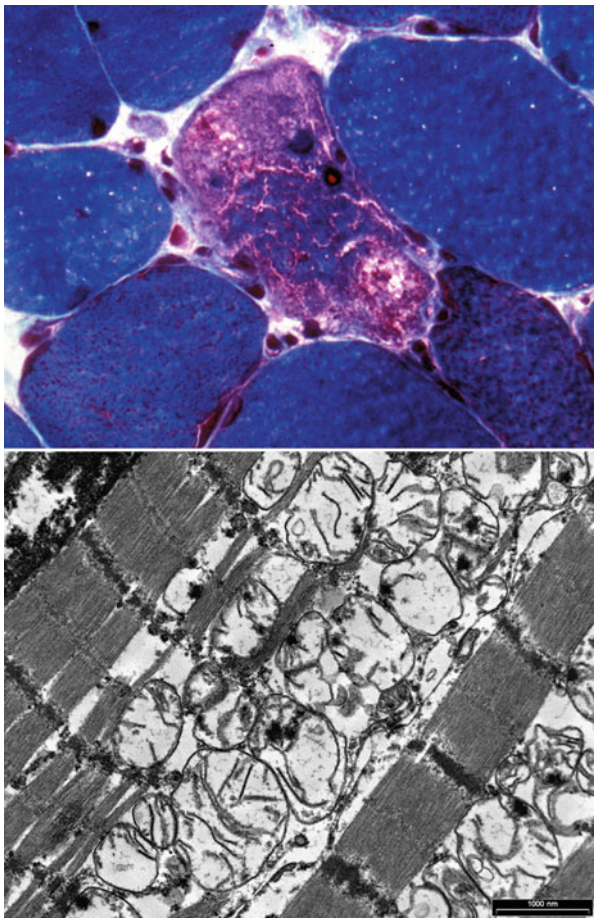

Fig. 32.10 Mitochrondrial cardiomyopathy. Photomicrograph of a trichrome-stained section of skeletal muscle (*upper panel*) showing a "ragged-red" fiber (*center*). This appearance results from subsarcolemmal loss of normal contractile elements and accumulation of abnormal mitochondria. Similar changes can occur in cardiomyocytes (not shown) (trichrome, ×400) (Courtesy Cheryl Palmer, MD; University of Utah). Electron photomicrograph from a neonate who died shortly after birth from mitochondrial myopathy (*lower panel*). The sarcomeres are intact but separated by abnormally swollen mitochondria with dense globular inclusions and altered cristal architecture (×12,000)

cardiomyopathy is occasionally first diagnosed at autopsy. When detected during life, treatment approaches include limiting exertion, coenzyme-Q_{10} supplementation, and administering redox substrates such as ascorbic acid, ubiquinol, and menadione (Ozawa 1994).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a genetic condition which can manifest at any age, including congenitally and within the pediatric population. It is thought to affect 1:500 in the general population. The risk of sudden death seems to be greatest in children and adolescents (Maron et al. 2005).

Defects in sarcomeric genes account for the majority of cases, but the molecular genetics is complicated. There are hundreds of mutation sites within each of the genes, and expressivity and penetrance are quite variable. Tying a mutation to a

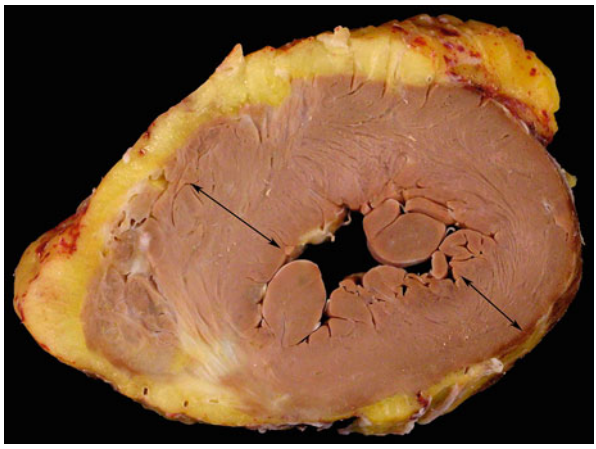

Fig. 32.11 Asymmetric septal hypertrophy in hypertrophic cardiomyopathy. Short-axis section through the ventricles of an explanted heart from an 18-year-old with hypertrophic cardiomyopathy. The septal thickness is greatly out of proportion to the left ventricle free wall thickness (*arrows*)

given phenotype has proven difficult, and using that mutation to screen and assess risk in families has also been a challenge (Van Driest et al. 2005; Towbin 2004). Still, commercial and academic laboratories offer screening for the more commonly mutated sarcomeric (MYH7, MYBPC3, TNNT2, TNNI3) and non sarcomeric (Caveolin3, LAMP2, SCO2, SURF1) genes. It is interesting to note that depending on whether the effect of a mutation results in gain of function versus loss of function for the same gene product, the phenotype may be either hypertrophic or dilated.

Because of the increased muscle mass in hypertrophic cardiomyopathy, electrocardiography shows amplification of QRS complex. Prior electrocardiograms, if available, can be a critical component to establishing the diagnosis of hypertrophic cardiomyopathy at autopsy. Electrocardiograms are also the most efficient means of screening family members in suspected cases.

Even with the advances in understanding of the genetic basis of this disease, hypertrophic cardiomyopathy is still a clinical diagnosis based on electrocardiographic and echocardiographic criteria. The principles of these criteria can be broadly applied to examination of cardiac specimens at autopsy, though the exact wall-thickness measurements cannot be relied upon given variability in the states of rigor-like contraction of the ventricles with formalin fixation (in general, wall thicknesses at autopsy are greater than end-systolic measurements from in vivo imaging studies).

One important criterion for hypertrophic cardiomyopathy is a ventricular septum to left-ventricle free-wall thickness ratio >1.4 (Fig. 32.11). This is easily applied to autopsy specimens but requires a dissection technique other than the standard inflow–outflow since the septum cannot be reliably measured by this technique. Short-axis sections through the ventricles or long-axis sections through the left-ventricular outflow tract (simulating a parasternal echocardiogram window) are recommended. This ratio abnormality is referred to as asymmetric septal hypertrophy and is the basis for dynamic-outflow obstruction due to transient systolic anterior motion of the anterior mitral leaflet due to Venturi forces.

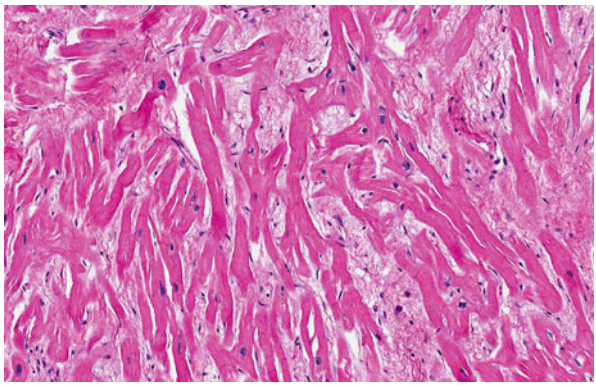

Fig. 32.12 Histopathologic features of hypertrophic cardiomyopathy. Photomicrograph showing the typical histologic features of hypertrophic cardiomyopathy, including myocyte hypertrophy (nuclear enlargement and binucleation), interstitial fibrosis, and myocyte disarray (Hematoxylin and Eosin, H&E ×200)

Asymmetric hypertrophy can affect any segment of the septum or involve the entire septum diffusely. Subaortic bulging (or "sigmoid" septum) is the most commonly seen pattern among older adults. Asymmetry that is most prominent in the mid-septum (also called "reverse" sigmoid pattern) is more common in younger patients. This "reverse" pattern is also the most highly correlated with mutations in sarcomeric genes, found in 79 % of patients with this pattern in one study (Binder et al. 2006). An apical variant has also been described.

Histopathologically, the myocardium in hearts affected by hypertrophic cardiomyopathy shows impressive, but nonspecific, changes including individual myocyte hypertrophy (manifest as frequent binucleation, enlarged hyperchromatic "boxcar" nuclei, and even markedly enlarged and irregular "bizarre" nuclei) and patchy foci of interstitial fibrosis (Fig. 32.12). There may also be endocardial thickening and fibrosis of the left-ventricle outflow tract due to trauma from the systolic anterior motion of the mitral valve (mitral contact lesion). The presence of architecturally disorganized myocytes or myocyte disarray has been touted as a pathognomonic finding for hypertrophic cardiomyopathy. However, the presence of myocyte disarray must be interpreted with an abundance of caution since this pattern can be seen normally in some segments of the ventricles (such as where the free walls merge with the septum anteriorly and inferiorly). Myocyte disarray should be taken in the context of the gross examination and the accompanying degree of myocyte hypertrophy and fibrosis, before ascribing it to hypertrophic cardiomyopathy. It should also be noted that the degree of disorganization varies in myocyte disarray, and there is a particular pattern referred to as "herringbone" that does not show the usual haphazard arrangement of myocytes, but still differs from normal laminar orientation of the surrounding myocardium (Hughes and McKenna 2005).

One important phenotypic mimic of hypertrophic cardiomyopathy that is also associated with sudden cardiac death is a glycogen-storage disease due to LAMP2 mutations, or Danon disease. The gross appearance can be virtually indistinguishable from hypertrophic cardiomyopathy, but histology demonstrates prominent vacuolization due to glycogen accumulation (Arad et al. 2005).

Table 32.1 Familial aneurysm syndromes and their associated genetic links

Familial aneurysm syndrome	Associated gene
Marfan	FBN1
Loeys–Dietz	TGFβR1,2
Arterial tortuosity	GLUT10
Aortic aneurysm – osteoarthritis	SMAD
Ehlers–Danlos, vascular type	COL3A
Pseudoxanthoma elasticum	ABCC6
Familial thoracic aortic aneurysm	
Type 1	AAT1 [11q]
Type 2	Locus on 5q
Type 4	MYH11
Type 6	ACTA2

Familial Aneurysm Syndromes

Aortic dissection and rupture of ascending aortic aneurysms is far less common in children than adults but still occurs with some frequency. One forensic study estimated an incidence as high as 5.4 % in patients aged 5–35 years with sudden cardiac death (Puranik et al. 2005). Nearly all cases in children and adolescents are related to a heritable connective-tissue disorder or familial aneurysm syndrome. Many of these disorders stem from perturbations in the transforming growth factor-β signaling pathways. These so-called TGFβ-opathies include Marfan syndrome, Loeys–Dietz syndrome, Ehlers–Danlos syndrome vascular type, arterial tortuosity syndrome, and autosomal recessive cutis laxa type 1 (Jain et al. 2011). The genes linked to some of these disorders are shown in Table 32.1. Screening panels for many of these disorders are commercially available and should be considered in young patients dying from aneurysm complications.

Marfan syndrome is associated with a characteristic body habitus and manifestations affecting the musculoskeletal, ocular, and cardiovascular systems. While the frequency of dissection and rupture are not well characterized in the pediatric population, root dilatation and ascending aortic aneurysm are quite common. Aortic-root dilatation has been reported in 35 % of children by age 5 years and in 68–80 % of adolescents (<19 years old) (van Karnebeek et al. 2001). Histologically, the aneurysm tissue classically shows medial degeneration ("cystic medial necrosis"), although this is highly variable even with thorough sampling and is not at all specific for this disorder (Homme et al. 2006).

Loeys–Dietz syndrome is a recently described condition with considerable phenotypic variation. More severely affected cases (type 1) show craniofacial anomalies (hypertelorism, craniosynostosis, and cleft palate) as well as prominent systemic vascular arterial tortuosity and may have Marfanoid body habitus. Less severe phenotypes, LDS type 2, may show cutaneous and ligamentous laxity similar to Ehlers–Danlos syndrome along with a curiously high rate of bifid uvula. Aortic aneurysms are common to both types, and the rate of size progression is accelerated compared to other aneurysm syndromes. The risk of rupture is much higher at lower

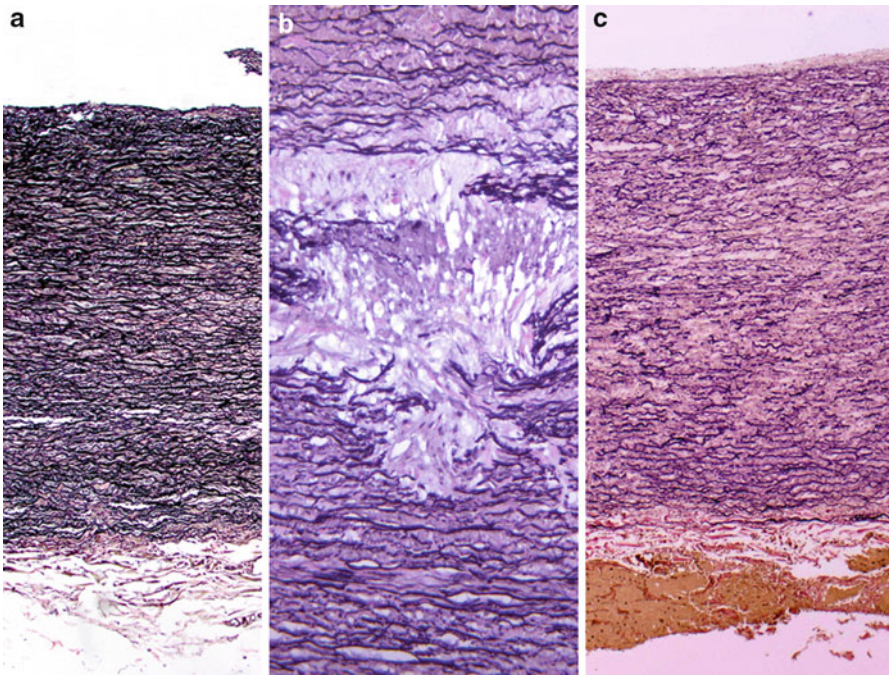

Fig. 32.13 Medial degeneration in Marfan syndrome and Loeys–Dietz syndrome. Photomicrographs showing characteristic patterns of aortic medial degeneration in these connective tissue disorders. (**a**) Normal laminar architecture, for comparison (elastic stain, ×10); (**b**) the so-called cystic medial degeneration, typical of Marfan syndrome (elastic stain, ×40); and (**c**) "diffuse medial degeneration" typical of Loeys–Dietz syndrome characterized by more diffuse and subtle disruption of elastic fibers and accumulation of mucopolysaccharide material (elastic stain, ×20)

aneurysm diameters, and surgical intervention is early and aggressive in these patients (Jain et al. 2011). Histologically, aneurysm tissue from patients with Loeys–Dietz syndrome demonstrates a "diffuse medial degeneration" (Fig. 32.13) pattern with loss of elastic tissue and aggregation of mucopolysaccharide material. These changes are more subtle and more transmural, without the discreet "cystic" lesions characteristic of Marfan syndrome (Maleszewski et al. 2008).

Ehlers–Danlos is one of the prototypic inherited connective-tissue diseases, linked to abnormal synthesis of collagens or related enzymes. There are several different types, but the vascular type (formerly type IV) has been associated with defects in collagen III (COL3A gene). This collagen is a major constituent of skin, vessel wall, and hollow-organ connective tissue, and patients manifest abnormalities in facial features and skin (laxity and easy bruising) and rupture of vessels or viscera. Tears involving the aorta and its major branches have devastating consequences and are a particular risk of Ehlers–Danlos, vascular type (Jain et al. 2011). These tears may occur in apparently nonaneurysmal arteries. There is reported to be a 25 % risk of major vascular complication by the age of 20 years

in these patients, and the average life expectancy is 48 years (Pepin et al. 2000). Histologically, findings in the vascular tissue may be quite subtle, with minimal medial degeneration but partial disruption of elastic laminae and occasionally organized fibrous tissue suggesting previous "near-miss" tearing events. Electron microscopy may be more helpful in establishing the diagnosis on the basis of irregular striated collagen fibers and "fibrinogranular" material in the associated matrix (Germain and Herrera-Guzman 2004).

Congenital Malformations

Coronary Anomalies

Anomalous origins of the coronary arteries are an important cause of sudden cardiac death in pediatric patients, even beginning in infancy (Herrman 1992). The prevalence of isolated coronary anomalies is estimated at 0.2–1.2 % (Frescura et al. 1998). These anomalies are more common in the setting of other congenital heart disease, approaching 2.2 % (Frescura et al. 1998). Almost every possible variation has been described, and careful examination of the left and right coronary systems from ostia to terminal branches is important at autopsy (Fig. 32.14). Cause of death attribution can be challenging when a coronary anomaly is discovered at autopsy, as some variants occur in patients without other cardiac pathology dying from noncardiac causes (Table 32.2). In general, the anomalies impairing flow to the left ventricle such as anomalous origin of the left coronary from the pulmonary artery or from the right sinus of Valsalva are more likely to be associated with cardiac death. Anomalies in which a proximal arterial segment passes between the great arteries and septal myocardium below the valve annulus also appear to be more significant and also more often associated with death following exertion or rapid changes in either aortic or pulmonary arterial pressure (Basso et al. 2000).

Findings supporting a causative role in a patient's death include intimal lesions with significant luminal compromise (particularly at distorted acute angles resulting from the altered course of the coronary) and evidence of prior ischemic injury to the downstream myocardium supplied by the anomalous artery (Eckart et al. 2006). The ostium should also be carefully inspected for a tangential takeoff or intramural course through the aortic wall, either of which could result in a flap valve with dynamic ostial obstruction.

It is important to distinguish true coronary anomalies from normal anatomic variants of coronary ostial anatomy (Fig. 32.15). These include accessory right ostia, most commonly of the conus artery (30 % of the population) and/or sinus-node artery (<5 %), as well as separate LAD and LCx ostia in the left sinus of Valsalva (i.e., absent left main) (<1 %). Lateral displacement of an ostium also occurs with some frequency. Bicuspid aortic valve, present in 1–2 % of the population, may also appear to have both ostia arising from a single sinus when the conjoined cusp results from right and left cusp fusion.

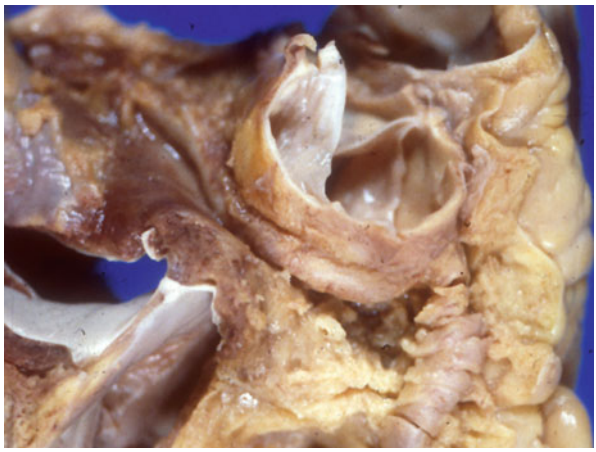

Fig. 32.14 Coronary anomaly (epicardial view). Autopsy heart specimen showing anomalous left coronary artery arising from the right sinus of Valsalva with a course posterior to the aorta. This dissection highlights the careful examination and identification of proximal coronary segments (Image courtesy Stephen Cohle, MD; Grand Rapids, MI)

Table 32.2 Coronary anomalies by association with sudden death

Anomaly	Sudden cardiac death	Other cardiac death	Noncardiac death
ALCAPA	38 %	62 %	–
LMA and RCA from R sinus	57 %	16 %	27 %
LMA and RCA from L sinus	25 %	4 %	71 %
LCx and RCA from R sinus	10 %	29 %	61 %
LMA/LCx from P sinus	29 %	24 %	47 %
Single right ostium	18 %	23 %	59 %
Single left ostium	9 %	36 %	55 %

Adapted from Taylor et al. (1992)
Abbreviations: *ALCAPA* anomalous left coronary arising from pulmonary artery, *LMA* left main coronary artery, *RCA* right coronary artery, *R* right, *L* left, *LCx* left circumflex coronary artery, *P* posterior

Structural Congenital Heart Disease (Septal Defects, Tetralogy, and Transposition)

The role of the autopsy in the setting of congenital heart disease includes establishing the primary diagnosis in cases where the defect was not detected during life as well as confirming and characterizing cases diagnosed before death. In the latter scenario, the autopsy can reveal any complications, characterize the extent of any anomalies, and further clarify the alterations seen on antemortem imaging studies. Data are sparse concerning the frequency of clinically undetected but significant congenital heart disease in children dying of other causes. In one study from the United Kingdom, this was the case in 56 of 1,074 infant autopsies.

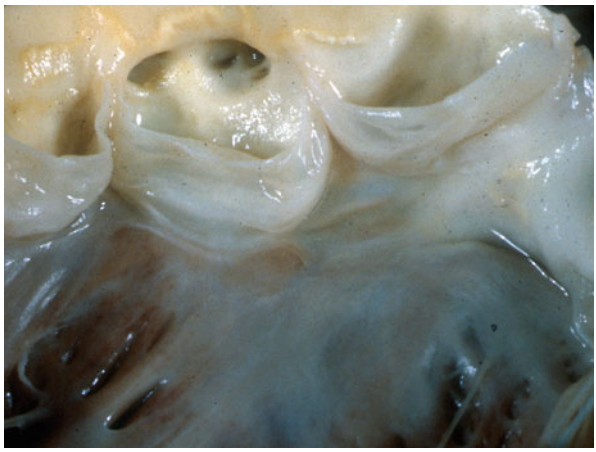

Fig. 32.15 Coronary anomaly (ostial view). Autopsy heart specimen showing both coronary ostia arising from a single sinus of Valsalva, emphasizing the importance of this view in careful inspection of autopsy hearts (Image courtesy Stephen Cohle, MD; Grand Rapids, MI)

About one-third of these cases showed no other congenital anomaly in any other organ system. The anomalies included hypoplastic left heart, truncus arteriosus, tricuspid atresia, pulmonary atresia, aortic stenosis, interrupted aortic arch, coarctation, transposition of the great arteries, and tetralogy of Fallot (Abu-Harb et al. 1994). Substantially more literature can be found on causes of death and findings from autopsies in patients with known congenital heart defects. Collectively, these suggest that noncardiac causes of death are just as significant in this population and that other associated anomalies are common. Sudden death due to ventricular hypertrophy and scarring, without any other acute complication, is also a common scenario (Vesterby et al. 1987; Samánek et al. 1986; 1988; Hegerty et al. 1985).

The sequential segmental approach to cardiac dissection is particularly important in the setting of pediatric autopsy, even when there is no known history of congenital heart disease. Some significant anomalies can be subtle and easy to overlook, and a methodical and comprehensive cardiac evaluation helps prevent this. The segmental approach begins with evaluating visceroatrial sidedness or the position of the right atrium relative to the stomach, liver, spleen, and bronchi prior to separating the heart from these other organs. The normal configuration is situs solitus, and aberrations include situs inversus (inverted) or situs ambiguus (ambiguous). After that, the position of the ventricles is identified on the basis of their internal morphological features (Table 32.3). Next, the relationships between the atria and ventricles and the ventricles and great vessels are determined. The possible configurations are atrioventricular (concordant, discordant, ambiguous, double inlet, absence of right or left connection) and ventriculoarterial (concordant, discordant, or double outlet). Last, a search is performed for any associated abnormalities of the cardiac chambers, septa, outflow tract, and great vessels, usually following a direction-of-blood-flow approach.

Defects in septal integrity, resulting in communication between left- and right-sided chambers, may be clinically inapparent and first detected at autopsy. Atrial septal

Table 32.3 Defining anatomic features of the cardiac chambers

Right atrium	*Large pyramidal appendage*
	Terminal crest and pectinate muscles
	Limbus of the fossa ovalis
Right ventricle	*Cordal and papillary muscle insertion onto septum*[a]
	Muscle separating semilunar and tricuspid valve[a]
	Trabeculated septal wall
Left atrium	*Small vermiform appendage*
	Trabeculae confined to appendage
	Absent terminal crest
Left ventricle	*Aorto-mitral fibrous continuity (no muscle separating semilunar and mitral valve)*[b]
	Absent cordal insertions to septum[b]
	Smooth septal wall

[a]These features define the tricuspid valve; the right ventricle is defined by that valve
[b]These features define the mitral valve; the left ventricle is also defined by that valve

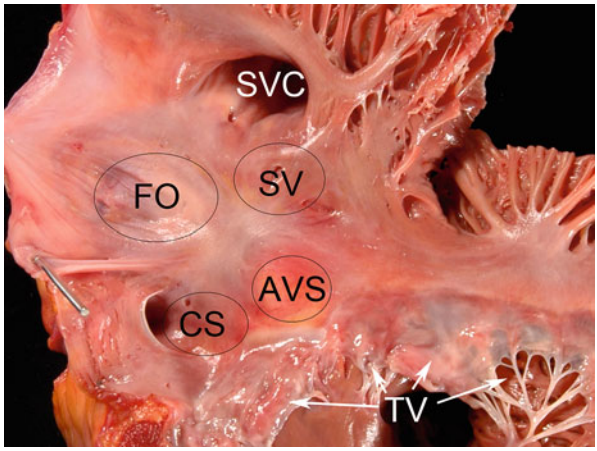

Fig. 32.16 Locations of atrial septal defects. Opened right atrium of a normal intact heart with the superior vena caval (*SVC*) orifice and tricuspid valve (*TV*) labeled for orientation. The approximate locations of foramen ovale (*FO*) or secundum, atrioventricular septal (*AVS*) or primum, sinus venosus (*SV*), and coronary sinus (*CS*) types of atrial septal defects are indicated by *circles*

defects are typically of the fossa ovalis or "secundum" type, though "primum" or atrioventricular septal, coronary sinus, and sinus venosus types of atrial septal defects also occur (Fig. 32.16). Defects in the ventricular septum are typically situated at the membranous septum, although outflow type and muscular defects also occur (Fig. 32.17).

Tetralogy of Fallot is one form of congenital heart disease which may evade detection antenatally and present with sudden death. This constellation of defects (pulmonary stenosis, ventricular septal defect, overriding aortic valve, and right-ventricular hypertrophy) all stem from an early mishap in the normal rotation of the aorta and pulmonary artery during embryological development. The rotation stops

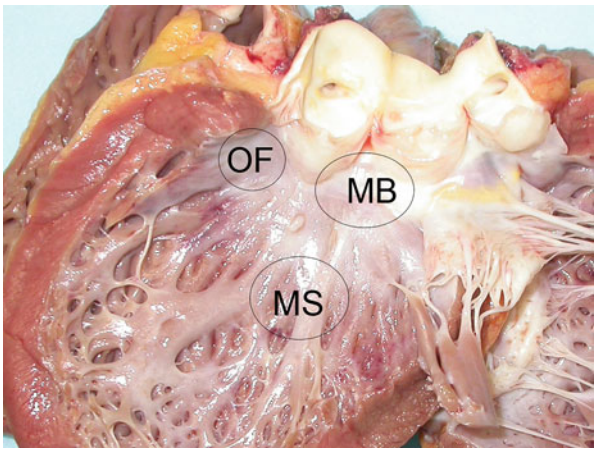

Fig. 32.17 Locations of ventricular septal defects. Opened left ventricular outflow view of a normal intact heart showing the approximate locations; membranous (*MB*), muscular (*MS*), and outflow (*OF*) types of ventricular septal defects are indicated by *circles*

short of its normal position, leaving an obstructed pulmonary orifice and overriding aortic root. The ingrowth of cardiac "cushion" tissue normally resulting in atrial and ventricular septal closure is also linked to this event, so a ventricular septal defect also results. The right-ventricular hypertrophy is not so much a defect as a consequence of stenotic right-ventricular outflow. This malformation is generally apparent on routine dissection, but the presence of either pulmonary stenosis/atresia or ventricular septal defect should prompt (re)examination for the other features of tetralogy of Fallot.

Transposition of the great arteries is also fairly straightforward conceptually, though there are two variants to recognize. An obligatory shunt must exist at some level in order for interconnection between pulmonary and systemic circulation to occur. In "D-type" transposition, a large atrial septal defect typically allows mixing of blood within the atria. In "L-type" or "congenitally corrected" transposition, the ventricular sidedness is inverted relative to the atria so that the flow of blood actually resembles the normal situation. Systemic circulation, however, is maintained by a morphological right ventricle and therefore cannot be sustained throughout the patient's lifetime (the right ventricle is inherently underpowered for this). Though a shunt is conceptually not necessary to be compatible with life, this variant of transposition is still often associated with septal defects in addition to pulmonary-outflow obstructions.

Congenital Semilunar Valvular Obstructions

When complete or critical occlusion of the semilunar valves occurs early in development, drastic structural consequences such as hypoplastic left heart, interrupted aortic arch, and right-ventricle hypertrophy in tetralogy of Fallot result. Less severe obstructions and those developing later in fetal life may be more subtle

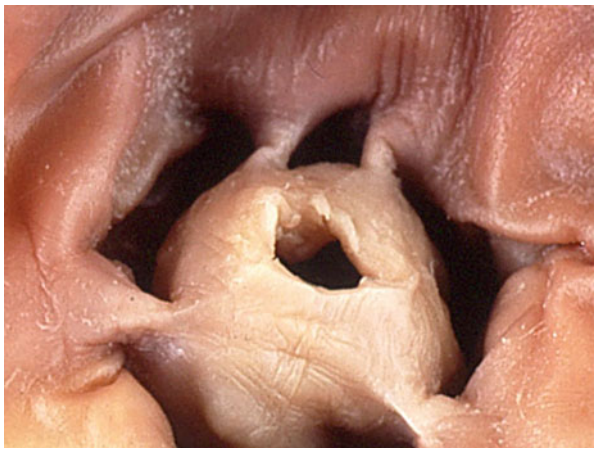

Fig. 32.18 Congenital semilunar valve stenosis. Opened pulmonary artery showing a congenitally dysplastic and stenotic pulmonary valve with a dome-shaped deformity and multiple raphes

and difficult to detect clinically, but can still lead to heart failure and sudden death. Valvular obstructions often occur in association with apparently unrelated cardiac malformations but can be isolated findings as well.

Congenital pulmonary stenosis is usually associated with malformed leaflets (unicuspid, dome-shaped; bicuspid; or dysplastic) that are markedly thickened and fused along the commissures (Fig. 32.18). The orifice diameter in large part determines the clinical significance. There may also be post-stenotic dilatation of the pulmonary artery. As expected, the right ventricle undergoes substantial hypertrophy in the face of increased opening pressures and flow restriction caused by pulmonary stenosis. The ventricular-cavity size decreases proportionately (Rowe et al. 1981a).

Patients with congenital pulmonary stenosis typically are of normal birthweight and have normal early development (again depending on its severity). Systolic murmurs are often the only clinical clue and may be inapparent in some cases (Rowe et al. 1981a).

Isolated congenital aortic stenosis may be due to obstructions at the valvular, subvalvular, or supravalvular levels. Valve malformations resemble the spectrum seen in pulmonary stenosis, and the annulus, leaflets, and commissures are all affected. Supravalvular tissue ridges and subvalvular membranes and fibromuscular "tunnels" mostly account for the other forms. The left ventricle is hypertrophied but may also show substantial dilatation due to frequent mixed valvular incompetence leading to volume-type hypertrophy as well (Rowe et al. 1981b). As with pulmonary stenosis, signs and symptoms can be inconspicuous early, and often a diagnosis is not made until later in infancy.

The treatment for semilunar valve obstructions is typically catheter-deployed balloon valvuloplasty. Complications of this procedure include acute valvular incompetence and distal embolization in the near term and eventual restenosis in the longer term. Valve replacement is the other alternative.

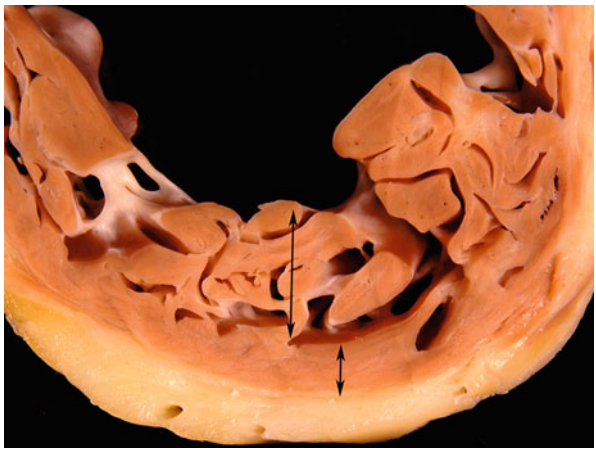

Fig. 32.19 Left ventricular noncompaction (hypertrabeculation). Closeup view of the left ventricle in a patient with noncompaction. Trabecular myocardium makes up more than half the thickness of the left ventricular wall (*arrows*)

Cardiomyopathies of Uncertain Etiology

Left-Ventricular Noncompaction (Hypertrabeculation) Syndrome

Though also associated with other forms of congenital heart defects, left-ventricular noncompaction (LVNC) syndrome is increasingly recognized as a specific cardiomyopathy. As the name implies, the left ventricle shows prominent *carnae trabeculae* comprising at least half of the total wall thickness, resulting in a spongy appearance with deep recesses and marked reduction in the "compacted" myocardial wall, reducing the force of ventricular contraction (Fig. 32.19). This phenotype is felt to result from an arrest in developmental processes by which individual embryological myocyte bundles consolidate to form the left-ventricle wall (Bleyl et al. 1997).

Clinically, LVNC shows no gender predilection and has been diagnosed from infancy to adulthood. Systolic heart failure predominates, and patients are at risk of ventricular arrhythmias. Mural thrombosis and embolic events are other significant complications (Burke et al. 2005). The diagnosis can be made by echocardiography and other tomographic imaging modalities. Criteria vary, but a ratio of noncompacted to compacted myocardium of >1.4 for children and >2.0 in adults is generally accepted. Electrocardiogram (EKG) changes are mostly nonspecific but include increased amplitude, repolarization changes, inverted T waves, ST-segment changes, axis shifts, intraventricular conduction abnormalities, AV block, and Wolff–Parkinson–White syndrome (Ichida 2009).

While essentially a gross diagnosis, histopathology can be helpful in delineating compacted from noncompacted myocardium in order to obtain an accurate ratio. Hypertrophic changes, interstitial fibrosis, fibroelastosis, and old organized thrombus may also be seen.

Early reports linked LVNC to genes on Xp28 in a cluster with Emery–Dreifuss muscular dystrophy and Barth syndrome (Bleyl). More recent association studies have implicated several additional genes, including LIM domain-binding protein 3 (ZASP), α-dystrobrevin (DTNA), tafazzin (TAZ/G4.5), lamin A/C (LMNA), and genes encoding the sarcomeric proteins, β-myosin heavy chain (MYH7), α-cardiac actin (ACTC), and cardiac troponin T (TNNT2) (Ichida 2009).

Histiocytoid Cardiomyopathy

Histiocytoid cardiomyopathy is an extremely rare form of cardiomyopathy affecting primarily infants. It is characterized by very distinctive histological appearance with distended granular sarcoplasm in subendocardial myocardial cells. It is believed to be a hamartomatous lesion of the Purkinje cells within cardiac conduction-system tracts (Gelb et al. 1993). It primarily occurs in the first 2 years of life and has a female-to-male ratio of 3:1. It mostly affects Caucasians (80 %), though African–American (15 %) and Hispanic (3 %) cases are also reported (Shehata et al. 2011). Supraventricular and ventricular arrhythmias are the most frequent clinical manifestation, and sudden death is common. Other congenital abnormalities, particularly involving the eyes, central nervous system, and endocrine organs, have also been associated with this disorder (Ruszkiewicz and Vernon-Roberts 1995).

Grossly, the heart may appear hypertrophic, and small yellow plaques may be seen in the ventricular septal endocardium. Endocardial fibroelastosis may also be present (Shehata et al. 1998; Ruszkiewicz and Vernon-Roberts 1995). Because of the subendocardial location and disturbances in conduction, it is possible to diagnose this condition on endomyocardial biopsy, particularly with electrophysiological mapping guidance. Microscopically, discrete lesions can be seen subendocardially comprised of distended myocytes with granular eosinophilic cytoplasm, variably described as "foamy, oncocytic, or histiocytoid" (Fig. 32.20). By electron microscopy, the sarcoplasmic distension is explained by accumulation of mitochondria, usually with abnormal morphology. Unlike mitochondrial cardiomyopathies, these changes are limited to discrete subendocardial populations of myocytes. Sparse wisps of myofibrils can be seen, confirming the myocytic (rather than histiocytic) nature of these cells (Ruszkiewicz and Vernon-Roberts 1995). Careful studies of the cardiac conduction system have suggested sparing of the sinoatrial node and atrial tracts as well as the atrioventricular node. The lesions appear to be confined to the His bundle, bundle branches, and distal pathways (Gelb et al. 1993).

Because of the female predominance, an X-linked inheritance has been proposed. Genomic studies on samples for the largest registry of histiocytoid cardiomyopathy cases have found associations with genes on 1q21.3c (S100A8, S100A9, S100A12) and 2q12.1a (ST2, IL18R1, IL18RAP) as well as a single gene on 9p24.1b (Il-33) (Shehata et al. 2011). So far, however, the diagnosis of histiocytoid cardiomyopathy still rests on morphological findings.

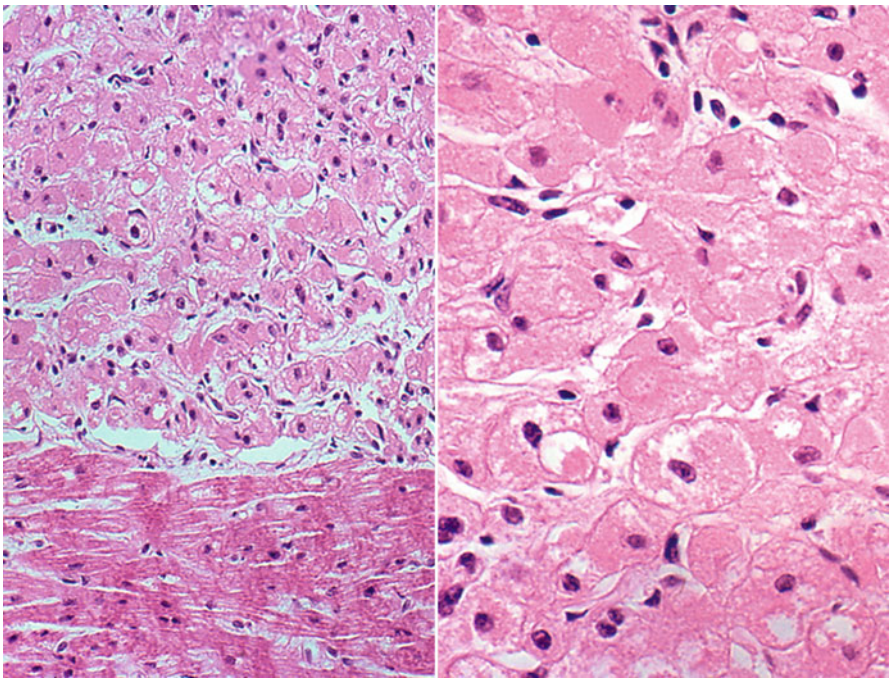

Fig. 32.20 Histiocytoid cardiomyopathy. Photomicrographs showing markedly vacuolated subendocardial myocytes from an infant with histiocytoid cardiomyopathy (*left*: Hematoxylin and Eosin, H&E ×100; *right*: Hematoxylin and Eosin, H&E × 400)

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (arrhythmogenic right-ventricular dysplasia) is a primary cardiac disorder characterized by fatty infiltration/replacement of the myocardium that is associated with ventricular arrhythmias and sudden cardiac death. The term arrhythmogenic cardiomyopathy is preferred because while the condition predominantly affects the right ventricle, there are well-documented cases of left-ventricular involvement as well (Lobo et al. 1999). "Dysplasia" should be avoided since it is no way a premalignant condition nor is it a congenital malformation.

The etiology is unclear, but there is growing evidence of a genetic link to mutations in genes encoding desmosome and other gap-junction proteins (Saffitz 2011). A possible link to myocarditis has also been proposed (Calabrese et al. 2006), given that viral genome can be demonstrated in the myocardium of some cases, and myocytes show evidence of apoptosis as the mechanism of fibrofatty replacement.

Both grossly and microscopically, the ventricular free wall shows extensive (usually transmural) replacement with fat (Fig. 32.21). The majority of cases also

Fig. 32.21 Gross appearance of arrhythmogenic cardiomyopathy. Full-thickness replacement of the inferior right ventricle wall in a patient with arrhythmogenic cardiomyopathy

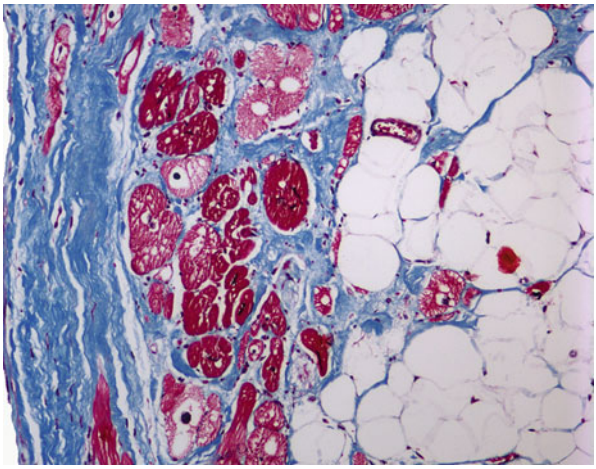

Fig. 32.22 Histopathologic features of arrhythmogenic cardiomyopathy. Photomicrograph showing the combination of fatty infiltration and fibrosis characteristic of arrhythmogenic cardiomyopathy. Pronounced myocyte hypertrophy is also seen (Trichrome, ×200)

show both fibrosis and myocyte hypertrophy (Fig. 32.22) in the neighboring myocardium. Since focal fat can be seen as a normal variant in the ventricle walls, these are important findings differentiating arrhythmogenic cardiomyopathy from a variant of normal. A purely fatty form (without fibrosis or hypertrophy) has been proposed but is apparently rare and should only be diagnosed with a supportive clinical history. The revised consensus guidelines indicate that fibrosis and hypertrophy should accompany the fatty replacement (Marcus et al. 2010). Another fairly specific feature for arrhythmogenic cardiomyopathy is the presence of small diverticula or outpouchings in the ventricle free wall, usually arising between the trabeculae. These tend to arise in the apical, inflow, and infundibular portions of the right ventricle (the so-called triangle of dysplasia).

There is considerable variability in the clinical presentation of arrhythmogenic cardiomyopathy as well. An evolution has been proposed from initially asymptomatic (but at risk of sudden cardiac death) to symptomatic arrhythmias and morphological changes on imaging studies to more diffuse disease with biventricular heart failure with or without ongoing ventricular arrhythmias. This may also progress to a typical dilated cardiomyopathy phenotype as the end stage of this evolution (Marcus et al. 2010).

Sudden death is most common in adolescents and young adults (Hughes and McKenna 2005). The diagnosis historically has been difficult to establish antemortem, but with improved tomographic imaging (particularly MRI) and electrophysiological mapping, this is becoming more feasible. Immunofluorescence testing for defects in desmosomal and gap-junction proteins can be performed on cardiac tissue as an adjunct to diagnostic histomorphology. Genetic testing for mutations in those genes is also available.

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Childhood Obesity

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Contents

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Abstract

Obesity in childhood is one of the most serious global public health issues of this century. While obesity results from an imbalance between energy intake and energy expenditure, that association is not the whole of the etiology. Numerous contributing factors have been identified and range from sedentary lifestyles to diets consisting predominantly of processed foods and unprecedented sugar intake, along with genetic predispositions and inherited metabolic factors. This chapter will focus on medical causes of obesity, the pathological conditions arising from and complicating obesity, and childhood deaths associated with obesity. Definitions will be provided for obesity in childhood, and an approach to the autopsy in a child dying of obesity-related conditions or complications will be suggested.

Introduction

According to the World Health Organization, the worldwide prevalence of obesity has more than doubled since 1980 (World Health Organization 2012). Children are not immune to this epidemic, and it is estimated that nearly 43 million children under the age of 5 years were overweight in 2010 (World Health Organization 2012). Moreover, overweight and obese children are more likely to become obese adults and to develop cardiovascular disease and diabetes at younger ages. They may be at risk of other diseases related to early obesity as well, including certain types of cancer. Obesity is generally seen as a preventable health problem; however, there are other medical conditions that may contribute to the development of overweight and obesity. In addition, numerous root causes for obesity have been examined, but ultimately the cause is that higher-calorie diets with sustained daily caloric excess over expended energy lead to weight gains and increased adiposity. However, there are numerous other modifiable risk factors which also may contribute to overweight and obesity in children, and further examination of these factors holds promise for measures that may reverse the global tide of obesity.

Definitions

A simple concept of the difference between overweight and obesity would be adiposity (accumulation of adipose tissue) of differing degrees, with associated differing degrees of health risk. Traditional definitions of "overweight" and "obese" in adults are derived using the body mass index (BMI) as a substitute for a direct measurement of body fat. BMI, also known as the Quetelet index, is a standard index of weight-for-height that is defined as an individual's weight in kilograms

divided by the square of his/her height in meters (kg/m^2). The formula can be represented as [weight in kg/(height in m)^2]. For adults, long-standing BMI criteria define overweight, and obesity, with those with a BMI between 25 and 30 being overweight and those with a BMI over 30 being obese (Centers for Disease Control and Prevention 2012). Morbid (or extreme) obesity in adults is defined as BMI greater than or equal to 40 kg/m^2 (Centers for Disease Control and Prevention 2012).

For children, however, defining overweight and obesity may not be so simple as a single estimation of body fat, due to changing body composition with age and growth. Infancy is a period of high adiposity, followed by a period of high rate of growth during which body fat reaches a nadir at age 5–6 years; adiposity then increases steadily until adulthood (Gahagan 2011). Simple BMI cutoffs such as those used for adults cannot be applied across differing pediatric age groups. In the past, the appearance of the infant or child was regarded by some as the best indicator of obesity (Barness 1997), due to the existence of multiple varying and even conflicting guidelines or definitions. More recently, body mass index percentiles, rather than body mass index raw values, have proven more useful. A consensus was reached by a committee convened by the joint efforts of the American Medical Association, the US Department of Health and Human Services, and the Centers for Disease Control and Prevention, resulting in significant changes to prior definitions (John-Sowah 2007). These important changes made by the committee to previous recommendations were in terminology, rather than changes to the BMI percentile cutoff values. According to the recommendations of the expert committee, BMI between the 85th and 95th percentiles for age and sex indicates overweight, while a BMI greater than or equal to 95th percentile indicates obesity and further is associated with an increased risk of complications (Barlow et al. 2007). Of interest, the term "overweight" as used here replaces the former recommended term "at risk for overweight" in children for the same percentiles, while "obese" replaces the former "overweight." These changes in terminology represent a vast improvement in comprehensibility and also provide some continuity with the terminology used in adults. The importance of the ability to diagnose obesity (rather than mere overweight) in children based on these recommendations cannot be overemphasized, as obesity (BMI >95th percentile for age) is associated with an increased risk of secondary complications (Krebs and Primak 2009). Severe obesity (the childhood terminology equivalent of adulthood morbid obesity) is identified as BMI greater than 99th percentile (Krebs and Primak 2009).

Normative BMI values are not available for children under 2 years of age. Infants and children under 2 can be assessed using weight-for-length growth charts, and a weight-for-length greater than 95th percentile may represent overweight and should provoke further assessment (Barlow et al. 2007; Krebs and Primak 2009). As a child approaches late adolescence, the percentiles approach BMI levels used for adult definitions of overweight and obesity. In older adolescents, for whom a BMI of 95th percentile may represent a BMI of 30 or higher, the adult cutoff for obesity

Table 33.1 Adult and pediatric criteria for overweight and obesity

Category	BMI range (kg/m^2), adults	BMI percentiles for age and sex, children over 2 years
Normal (healthy weight)	18.5–24.9	5th–84th percentiles
Overweight	25–29.9	85th–94th percentiles
Obese	30–39.9	95th–99th percentiles
Morbidly/ severely obese	40 and above	Above 99th percentile

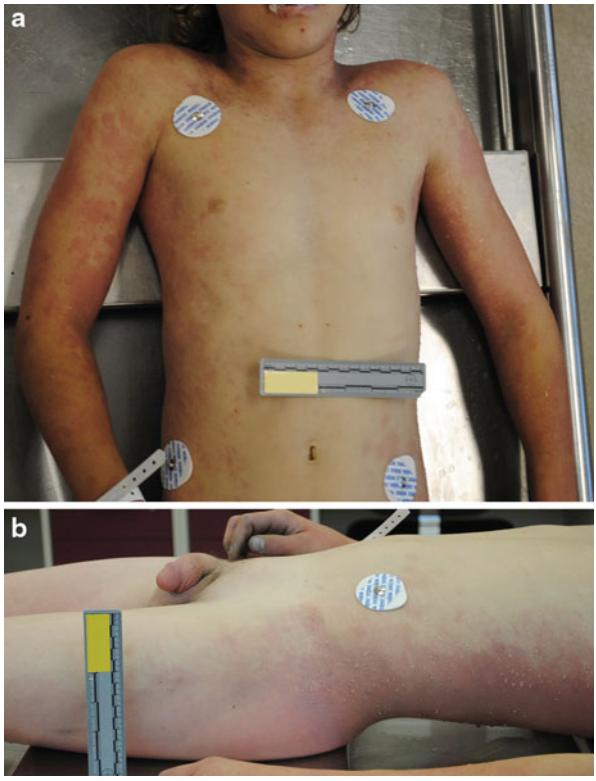

Fig. 33.1 Normal-weight boy, age 13, BMI 19.3 kg/m^2

may be applied (Barlow et al. 2007). Table 33.1 compares and contrasts adult and pediatric criteria for obesity and overweight. Figures 33.1, 33.2, and 33.3 contrast the physical appearances of three boys of normal weight, overweight/obese weight, and morbidly obese weight, respectively.

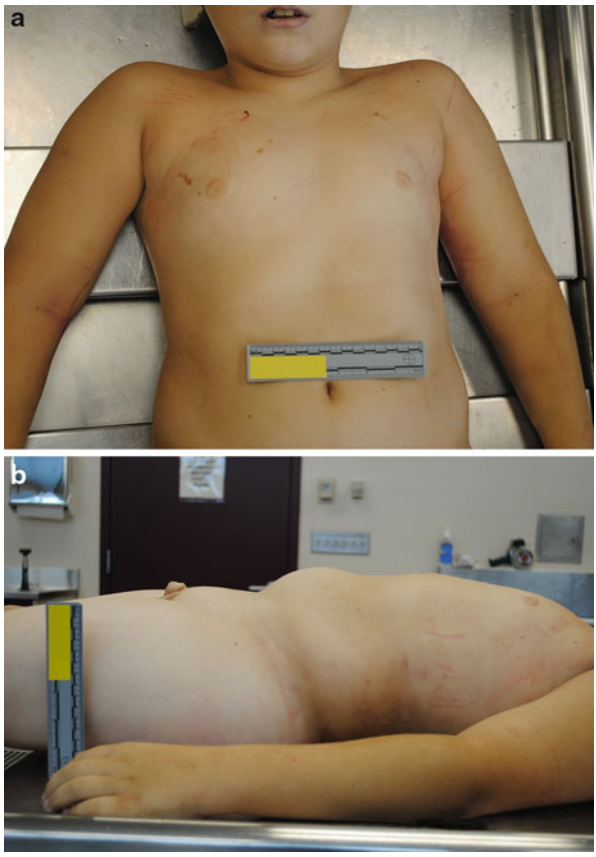

Fig. 33.2 Obese boy, age 8, BMI 23.7 kg/m^2, BMI greater than 95th percentile for age

Epidemiology

While humans' ability to store energy in the form of adipose tissue ensured the survival of our species during times of famine, in the current era of tremendous food availability, this feature has in fact proven a liability for those prone to excess weight.

The prevalence of obesity has increased 300 % in children over the past 40 years (Gahagan 2011). During that same time period, the food environment has changed dramatically in ways that increase consumption of higher-calorie foods and drinks, concomitant with changes in the constructed physical environment, with more reliance on travel by cars than ever. Between 1980 and 2002, overweight prevalence tripled in children and adolescents aged 6–19 years (Ogden et al. 2006). A significant increase was seen from 1999 to 2004, when one large study found that 17 % of children over the age of 2 years were obese (BMI greater than 95th percentile for age) in the years 2003–2004, amounting to 12.5 million children and teens (Ogden et al. 2006). Certain racial and ethnic groups were at higher risk of overweight and obesity

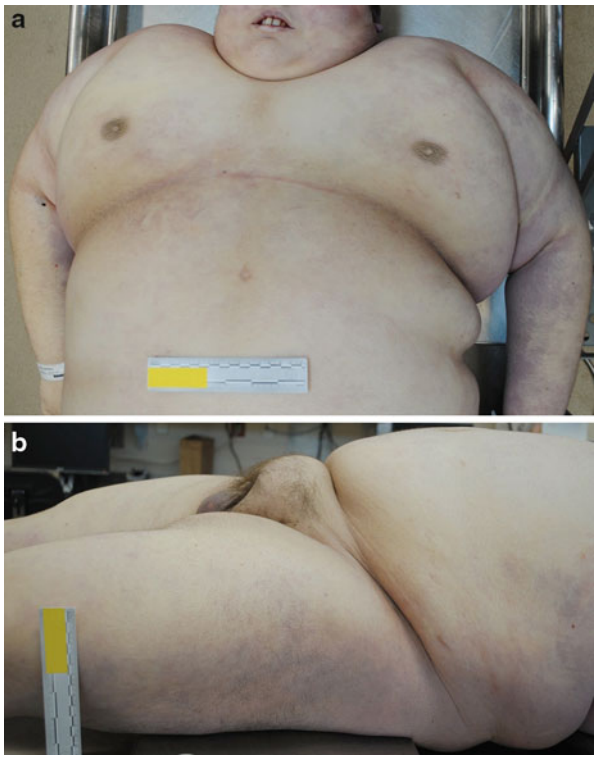

Fig. 33.3 Morbidly obese boy, age 12, BMI 56.8 kg/m^2

during that time frame (Ogden et al. 2006). In general, non-Hispanic black female children and adolescents, Mexican-American or Hispanic male children and adolescents, and some Native American groups are at higher risk compared to other racial/ethnic groups (Gahagan 2011; Ogden et al. 2006). Interestingly, these same racial/ethnic groups overall are most at risk of developing type II diabetes mellitus. More recent data from the same authors indicates that in 2007–2008, 9.5 % of infants and toddlers were above the 95th percentile of the weight-for-length growth charts and 31.7 % of children aged 2 through 19 years were overweight or obese (at or above the 85th percentile of BMI for age) (Ogden et al. 2010).

In some populations, more than 30 % of children are overweight or obese by current definitions, and analysis over the entire range of BMI values for those populations reveals that in the majority the change has occurred in the heaviest members (Troiano and Flegal 1998). What this translates to, unfortunately, is that the fattest children are becoming fatter. This trend indicates that more children will remain obese as adults, as the more severe the childhood overweight or obesity, the more likely it is to continue into adulthood (Guo et al. 1994; Serdula et al. 1993). A concomitant increase in the prevalence of obesity in adults seems to be bearing this principle out, not only in the United States (USA) but also in Great Britain, the rest of Europe, and Australia.

Etiology and Risk Factors

The concept that obesity results from positive energy balance representing an excess of caloric intake and/or deficit in energy expenditure is a gross oversimplification of the complex etiology of obesity. The obese individual is the result of the complex interaction of genetic predisposition for body habitus, metabolic factors (some predetermined and others dependent on diet), appetite (with its endocrine regulators), diet/nutritional intake, level of physical activity, and other energy expenditure. However, it is easiest to focus on the behavioral aspects of the equation, as they are modifiable and may allow for successful treatment.

Genetics and Genetic Conditions

Obese children often have a family history of obesity; a child is three times more likely to be obese if one parent is obese, but more than ten times more likely if both parents are obese (Krebs and Primak 2009).

Individual susceptibility to obesity may be largely genetically determined. Genetic determinants, as well as specific genetic conditions, are important in the etiology of obesity. Certain genetic conditions, such as Down syndrome, Turner syndrome, and Prader-Willi syndrome with its hyperphagia, are well known to result in obesity (Gahagan 2011). Obesity can also be caused by rare single-gene mutations or deletions, such as *FTO* (fat mass and obesity) and *INSIG2* (insulin-induced gene 2) mutations, and deficiencies of leptin or pro-opiomelanocortin (Gahagan 2011). More commonly, however, the genetic predisposition to an obese body habitus is multifactorial, with many genes involved. Parental obesity is perhaps the strongest risk factor for obesity in a given child, doubling the risk that a child under age 10 years, whether obese or nonobese in childhood, will become an obese adult (Whitaker et al. 1997). This of course may not be due only to genetics but also to learned behaviors and lifestyle choices.

Environment and Lifestyle

The fundamental causes of the obesity epidemic are rooted in environment and lifestyle: sedentary habits and a high-fat, energy-dense diet (WHO 2000). The US population has steadily moved toward a more sedentary lifestyle during the latter half of the last century (McGinnis 1992). Children in particular have diminished opportunities or encouragement to physical activity, given the many changes in the physical environment, urbanization and industrialization (WHO 2000); changes in perceptions regarding safety and the danger of strangers; and the new availability of many different forms of sedentary indoor recreation (computers, video games, television, and so on), although studies conflict regarding the demonstration of a direct effect of television-watching on overweight (Troiano and Flegal 1998). Half or fewer of secondary-school students are enrolled in coursework in

physical education (Heath et al. 1994). Concomitantly, more calorie-dense foods are readily available, and taste is often valued above nutritional concerns, especially in marketing. The World Health Organization suggests that a reduction in fat intake to approximately 20–25 % of energy is necessary to minimize weight gain in sedentary individuals (WHO 2000). Prevention is highly preferable to treatment, in this case, since most methods for weight loss are unsuccessful over time (NIH Technology Assessment Conference Panel 1993). Finally, lower socioeconomic status is an important predictor for obesity prevalence in US children.

Endocrine, Metabolic, and Neurophysiological Factors

The complex interplay of endocrine and metabolic factors with neurophysiological hormonal status and developmental programming is a topic warranting a degree of detail in its discussion that is beyond the scope of this chapter. Much research is ongoing regarding the relationship between obesity, metabolic disease, and inflammation, including research into biomarkers in children such as C-reactive protein and interleukin-6, which have been shown to have a relationship with diabetes mellitus and cardiovascular disease (Sacheck 2008). Furthermore, developmental programming, including the prenatal environment as determined by maternal nutrition and hormonal status, and the immediate postnatal environment, including birth weight and breastfeeding, among other factors, is seen as increasingly important in the development of childhood obesity and its sequela, adulthood obesity (Taylor and Poston 2007). Breastfeeding has been identified as having a protective effect against the development of childhood obesity, while the introduction of solid foods in formula-fed infants before the age of 4 months is associated with a sixfold increase in the odds of obesity at age 3 years (Huh et al. 2011).

The neuroendocrine regulation of appetite and weight involves a negative-feedback system, balanced between the short term (control of appetite, by neuropeptides including ghrelin, neuropeptide Y, and pancreatic polypeptide Y) and the long term (adiposity, largely controlled by leptin and adiponectin) (Gahagan 2011). The hormone leptin is one of the single most important gene products involved in the development of obesity. This key protein hormone plays a role in regulating energy intake and expenditure, including appetite and metabolism. Leptin is directly involved in satiety, acting at receptors in the hypothalamic neuroendocrine arcuate nucleus (not to be confused with the arcuate nucleus in the medulla oblongata), as low leptin levels stimulate food intake, and high leptin levels inhibit hunger/appetite in healthy humans (Gahagan 2011). Increased adiposity results in increased leptin levels, and leptin resistance develops. Increased serum-leptin levels in children have been linked to weight gain, related to leptin resistance (Fleisch et al. 2007). Furthermore, leptin is a proinflammatory hormone, stimulating the expression of interleukin-6, interleukin-1β, and tumor necrosis factor-α, in connection with the inflammation theory of obesity and its sequelae (Sacheck 2008). In addition, adiponectin is an anti-inflammatory hormone and is reduced in the obese as compared to lean individuals.

Medical Causes of Obesity

Aside from specific genetic conditions known to cause obesity, as mentioned above, consideration should be given to endocrine disorders as a single etiology of obesity. Growth hormone deficiency, Cushing syndrome, and hypothyroidism can all lead to obesity, and so these conditions should be considered, and tested for when possible, at autopsy. These children may also exhibit short stature coexisting with obesity, a clue to the fact that they are not simply consuming excess calories (Gahagan 2011). Nutritionally obese children, by contrast, exhibit above-average-for-age height as well as weight, indicating accelerated linear growth in both parameters due to excess calories. Chronic debilitating conditions and conditions associated with fatigue or physical weakness, such as muscular dystrophy, can lead to obesity due to inability to sustain an adequate level of physical activity. Medications can also lead to weight gain, particularly psychiatric and behavioral medications including atypical antipsychotics and steroids.

Sequelae of Obesity

High levels of adiposity are associated with increasing health risks. The comorbidities associated with obesity in childhood and adolescence are similar to some of those seen in adult obesity and can unfortunately begin in childhood and persist into adulthood, meaning that the obese adult who is a formerly obese child is even more at risk due to the number of years in the obese state. Those individuals in particular are at increased risk of cardiovascular death. Table 33.2 presents a summary of childhood obesity–related pathology by organ system.

Cardiovascular

Cardiovascular disease (CVD) is the leading cause of mortality in the USA and is increasing in importance in worldwide mortality. Evidence is mounting that shows obesity to be an important risk factor for CVD for adults, but moreover, recent studies show that obesity-related CVD risk starts in childhood. One study demonstrated that 39 % of obese children had at least two cardiovascular risk factors and 59 % of severely obese children (>99th percentile BMI for age) had two or more (dyslipidemia, hypertension, and elevated insulin levels) (Freedman et al. 2007). A later report from the same data (the Bogalusa Heart Study) reported that 69 % of obese children had one or more additional cardiovascular risk factors (Freedman et al. 2009). Dyslipidemia in children leads to intimal "fatty streaking" of early atherosis in large vessels, particularly the aorta, as well as the coronary arteries. There is no evidence of significant coronary artery disease (i.e., critical coronary stenosis or myocardial infarct) in obese children so far; however, there are numerous anecdotal cases of young adults dying of these conditions whose atherogenesis most certainly began in childhood.

Table 33.2 Pathology of obesity by organ system

Organ system	Pathology/symptomatology
Cardiovascular	Hypertension (left ventricular hypertrophy)
	Cardiomyopathy of obesity (cardiomegaly, left ventricular hypertrophy, dilation)
	Atherosis
Pulmonary	Obstructive sleep apnea
	Obesity hypoventilation (Pickwickian) syndrome, with or without secondary right ventricular hypertrophy and/or failure
	Pulmonary thromboembolism due to deep venous thrombosis
	Asthma
Endocrine	Metabolic syndrome
	Type II diabetes mellitus
Gastrointestinal/ hepatic	Nonalcoholic fatty liver disease: steatosis, steatohepatitis, fibrosis, cirrhosis
	Cholelithiasis
Musculoskeletal	Joint pain, frequent strains, and sprains
	Blount disease (tibia vara)
	Slipped femoral capital epiphysis
Nervous system	Pseudotumor cerebri
Skin	Acanthosis nigricans
	Intertrigo
	Tinea corporis
	Acrochordon (skin tag)
	Striae

The problems associated with a Western diet with resultant obesity in childhood are also seen in Asian countries that are rapidly Westernizing their lifestyles and eating habits. Urban Japanese children now have plasma total cholesterol and LDL cholesterol levels that exceed those of their US counterparts (Deckelbaum and Williams 2001). In some areas of Japan, type II diabetes is now more common than type I in children (Deckelbaum and Williams 2001), an astounding phenomenon outpacing even the increased development of type II diabetes in children in the USA.

Obese children and adolescents show impairments in endothelial function by up to 50 % compared to normal-weight peers, as demonstrated by flow-mediated dilation (Short et al. 2009). Additionally, increased-serum inflammatory markers such as C-reactive protein and total cholesterol, seen in obese children, are also associated with impaired endothelial function, while the connection of impaired macro- and microvascular function with type II diabetes mellitus is not established yet in children as it is in adults (Short et al. 2009). Interestingly, hypertension is eight times more frequent in adolescents with type II diabetes compared to those with type I diabetes, and at presentation with type II diabetes up to a third of pediatric patients are hypertensive, as defined by systolic or diastolic pressure >95th percentile for age (Short et al. 2009).

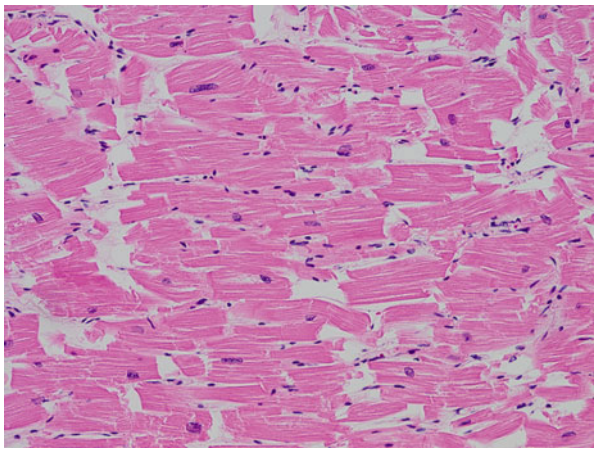

Fig. 33.4 Patchy cardiomyocyte hypertrophy in the left ventricle of morbidly obese boy pictured in Fig. 33.3 (Hematoxylin and Eosin, H&E × 20)

Obesity in childhood can result in increased systolic blood pressure and compensatory left-ventricular hypertrophy with cardiomegaly, also known as cardiomyopathy of obesity, which can prove fatal, particularly in the morbidly obese teen. There is an increase in the left-ventricular mass in obese children, similar to adults, most associated with morbid obesity. Late in the course of cardiomyopathy of obesity, left-ventricular and then biventricular dilation may develop, as in a case of the author. A morbidly obese, 16-year-old male with a BMI of 54 kg/m^2 (body weight, 492 lb) had a massively enlarged heart (890 g) that showed biventricular dilation as well as right-atrial dilation. Microscopic findings in cardiomyopathy of obesity in childhood and adulthood are very similar to those of hypertension: hypertrophy of the left-ventricular cardiomyocytes (Fig. 33.4), along with mild interstitial and perivascular fibrosis. Progressive congestive heart failure and/or sudden cardiac death can result from cardiomyopathy of obesity.

Endocrine/Pancreas

While type I diabetes is often referred to as "juvenile diabetes," type II diabetes mellitus has typically been considered a disease of adults, known as "adult-onset diabetes," until recently. An extremely high prevalence of type II diabetes has emerged in obese children, with rates increasing from four- to tenfold in certain geographic populations during the 1990s. In 2001, the SEARCH study demonstrated that among youth aged 10–19 years, type II diabetes represented from 6 % (non-Hispanic whites) to an incredible 76 % (Native Americans) of the diabetes cases occurring in this age group (SEARCH for Diabetes in Youth Study Group 2006). In the SEARCH study, the mean age at diagnosis was 8.4 years. The metabolic syndrome (including central adiposity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension) is both a precursor to diabetes and coexists

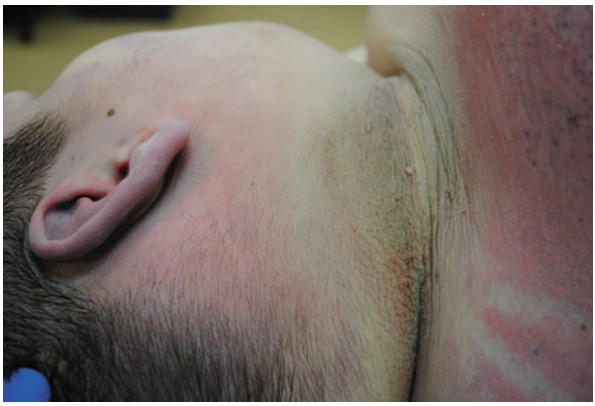

Fig. 33.5 Acanthosis nigricans and skin tags, neck of boy in Fig. 33.3

with the disease in children; it is unclear whether the cardiovascular effects of the metabolic syndrome are as dire in children as they are in adults.

Childhood deaths due to type 2 diabetes mellitus are due to diabetic ketoacidosis or hyperosmolar (nonketotic) diabetic coma and should be approached at autopsy in a similar manner to adults. Diabetic ketoacidosis (DKA) can frequently be the initial presentation of type II diabetes mellitus in the obese child, with the prevalence of DKA at the time of diagnosis of any type of diabetes in childhood being about 25 % (Rewers et al. 2008). For youth aged 10–19 years with type II diabetes specifically, the prevalence of DKA at the time of initial diabetes diagnosis was 9–11 % (Rewers et al. 2008). DKA is a high anion-gap metabolic acidosis due to an excessive blood concentration of ketone bodies. Three major ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone) are released into the blood from the liver when hepatic lipid metabolism shifts to a state of increased ketogenesis.

The symptoms of type II diabetes in children are similar to those seen in adults, namely, polydipsia and polyuria. Physical findings can include acanthosis nigricans, a velvety thickening of the skin with brown-gray to black discoloration of the skin folds of the neck, axillae, and/or elbows associated with insulin resistance (Fig. 33.5). Diabetes can be diagnosed at the time of autopsy, based on the glucose level in the vitreous fluid using the same criteria used for fasting blood glucose. While the glucose level may decrease as the postmortem interval increases, a diabetic child dying of DKA or hyperosmolar coma will usually retain a high vitreous level of glucose. Furthermore, the diagnosis of DKA in the postmortem state can be established on the basis of acetone or the other ketone bodies in the blood; acetone in particular is a convenient marker as it is often routinely tested for with gas chromatography when testing for volatiles (including ethanol) in most forensic autopsy cases. Other ketone bodies, such as β-hydroxybutyrate, may require special testing.

It is anticipated that the early appearance of type II diabetes in childhood may result in a major societal burden on the next generation, due to earlier onset of adulthood debilitating cardiovascular comorbidities related to diabetes mellitus (Freedman et al. 2009).

Pulmonary

Obesity hypoventilation syndrome (also known as Pickwickian syndrome) and obstructive sleep apnea (OSA) are related major pulmonary complications associated with childhood and adolescent obesity. Both can result in right-ventricular hypertrophy followed by right-ventricular failure. While OSA results in carbon dioxide retention, hypoxia, and daytime somnolence, the obesity hypoventilation syndrome is more severe with chronic hypoventilation, somnolence, hypoxia, polycythemia, greater incidence of right-ventricular hypertrophy and failure, and possibly pulmonary embolism (Styne 2001). All severely obese children snore, but only about a third actually have OSA (Styne 2001).

Habitual snoring during sleep is common during childhood, with an up to 27 % prevalence, and the obesity epidemic has affected the epidemiology of snoring, increasing the prevalence. For every 4–6 snorers, one is diagnosed with obstructive sleep apnea (Kliegman et al. 2011). Childhood asthma is more prevalent in obese children, and obese children tend to present with more serious episodes and more complicated courses (Styne 2001). Finally, as with all obese individuals, there is an increased risk of pulmonary thromboembolism as a complication of deep-venous thrombosis of the lower extremities.

Gastrointestinal/Hepatic

Non alcoholic fatty liver disease (NAFLD) occurs in 10–25 % of obese adolescents (Gahagan 2011) and can progress to steatohepatitis and cirrhosis (Gahagan 2011; Styne 2001). Furthermore, NAFLD is the most common cause of childhood liver disease, and alarmingly, its prevalence is increasing as obesity rates increase in children (Hardee et al. 2013). The fatty liver is grossly enlarged, yellow-brown, and greasy in texture. Obesity-related steatosis is macrovesicular on microscopic examination, as demonstrated in Figs. 33.6 and 33.7, showing milder steatosis without inflammation and a severe steatosis with associated chronic lymphocytic portal triaditis, respectively. The histopathologic features of fatty liver disease range from simple steatosis to steatosis with acute and chronic inflammation, ballooning degeneration, and perisinusoidal and pericellular fibrosis (nonalcoholic steatohepatitis, NASH), to cirrhosis. The histological pattern of childhood NASH differs somewhat from that of adulthood, with differences most notable in the zonal location of steatosis (Hardee et al. 2013). While adult steatosis in NASH is typically located around the centrilobular vein (zone 3), in pediatric NASH the fat droplets can be in hepatocytes in the periportal areas (zone 1), in a random distribution, or panacinar. Furthermore, ballooned hepatocytes, lobular inflammation, and perisinusoidal fibrosis may be less common in children, though there is some overlap between adult and pediatric appearances of NASH (Hardee et al. 2013).

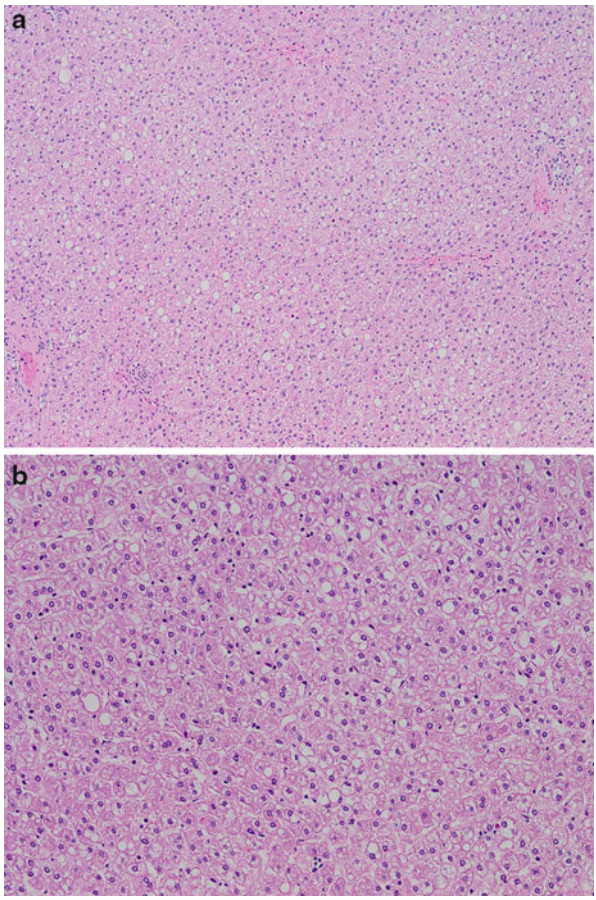

Fig. 33.6 Mild hepatic steatosis, liver of obese boy in Fig. 33.2 (Hematoxylin and Eosin, H&E a ×10; b ×20)

In addition to the risk of liver dysfunction and cirrhosis, nonalcoholic fatty-liver disease in childhood has been identified as a marker for increased risk of early carotid atherosclerosis (Pacifico et al. 2008).

Gallbladder disease is associated with obesity, although it is uncommon in childhood. Cholelithiasis is typically seen in obese adolescent females, who are four times more likely than non obese girls to suffer from gallstones (Styne 2001).

Orthopedic

Blount disease (tibia vara) is characterized by severe bowing of the tibia with knee pain and limp, due to irregular growth of the proximal medial tibial physis. The condition has been linked to obesity, and obesity-related cases tend to have younger age at onset and bilateral involvement (Styne 2001).

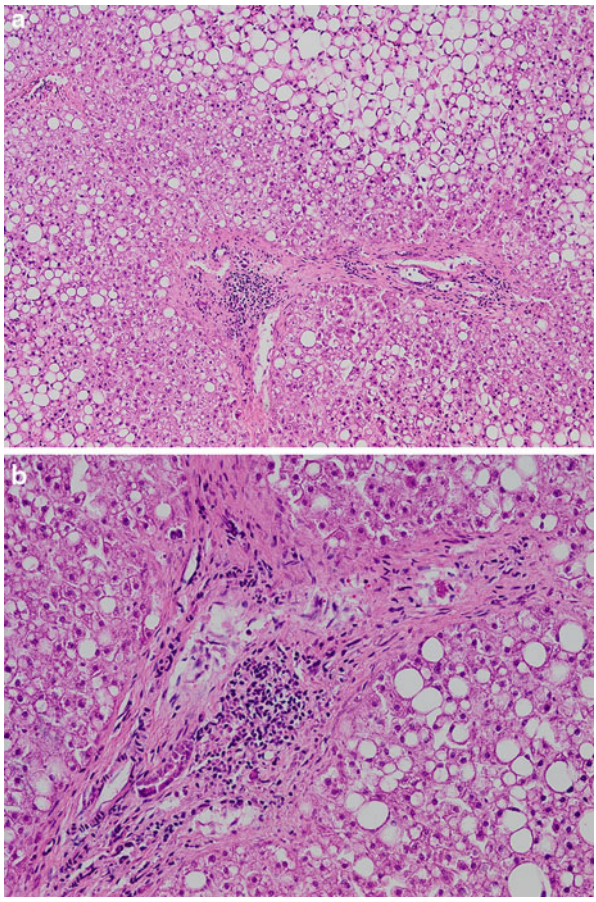

Fig. 33.7 Severe hepatic steatosis with steatohepatitis, liver of morbidly obese boy in Fig. 33.3 (Hematoxylin and Eosin, H&E a ×10; b ×20)

Slipped femoral capital epiphysis is a condition of the hip affecting adolescents, usually between 11 and 16 years of age, involving failure of the physis and displacement of the femoral head in relation to the femoral neck (Kliegman et al. 2011). Obesity is the most associated risk factor, with 65 % of affected youths having a greater than 90th percentile weight-for-age (Kliegman et al. 2011).

General musculoskeletal problems, such as back pain, hip pain, knee pain, and frequent strains or sprains, are also common in obese children and adolescents. Osteoarthritis and degenerative joint disease, typically thought of as "older age" problems stemming from cumulative damage over a lifetime, may be accelerated in their onset at a younger age in an obese adult who was a child with higher BMI and could even manifest in adolescence in severely obese children. Not only is obesity a proinflammatory state, but additional weight on the joints results in altered joint

movement and function, with compensatory alterations in gait in obese children that may result in earlier onset of osteoarthritis in the knees in particular (Gushue et al. 2005).

Neurological

Pseudotumor cerebri, or benign intracranial hypertension, is a condition more common in the obese, with symptoms of headaches, vision changes, and papilledema associated with increased intracranial pressure. Obesity is the most common cause of pseudotumor cerebri in children, if other medical conditions and other causes of venous obstruction are ruled out (Styne 2001).

Dermatologic

Superficial fungal infections are commonly seen in obese children, including candidal manifestations such as intertrigo and tinea corporis. Other skin problems, such as chafing of the thighs or other areas that rub, skin tags around the neck and axillae, and striae on the abdomen, hips, and thighs, are also prevalent.

Iatrogenic Complications

Obese children may have a higher rate of postoperative complications, with common surgical procedures in obese adolescents including appendectomy, reduction mammoplasty and, less commonly, gastric bypass. Childhood obesity is also associated with a lower rate of survival-to-hospital discharge after in-hospital cardiopulmonary resuscitation (Srinivasan et al. 2010).

Accidental Deaths

Obesity is associated with an increased risk of positional asphyxia during intoxication or suspension (such as during inverted suspension in a rollover motor vehicle collision with use of a seatbelt). Some authors have reported an increased severity of risk-taking behavior in obese adolescents/teens and a similar prevalence of these behaviors to normal-weight cohorts, which could lead to accidental deaths (Ratcliff et al. 2011).

Psychological/Psychosocial Impact

Anxiety and depression, low self-esteem, disordered eating, poor school performance, social isolation, problems with bullying, psychosocial stress, and suicide

have all been associated with obesity in the adolescent and teen years (Gahagan 2011; Styne 2001; Ratcliff et al. 2011). Body mass index is associated significantly with suicide ideation and attempts among high-school students, with both extreme underweight and extreme overweight being more than twice as likely as normal-weight peers to have suicide ideation (Eaton et al. 2005).

Risk of Adulthood Obesity

Numerous studies have demonstrated that obese children are at higher risk of becoming obese adults than are their non obese cohorts. The longer a child is obese during childhood, the greater the risk that the child will be obese as an adult. An obese child at 4 years of age has a 20 % probability of being an obese adult, while an adolescent who is obese has an 80 % probability of obesity in adulthood (Krebs and Primak 2009). The secondary complications of obesity if acquired in childhood are also likely to persist into adulthood, and obese adults who were obese children will experience obesity-related complications earlier in life than if obesity had started in adulthood.

Autopsy of the Obese Child

Unfortunately, obese children are at increased risk of death. These cases often require autopsy, falling under the jurisdiction of the forensic pathologist/medical examiner, due to the sudden and unexpected (if not entirely unpredictable) nature of the deaths and the young age of the decedents. Such cases may include deaths due to diabetic ketoacidosis, intra- or postoperative complications, and infectious diseases such as pneumonia, as well as nonnatural deaths. The autopsy should include careful measurement of height and weight for an accurate calculation of the BMI, as well as measurement of the thickness of the subcutaneous fat layer at the level of the umbilicus and over the chest. The BMI should be compared to CDC growth charts to determine the BMI percentile, using the previously described definitions to diagnose obesity and severe obesity, respectively. Cutaneous findings should be sought, including acanthosis nigricans and cutaneous fungal infections. Truncal obesity associated with the metabolic syndrome results in large deposits of intra-abdominal adipose tissue, including copious perivisceral fat. The heart may be enlarged and should be weighed and compared to age-matched control standards and/or tables for adult hearts by body height and body weight in the adolescent child who has reached an adult size. Similarly, hepatomegaly may be diagnosed by comparison with age-matched control standards for liver weight, and the gross impression of an enlarged, greasy, yellow–brown (fatty) liver can be confirmed on microscopy. Microscopic examination will often be enlightening in sudden deaths of obese children and should include a survey of all major organs including endocrine glands.

Appropriate ancillary testing includes toxicology, microbiology when indicated, and vitreous chemistry to include glucose and ketones. In addition to glucose testing performed on vitreous fluid and screening for ketone bodies, hemoglobin A_1C testing on blood can also be successfully completed in the postmortem state to confirm a suspicion of diabetes mellitus. Toxicology testing may be enlightening not only in searching for a potential cause of death but also in detecting those drugs previously noted which may contribute to childhood obesity.

When an obese child dies and has not had a thorough antemortem clinical work-up for medical causes of obesity, it may be prudent to consider those potential causes in a thorough postmortem investigation, including a review of antemortem symptomatology that could point to a particular endocrine syndrome. In addition to the potential gross and microscopic pathological findings of major endocrine causes like hypothyroidism and Cushing syndrome, postmortem laboratory testing of serum could be helpful, including thyroid-stimulating hormone (TSH), free thyroid hormone (T4), adrenocorticotropic hormone (ACTH), and cortisol levels (though the latter are highly variable based on diurnal rhythms and other factors). Unfortunately, some clinical testing used in the antemortem state requires a physiologic response and does not apply in the postmortem state (e.g., growth hormone stimulation test to diagnose growth hormone deficiency or dexamethasone suppression test in Cushing syndrome). Depending on availability, alternative testing such as insulin growth factor-1 (IGF-1) may be employed in suspected growth hormone deficiency. However, postmortem degradation of serum elements may affect the results of all such postmortem serological tests, particularly if the specimen is hemolyzed; therefore, the results should be interpreted with caution.

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Pediatric Metabolic Diseases

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Abstract

Since 20,000–25,000 genes are believed to constitute the human genome, at least the same number of genetic errors are possible. Each of these may be diagnosed by a specific test, whether biochemical, histological, genetic, or other. Meticulous attention to history and physical examinations is required followed by appropriate screening tests including biochemistry, radiology, or other modalities, and finally specific enzyme, protein, or gene analysis. Most of these disorders are inherited as autosomal recessive traits, some are X-linked, and others are inherited as dominant traits. Mitochondrial disorders form a genetically separate category: mitochondrial enzymes are coded both by the maternal nuclear genome and by the mitochondrial DNA. Many of these disorders may cause sudden and unexpected death.

Introduction

Diagnosis of Metabolic Diseases

The diagnosis of inborn errors of metabolism requires an understanding of the underlying defects, clinical presentations, and various laboratories and analytical tests available. Accredited laboratories performing genetic testing can be found at www.ncbi.nlm.nih.gov/sites/genetests/lab (Applegarth et al. 1989).

Common historical/clinical, physical, and laboratory findings are summarized in Table 34.1.

Even after death, some of the techniques used in the living may be helpful in detecting inborn errors of metabolism. For example, small amounts of urine may be found in the bladder and should be aspirated and saved. Within 6 hours after death, serum, tissues, and body fluids should be obtained and maintained in a state suitable for the tests desired. Blood samples should be collected in heparin and fluoride. Plasma should be separated and frozen at −20 °C. Red cells should be stored at +4 °C. Skin for

Table 34.1 Abnormalities suggesting inborn errors of metabolism

Neurologic	Hypo- or hypertonia
	Coma
	Persistent lethargy
	Seizures/movement disorders
	Developmental delay
	Progressive psychomotor degeneration
Gastrointestinal	Poor feeding
	Recurrent vomiting
	Jaundice
	Failure to thrive
	Hepatomegaly
	Hydrops, ascites
Eyes	Cataract, corneal clouding
	Cherry-red macula
	Dislocated lens
	Glaucoma/retinitis
Skin	Eczema
	Angiokeratoma
	Photosensitivity
	Xanthoma
	Edema
Muscle, joints	Myopathy
	Arthritis
	Abnormal mobility
	Cramps
Other	Dysmorphic features
	Neonatal deaths
	Consanguinity
	Self-mutilation
	Abnormal body or urine odor
	Abnormal hair
	Splenomegaly, cardiomegaly
	Recurrent acidosis with or without ketosis
	Deafness
Routine laboratory findings abnormal	Blood glucose
	Serum pH
	Cytopenia, chronic
	Liver function tests
	Porphyrinuria
	Anion gap
	Electroencephalography
	Radiography of bones
	Sweat test

(*continued*)

Table 34.1 (continued)

Abnormal odor of urine	Sweaty feet
	Mousy or musty
	Maple syrup
	Tomcat urine
	Cabbage
	Rotting fish
	Hop-like
	Swimming pool

Modified from Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007

Table 34.2 Presence of vacuolated lymphocytes in storage disorders

Disease	Vacuolated lymphocytes
GM_1, gangliosidosis, infantile	Frequent, large
Niemann–Pick A	Occasional, small
Niemann–Pick C	Occasional, small
Sialidosis	Frequent, large
Aspartylglycosaminuria	Frequent, large
Mannosidosis	Frequent, large
Fucosidosis	Occasional, small
Sialic acid storage disorders	Frequent, large
Mucolipidosis types II and III	Frequent, large
Juvenile neuronal ceroid lipofuscinosis	Occasional, variable
Glycogenosis type II	Occasional, small
Wolman disease	Occasional, small
Mucopolysaccharidoses type II and III	Frequent, large

From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Mosby; 2007, with permission

fibroblast culture should be placed in a sterile isotonic saline or transport medium at +4 °C. Tissue samples for enzyme analysis need to be stored at −70 °C. A simple test for screening of cytoplasmic vacuoles in the lymphocytes of peripheral blood may be the first indication of a storage disorder (Table 34.2). A number of metabolic disorders cause liver cirrhosis in infants and children, and some may be suggested or diagnosed by microscopic investigation of the liver sample. Skin specimens submitted for fibroblast cultures or electron microscopic (EM) investigation may direct the biochemical analysis of the fibroblasts (Table 34.3) (Vogler et al. 1987; O'Brien et al. 1975). Electron microscopic (EM) investigation of white blood cells and urine sediment may also be helpful in diagnosis. Routine placental examination may disclose fetal metabolic storage disease by the presence of vacuolization of syncytiotrophoblast, intermediate trophoblast, and stromal Hofbauer cells (Roberts et al. 1991).

Table 34.3 Tissues used for diagnosis of metabolic disorders

Skin
Fibroblasts
Lysosomes (EM)
Enzymes
Conjunctiva
Lysosomes (EM)
Intestinal-neurogenic plexus (*rectal biopsy*)
Gangliosides
Neuronal ceroid lipofuscinosis
Sphingolipidosis
Niemann–Pick
Peripheral nerve
Fabry
Niemann–Pick
Metachromatic leukodystrophy
Muscle
Carnitine
Glycogen
Enzyme histochemistry
Peripheral lymphocytes
Bone marrow
Cystinosis
Gaucher
Niemann–Pick
Amniocytes
Gaucher
Mucopolysaccharidoses
Gangliosidoses
Brain biopsy
Severe neurologic deterioration when no other method available
Cartilage–bone biopsy
Mucopolysaccharidoses
Skeletal dysplasias

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For many hereditary metabolic disorders, no specific therapy is available, but accurate diagnosis is important for prognosis, genetic counseling, and prenatal diagnosis in future pregnancies. The lysosomal storage disorders are among those metabolic errors most likely to present with dysmorphic features (Table 34.4). For an in depth and comprehensive review of metabolic diseases, see Gilbert-Barness 2007, Chap. 12, Metabolic disorders.

Table 34.4 Metabolic diseases associated with dysmorphologic features

Disease	Phenotype
Glutaric aciduria type II	Glomerulopathy
	Renal cystic dysplasia
	Cerebral dysgenesis
	Facial dysmorphism
	Congenital heart disease
	Genital anomalies
Pyruvate dehydrogenase	Microcephaly "fetal alcohol" facies
	Agenesis of corpus callosum
Peroxisomal disorders	Renal microcysts
Zellweger syndrome	Epiphyseal calcification
	Facial dysmorphism
	Congenital heart disease
	Cerebral dysgenesis
	Hepatopathy
Rhizomelic chondrodysplasia punctata	Facial dysmorphism
GM_1 gangliosidosis	Rhizomelic limb shortening
Congenital adrenal hyperplasia	Frontal bossing, low-set ears
Sialidosis	Ambiguous genitalia
	Coarse facial features, stippled epiphyses
Mucolipidosis type II	Coarse facial features
Mucopolysaccharidoses	Coarse facial features
Infantile sialic acid storage disease	Coarse facial features
Hydroxylisobutyryl-CoA deacylase	Congenital heart defects
	Agenesis of corpus callosum
	Dysmorphic facies
Gaucher-like storage disease	Arthrogryposis
Muscle phosphorylase deficiency	Arthrogryposis

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Storage Diseases

Mucopolysaccharidoses

Mucopolysaccharidoses (MPSs) are a group of lysosomal storage diseases resulting from a genetic defect of a variety of hydrolases capable of hydrolyzing carbohydrates (Muenzer 2011). They are characterized by storage of glycosaminoglycans (mucopolysaccharides) and glycolipids in the lysosomes of different cell types, including fibroblasts, macrophages, white blood cells (WBCs), parenchymal cells of liver, kidneys, brain, and other organs, and neurons, and by excretion of mucopolysaccharide in the urine (Neufeld and Muenzes 2001).

Glycosaminoglycans (GAGs) are long-chain polyanionic carbohydrates with disaccharide repeating units, one component of which consists of D-glucosamine or D-galactosamine and the other of either D-glucuronic or L-iduronic acid. The amino group and the fourth or sixth carbon of hexosamine are often either acetylated or sulfated.

GAG-synthesizing cells such as fibroblasts, endothelial cells, and leukocytes secrete proteoglycans (GAGs attached to proteins). Those not secreted enter lysosomes and are degraded by various lysosomal hydrolases, including proteases. With enzyme deficiency, GAGs accumulate within the lysosomes, leading to lysosomal overloading in the non-GAG-synthesizing cells, causing skeletal deformities, corneal clouding, and hepatosplenomegaly. Free GAGs appear in the urine. In the first year of life, similar compounds may be found in the urine of unaffected infants. Mucopolysaccharidoses are shown in Table 34.5.

Good screening results have been obtained with a diagnostic test based on dimethylmethylene blue (DMB) as the dye. Positive screening tests for GAGs have been described in mucosulfatidosis and mucolipidosis III and in a number of acquired diseases and clinical conditions. The prototype of MPS is Hurler syndrome (Fig. 34.1). The heart is enlarged owing to infiltration of GAGs within the myocardial cells, and the heart valves are thickened and distorted by storage material that is present within histiocytes. Hepatocytes and Kupffer cells (Fig. 34.2) and histiocytes of the spleen become distended. Storage material accumulates within histiocytes of the bone marrow and at the costochondral-junction growth plates in long bones, ribs, and vertebrae, thus impeding linear growth.

Since GAG binds strongly with such dyes as Alcian blue, a spot test on filter paper can provide a rough estimation of mucopolysaccharide excreted in the urine. The storage lysosomes in visceral cells in the MPSs contain GAG and glycolipid seen as membranogranular material and a lamellar pattern of the lipid within lysosomes. Both polysaccharide and glycolipid breakdown are impaired by a single-enzyme defect because groups of compounds of carbohydrate chains have the same terminal sugar, and the inability to be removed prevents further degradation of the molecule. Probably in all of these diseases, there is also impaired breakdown of glycoprotein. In the neuron, the material distending the cytoplasm shows PAS reactivity that is amylase (and diastase) resistant indicating that the substance is not glycogen, metachromasia with toluidine blue, and staining with Sudan black B, Nile blue, or Alcian blue. The material can be extracted with a chloroform–methanol mixture. These characteristics indicate the glycolipid nature of the accumulated material. Ultrastructurally, the lysosomes are filled with parallel lamellae, usually perpendicular to the limiting membrane, which are appropriately called zebra bodies (Fig. 34.3) (van de Kamp et al. 1981).

Children with mucopolysaccharidoses present with coarse facial features, developmental delay, behavioral problems, and mental retardation.

MPS IV is characterized by severe skeletal deformities. Cervical cord compression often requires posterior spinal fusion (Fig. 34.4). Mental development is usually normal. Most patients die in their twenties from cardiorespiratory failure.

Table 34.5 Mucopolysaccharidoses (MPS)

	Inheritance	Defective enzyme	Clinical pathologic features
MPS IH (Hurler)	AR	α-L-iduronidase	Abnormal facies, visceromegaly, skeletal changes, cardiovascular disease, mental retardation, corneal clouding
MPS IS (Scheie)	AR	α-L-iduronidase (defect allelic with above)	Cardiac valve disease, corneal clouding, joint stiffness, normal intelligence
MPS IH/IS genetic compound	AR	α-L-iduronidase	Intermediate between above
MPS IIA (Hunter, clinically severe subset)	XLR	Sulfoiduronate sulfatase	Abnormal facies, growth retardation, hepatosplenomegaly, cardiovascular disease, death by second decade
MPS IB (Hunter, clinically milder subset)	AR	Sulfoiduronate sulfatase (? defect allelic with IIA)	Features less severe than above with longer survival
MPS IIIA (Sanfilippo A)	AR	Heparin sulfate sulfatase	Visceral/skeletal features, slight; mental defect, severe
MPS IIIB (Sanfilippo B)	AR	N-α-Acetyl-D-glucosaminidase	Similar to above
MPS IIIC (Sanfilippo C)	AR	N-acetyltransferase	Similar to above
MPS IIID (Sanfilippo D)	AR	N-Acetylglucosamine 6-sulfate sulfatase	Similar to above
MPS IVA (Morquio A)	AR	Galactosamine-6-sulfate sulfatase	Thoracic skeletal deformity, aortic valve disease, corneal clouding
MPS IVB (Morquio B)	AR	β-galactosidase (allelic with forms of generalized GM_1 gangliosidosis)	Skeletal disease, corneal clouding mild, intellect normal
MPS VI (Maroteaux–Lamy)	AR	Arylsulfatase B	Skeletal abnormalities, corneal clouding severe, intellect normal until late in course Short stature, major feature
MPS VII (Sly)	AR	β-glucuronidase	Short stature, hepatomegaly, mental retardation, normal corneas
MPS IX	AR	Hyaluronidase deficiency	Short stature, joint masses, normal corneas

From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Mosby; 2007, with permission
AR autosomal recessive, *XLR* X-linked recessive

In addition to the mucopolysaccharidoses discussed above, intracellular mucopolysaccharide accumulation can also be found in some other clinically quite different diseases such as Fabry disease (a lipid-storage disease), Marfan syndrome (a heritable disorder of connective tissue), and cystic fibrosis (a membrane-transport disorder).

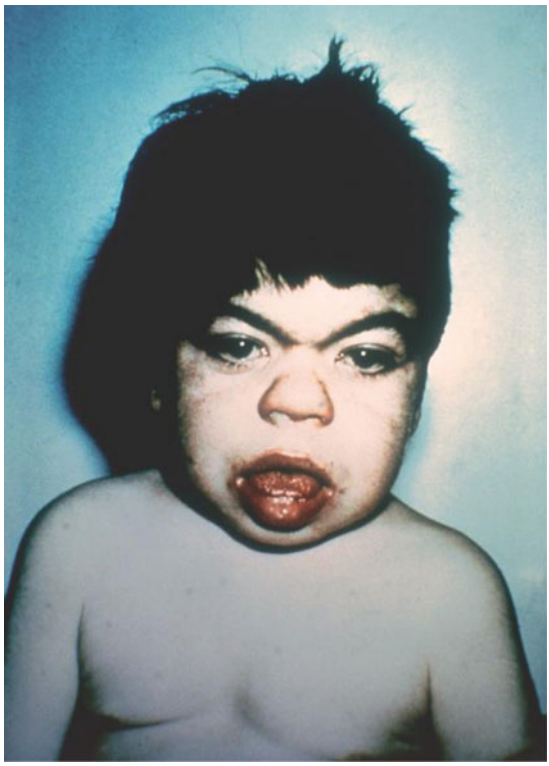

Fig. 34.1 Hurler syndrome. Phenotypic appearance showing coarse features, prominent supraorbital ridges, and depressed nasal bridge (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

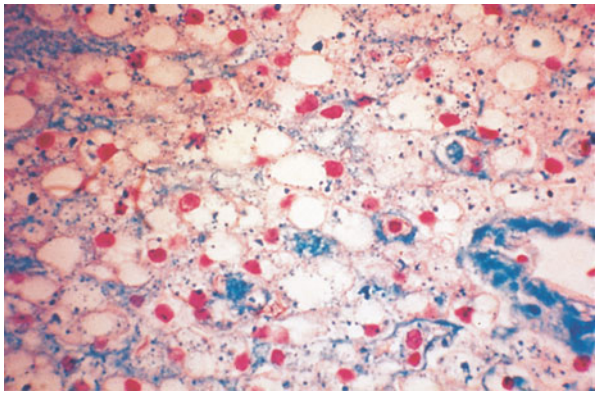

Fig. 34.2 Microscopic section of liver with granular deposits of mucopolysaccharide (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission) (× 20)

Glycoprotein Storage Diseases

Deficiency of specific lysosomal acid hydrolases results in failure to remove carbohydrate residues from the oligosaccharide chains.

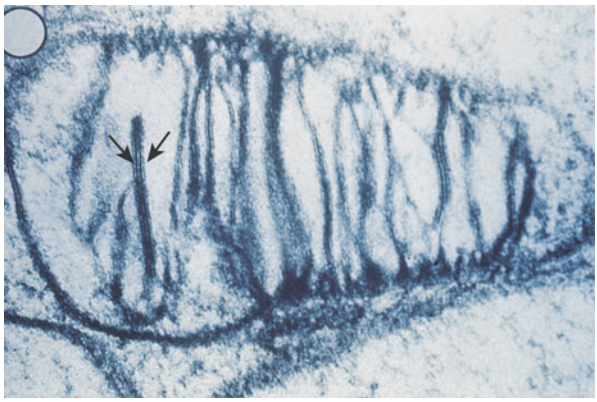

Fig. 34.3 Electron micrograph of a neuron showing stacked lipid lamellae (*arrows*) within lysosomes, the so-called zebra body (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

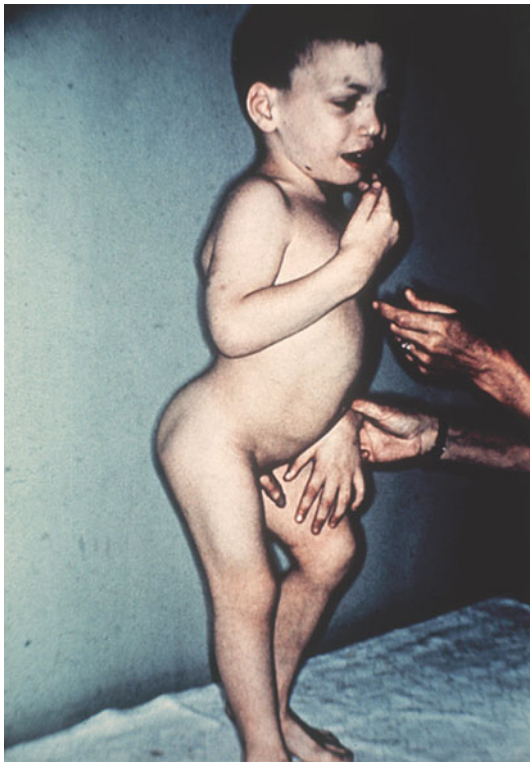

Fig. 34.4 Mucopolysaccharidosis IV (Morquio disease) in a child with severe skeletal deformities (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

Table 34.6 lists the glycoprotein-storage diseases. Patients with mannosidosis, fucosidosis, sialidosis, aspartylglycosaminuria, glutamylribose-5-phosphate disorder, and geleophysic dwarfism present with a phenotype similar to Hurler disease. Canavan disease, α_1-antitrypsin deficiency, and glycoprotein-storage disorder (Gilbert-Zugibe) (Zugibe et al. 1969) phenotypes differ.

Table 34.6 Glycoprotein storage diseases[a]

McKusick #	Disease	Genetic pattern	Enzyme defect
230000	Fucosidosis type I	AR	α-1-Fucosidase
230000	Type 2	AR	α-1-Fucosidase
230000	Type 3	AR	α-1-Fucosidase
248500	α-Mannosidosis	AR	α-Mannosidosis
248510	β-Mannosidosis	AR	β-Mannosidosis
107400	α_1-Antitrypsin	AR	α_1-Antitrypsin (protease inhibitor deficiency)
208400	Aspartylglycosaminuria	AR	N-Aspartyl
269920	Sialic acid storage diseases	AR	β-Glucosaminidase
604369	Salla disease	AR	Sialidase
269920	Infantile sialic acid storage disease	AR	Sialidase
269921	Sialuria		UDP acetylglucosamine epimerase
271900	Canavan disease	AR	N-acetylaspartase
305920	Glutamyl ribose-5-phosphate storage disease	AR	ADP-ribose protein hydrolase
232900	Glycoprotein storage disease (Gilbert–Zugibe)	AR	Not known
231050	Geleophysic dysplasia	AR	Not known
212065	Carbohydrate-deficient glycoprotein syndrome	AR	Not known

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AR autosomal recessive

[a]A degree of glycoprotein accumulation presumably occurs in some mucopolysaccharidoses and mucolipidoses, in addition to accumulation of polysaccharides and glycolipids

Mannosidosis

The gene that codes for acid α-mannosidase has been sequenced and maps to 19p13.2, and so molecular diagnosis is possible (Stensland et al. 2011). The severe infantile form includes psychomotor retardation, facial coarsening, some degree of dysostosis multiplex, recurrent bacterial infections, deafness, hepatomegaly, and lenticular or corneal opacities. The milder juvenile–adult form is characterized by a more normal early development but with the appearance of mental retardation during childhood and adolescence.

More rarely, β-mannosidase may be deficient, with or without an associated reduction of heparin sulfaminidase. A severe form is characterized by status epilepticus, severe quadriplegia, and death by 15 months of age.

Fucosidosis

Type I fucosidosis is fatal infantile fucosidosis that presents in infancy with psychomotor retardation, coarse facies, corneal opacities, dysostosis multiplex, neurological deterioration, growth retardation, and cardiomegaly. Hepatomegaly, splenomegaly, seizures, and increased sweat chloride are also found. Type 2 fucosidosis is milder, first signs occur at 1–2 years of age, and angiokeratomas develop. Brain magnetic resonance imaging (MRI) scan in fucosidosis may show findings of hypomyelination in the globus pallidus and often in the substantia nigra (on T2-weighted images) (Steenweg et al. 2011).

Aspartylglycosaminuria

Aspartylglycosaminuria (AGA) is an autosomal recessive disease resulting in deficient activity of aspartylglucosaminidase. AGA results in accumulation of aspartylglucosamine in the lysosomes of almost all cells. This disorder occurs predominantly in Finland. It manifests as a dysmorphic syndrome with coarse facies, hypotonia, mental delay, hepatomegaly, and spasticity. Death occurs in the fourth or fifth decade.

Enzyme status is measured in skin fibroblasts or leukocytes. Prenatal diagnosis can be made on the basis of amniotic fluid cells, fibroblasts, or chorionic villus samples. The gene for AGA resides in the long arm of chromosome 4 (4q32-q33) (Aula et al. 1984). Because one mutation appears to account for about 98 % of the AGA alleles in the Finnish population, a DNA-based test suitable for the detection of the mutation has been developed and is suitable for this population (Ikonen et al. 1993; Enomaa et al. 1992).

Sialic Acid Disorders

Clinically, Salla disease (SD) shows relatively mild but progressive neurological signs and mental retardation, beginning in infancy and leading to a developmentally delayed adult with a long life span. No radiological skeletal changes are evident except for a thickened calvarium. Infantile sialic acid storage disease shows neonatal and infantile organomegaly and severe mental retardation, ending in death during infancy or childhood (Table 34.7).

The routine diagnostic test for both SD and infantile sialic acid storage disease (ISSD) is demonstration of elevated levels of free sialic acid in the urine, generally done by thin-layer chromatography.

The definitive diagnosis of sialidosis is based on the direct measurement of sialidase activity in fresh tissue samples. Tissue samples should not be frozen or exposed to prolonged sonication. The substrate of choice appears to be 4-methylumbelliferyl-β-N-acetylneuraminic acid (Myers et al. 1980). Measurement of carboxypeptidase activity should also distinguish galactosialidosis patients who lack this activity from sialidosis patients who have normal levels of this enzyme (Tranchemontagne et al. 1990).

Table 34.7 Comparison of clinical findings in Salla disease and infantile sialic acid storage disease (ISSD)

	Salla disease	ISSD
Intrauterine	No findings	Hydrops fetalis 10 %
Neonatal	Normal	Hepatosplenomegaly and ascites 50 %
Infancy	Hypotonia, ocular nystagmus, ataxia, failure to thrive	Failure to thrive, dysmorphic features
Childhood	Developmental delay, impaired speech, growth retardation	
Adulthood	Severe mental retardation, ataxia, abnormal tendon reflexes, exotropia of eyes	
Age of death	35–74 years	3 months–4.5 years (mean 20 month)

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α_1-Antitrypsin (α_2-Antiprotease) Deficiency

α_1-Antitrypsin (α_1AT), a glycoprotein of molecular weight 52 kDa, is a major plasma protease inhibitor and accounts for 80 % of serum α_1-globulin. The physiological substrate is elastase, particularly important for the integrity of the lower respiratory tract. The Pi locus (protease inhibitor) for α_1AT is on chromosome 14q31-32.1; α_1AT shows considerable genetic variability, with more than 60 genetic variants (Cox 2001). For the most common variants, letters are used according to their electrophoretic mobility: F (fast), S (slow), and Z (very slow). The normal phenotype is PiMM and has 100 % activity. Reference and interpretive ranges for α1-antitrypsin have recently been reported (Donato et al. 2012).

The genotype of the most severe form of α_1AT deficiency is PiZZ with 10–20 % activity. Homozygous PiZZ has an incidence of 1 in 1,600 to 2,000 live births in North America and Northern Europe. α_1AT is retained in the cytoplasm of the cells (Perlmutter 1991). In children, liver involvement is most frequent (Cario 1990) with the hepatocytes containing eosinophilic, hyaline-like globules, usually in periportal hepatocytes. Utilizing PAS staining followed by diastase digestion (PASD), these inclusions are easily visualized as brilliant pink globules in the cytoplasm, most prominent in the periportal hepatocytes (Quizilbash and Young-Pong 1983). In newborn infants, the intracytoplasmic inclusions may be fine, granular, and indistinguishable from other granules such as bile. Immunohistochemical stains are useful to confirm the identity of the material using an antibody to α_1AT. By EM, the storage material is present within the cisternae of the endoplasmic reticulum (Cutz and Cox 1979). The most common presentation of liver involvement is characterized by conjugated hyperbilirubinemia, raised serum aminotransferase levels, and often hepatosplenomegaly. In addition to giant-cell transformation, hepatocellular injury, fibrosis, cholestasis, and bile-duct

proliferation can be seen in liver biopsies. There is an increase in the HLA-DR3-Dw25 haplotype in α_1AT-deficient persons with liver disease. The liver injury in α_1AT deficiency is a direct consequence of the intracellular accumulation of mutant α_1AT molecules and does not result from a deficiency in antielastase activity (Carlson et al. 1988). Secondary hepatocellular carcinoma may occur (Lieberman 1974).

Liver involvement is usually noticed in the first 2 months of life because of persistent jaundice. Serum transaminases are slightly elevated. The liver may be enlarged. These infants are generally admitted with a diagnosis of neonatal hepatitis syndrome. Liver complications may result in liver failure and sudden death.

Lysosomal Lipid Storage Diseases

The large number of diseases of lysosomal lipid storage (Table 34.8) reflects a wide variety of molecules including triglycerides, sterols, sphingolipids, sulfatides, sphingomyelins, gangliosides, and lipofuscins that must be degraded by the lysosomal acid-hydrolase system.

Tissues useful in the diagnosis of lysosomal storage diseases are shown in Table 34.9.

Wolman Disease and Cholesteryl Ester Storage Disease

Both of these diseases are autosomal recessive and are secondary to a deficiency of lysosomal acid lipase (Fasano et al. 2012). Deficiency of two allelic forms of the enzyme results in either Wolman disease or cholesteryl ester storage disease and the accumulation of cholesteryl esters. The definitive diagnosis of both disorders is made by assay for lysosomal acid lipase activity in cultured fibroblasts, lymphocytes, or other tissues (Kyriakides et al. 1972). The gene encoding lysosomal acid lipase has been linked to chromosome 10q23.3.

Wolman Disease

Wolman disease presents in early infancy and is rapidly progressive with hepatosplenomegaly, jaundice, anemia, failure to thrive, lipid-laden histiocytes in the bone marrow and peripheral blood, and acanthocytosis. Plasma lipids are at the low end of the normal range. Cholesteryl triglycerides can be identified histochemically (Schaub et al. 1980). The adrenal glands contain necrotic cells and foam cells and become calcified.

Cholesteryl Ester Storage Diseases (CESD)

Cholesteryl ester storage disease is mild and usually does not present until childhood or later.

Table 34.8 Lysosomal lipid storage diseases

McKusick #	Disease	Inheritance	Deficient enzyme
Cholesteryl ester storage disease			
278000	Wolman, infantile	AR	Acid lipase (cholesterol ester hydrolase)
278000	Wolman, late infantile, juvenile	AR	Acid lipase
278000	Cholesteryl ester storage disease	AR	Acid lipase
Sphingomyelin storage diseases			
257200	Niemann–Pick A (infantile cerebral type)	AR	Sphingomyelinase
607616	Niemann–Pick B (juvenile non-cerebral type) Niemann–Pick (neonatal malignant cholestatic jaundice)	AR AR	Sphingomyelinase Presumably sphingomyelinase subset of NP-A
257220	Niemann–Pick C (subacute juvenile neuronopathic type)	AR	Deficient esterification of exogenous cholesterol
257220	Niemann–Pick D (subacute juvenile neuronopathic type	AR	Deficient esterification of exogenous cholesterol
257220	Niemann–Pick D (subacute juvenile/ adult neuronopathic type)	AR	Same as above
257220	Niemann–Pick E (adult non-cerebral type)	AR	Same as above
Cerebroside storage diseases			
230900	Gaucher $_2$A (infantile cerebral type)	AR	Glucocerebrosidase
	Gaucher $_2$B (rapidly progressive with ichthyosis)	AR	Glucocerebrosidase
231000	Gaucher $_3$ (chronic neuropathic or Norrbottnian type)	AR	Glucocerebrosidase
230800	Pseudo-Gaucher disease	AR	Glucocerebrosidase
245200	Krabbe, infantile type	AR	Galactocerebroside β-galactosidase
245200	Krabbe, late infantile/ juvenile type	AR	Galactocerebroside β-galactosidase

(*continued*)

Table 34.8 (continued)

McKusick #	Disease	Inheritance	Deficient enzyme
301500	Farber lipogranulomatosis		
	a. Early onset	AR	Ceramidase
	b. Infantile type	AR	Ceramidase
	c. Late onset	AR	Ceramidase
	d. Neonatal type	AR	Ceramidase
	e. Malignant histiocytosis type	AR	Ceramidase
301500	Fabry (angiokeratoma corporis diffusum)	XLR	α-Galactosidase A (ceramide trihexosidase)
Gangliosidoses			
230500	GM_1 gangliosidosis, type 1 infantile	AR	B-Galactosidase
230600	GM_1 gangliosidosis, type 2 infantile (Derry)	AR	As above, presumably allelic
230650	GM_1 gangliosidosis, type 3 adult	AR	As above, presumably allelic
Note: Above three conditions presumably allelic with mucopolysaccharidosis IVB (Morquio B, q.v.)			
272800	GM_1, type 1 gangliosidosis infantile (Tay–Sachs disease, B form)	AR	Hexosaminidase A (α-unit mutation)
272750	Tay–Sachs disease, AB form	AR	Hexosaminidase activator (saposin)
272800	Tay–Sachs disease, B_1 form, GM_2 type 3 (juvenile type)	AR	Hexosaminidase A, α-unit (mutation gives gly 269 ser change in Hex A gene) (allelic with Tay–Sachs α-unit mutations)
268800	GM_2 type 2 gangliosidosis, infantile generalized form (Sandhoff)	AR	Hexosaminidases A and B (β-unit mutation)
230700	GM_2, gangliosidosis juvenile, β-unit mutation	AR	As above
230710	GM_2, gangliosidosis, juvenile, α-unit mutation	AR	Hexosaminidase A α-unit
	GM_2, gangliosidosis, chronic	AR	As above
	GM_2, gangliosidosis, chronic, α-unit mutation	AR	Hexosaminidases A and B

(*continued*)

Table 34.8 (continued)

McKusick #	Disease	Inheritance	Deficient enzyme
256540	Galactosialidosis (Goldberg)	AR	B-Galactosidase, neuraminidase (note early and late infantile forms due to deficiency of "protector protein" for above lysosomal hydrolases, adult type due to abnormality of processor protein)
Sulfatide storage diseases			
250100	Metachromatic leukodystrophy, infantile	AR	Arylsulfatase A (cerebroside sulfate sulfatase) (allele $_1$ mutation)
250100	Metachromatic leukodystrophy, juvenile	AR	As above, presumably allelic with above (allele A mutation); genetic compound of allele $_1$ and allele A mutations presumably occur
250100	Metachromatic leukodystrophy, adult onset	AR	Same as above (? If spectrum of severity with other forms); pseudodeficiency gene occurs; some patients presumably genetic compound of MLD mutation and pseudodeficiency gene
249900	Metachromatic leukodystrophy	AR	Saposin B (sulfatase activator protein1)

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AR autosomal recessive, *XLR* X-linked recessive

Niemann–Pick Disease (NPD)

Sphingomyelin lipidosis is associated with deficiency of isoelectric forms of sphingomyelinase. Six types of this disorder have been characterized (Crocker 1961; Schuchman and Desnick 2001; Patterson et al. 2001). Type A is the infantile form in which hepatosplenomegaly and central nervous system (CNS) degeneration begin within the first year of life. Type B is the non neuronopathic form and is less severe than type A. Type C (Patterson et al. 2001), the juvenile form, is characterized by CNS degeneration beginning after the first year of life, with less severe hepatosplenomegaly than is found in type A, and is often accompanied by predominance of cerebellar symptoms. Macular cherry-red spots are seen in types A and C. In type C, defects in the esterification of cholesterol have been

Table 34.9 Tissues useful in diagnosis of storage diseases

Organ or tissue	Manifestation	Disease to be considered	Presumptive test	Diagnostic test
Liver	Increased size; disordered liver function tests may be seen in some, but not all, patients with disease	α1-Antitrypsin deficiency	Plasma α_1-antitrypsin	Electrophoresis and Pi typing; liver biopsy, immunopathology, electron microscopy
		Cholesteryl ester storage disease	Liver biopsy	Fibroblast acid lipase
		Mucopolysaccharidoses	Urine mucopolysaccharide quantitation; electron microscopy of conjunctival biopsy	Specific enzyme analysis
		Glycoproteinoses	Urine oligosaccharides; electron microscopy of conjunctival biopsy	Specific enzyme analysis
		Mucolipidoses II, III	Urine oligosaccharides; electron microscopy of conjunctival biopsy	Fibroblast lysosomal enzymes
		Glycogen storage disease	Conjunctival biopsy (type II), liver biopsy, electron microscopy	Electron microscopy (type II)
		Gaucher disease	Gaucher cells in liver, bone marrow; increased serum total hexosaminidase or acid phosphatase	Leukocyte or fibroblast β-glucosidase; electron microscopy
		Niemann–Pick disease	Conjunctival, liver biopsy, electron microscopy	Leukocyte or fibroblast sphingomyelinase
		Wolman disease	Liver biopsy	Fibroblast acid lipase
Spleen	Increased size	Mucopolysaccharidoses	Urine mucopolysaccharide quantitation; electron microscopy of conjunctival biopsy	Specific enzyme analysis
		Gaucher disease	Gaucher cells in bone marrow	Leukocyte or fibroblast β-glucosidase; electron microscopy
		Niemann–Pick disease	Conjunctiva, bone marrow or liver biopsy, electron microscopy	Leukocyte or fibroblast sphingomyelinase

(*continued*)

Table 34.9 (continued)

Organ or tissue	Manifestation	Disease to be considered	Presumptive test	Diagnostic test
Bone and joint	Dysostosis multiplex, other radiographic changes	Mucopolysaccharidoses	Urine mucopolysaccharide quantitation; electron microscopy of conjunctival biopsy	Specific enzyme analysis
		Glycoproteinosis	Urine oligosaccharide determination; electron microscopy of conjunctival biopsy	Specific enzyme analysis
	Swollen joints, soft tissue nodules	Farber disease	Tissue biopsy for electron microscopy	Fibroblast culture; lysosomal acid ceramidase
Eye	Macular cherry-red spot	Tay–Sachs disease	Serum hexosaminidase A	Leukocyte or fibroblast hexosaminidase A
		Sandhoff disease	Serum total hexosaminidase	Leukocyte or fibroblast total hexosaminidase
		Niemann–Pick disease	Conjunctival, bone marrow, or liver biopsy, electron microscopy	Leukocyte or fibroblast sphingomyelinase
		Generalized gangliosidosis	White cell β-galactosidase; occasionally urine oligosaccharide increases can be seen by thin-layer chromatography, conjunctival, bone marrow biopsy; electron microscopy	
		Sialidoses	Urinary oligosaccharide excretion, conjunctival biopsy for electron microscopy	Fibroblast sialidase
	Corneal clouding	Mucopolysaccharidoses (Hurler, Scheie, Morquio, Maroteaux–Lamy, β-glucuronidase deficiency) Mucolipidoses II, III	Urine mucopolysaccharides; conjunctival biopsy for electron microscopy Urinary oligosaccharide excretion; conjunctival biopsy for electron microscopy	Specific enzyme analysis Fibroblast lysosomal enzymes
	Crystals in lens	Cystinosis	Cystine crystals in tissues	Cystine in leukocytes/ fibroblasts

Adrenal gland	Bilateral adrenal calcification	Wolman disease	Liver biopsy	Fibroblast acid lipase
Muscle – cardiac/ skeletal	Cardiomegaly; heart failure; myopathy involving skeletal muscle	Pompe disease	Electron microscopy, conjunctiva, lymphocytes or skin	Lymphocyte or fibroblast
		Glycogen storage diseases type III, IV	Liver biopsy for electron microscopy	α –glucosidase; electron microscopy; specific enzyme analysis
Brain	Progressive mental and motor dysfunction; retardation	Krabbe disease	Conjunctival biopsy for electron microscopy; CSF protein (increased)	Galactocerebroside B-galactosidase, leukocytes or fibroblast culture
		Metachromatic leukodystrophy	Conjunctival biopsy for electron microscopy	Arylsulfatase A, fibroblast culture
		Neuronal ceroid lipofuscinoses	CSF protein, (increased); sural nerve biopsy; nerve conduction studies	Peripheral blood lymphocytes, skin, conjunctival biopsy for electron microscopy
		Niemann–Pick disease	Conjunctival, bone marrow, or liver biopsy	Leukocyte or fibroblast sphingomyelinase
		Mucopolysaccharidoses	Urine mucopolysaccharide quantitations; electron microscopy of conjunctival biopsy	Specific enzyme analysis

(*continued*)

Table 34.9 (continued)

Organ or tissue	Manifestation	Disease to be considered	Presumptive test	Diagnostic test
		Glycoproteinoses	Urine oligosaccharide determination; electron microscopy of conjunctival biopsy	Specific enzyme analysis
		Tay–Sachs disease	Serum hexosaminidase A	Leukocyte or fibroblast hexosaminidase A
		Sandhoff disease	Serum total hexosaminidase	Leukocyte or fibroblast hexosaminidase
		Generalized gangliosidosis	White cell β-galactosidase; GM_1	Leukocyte or fibroblast β-galactosidase
				Urine oligosaccharide thin-layer chromatography; conjunctival, bone marrow biopsy for electron microscopy

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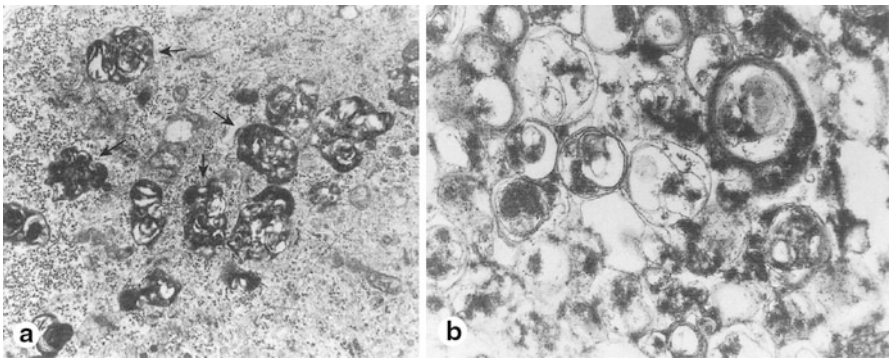

Fig. 34.5 Niemann–Pick disease electron micrographs (**a**) Pleomorphic lipid profiles in the liver. (**b**) Cultured fibroblast with pleomorphic lipid profiles (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

identified (Gal et al. 1975; Gilbert et al. 1981). Recently alternations in autophagic pathways have been described, and it has been proposed that this may contribute to the development of the neuropathology in type C (Elrick et al. 2012). The ultrastructural appearance of the lipid inclusions consists of concentrically laminated, myelin-like figures with a periodicity of approximately 50 nm, resembling membranous cytosomes and other pleomorphic lipid profiles in the nervous system (Fig. 34.5a). Cultured fibroblasts have similar inclusions, and cultured amniotic cells contain storage material (Fig. 34.5b). Histochemical staining of NPD, Gaucher disease, and gangliosidosis is shown in Table 34.10.

The most common and severe variant is type A, the acute neuronopathic form. These patients, often of Eastern European Jewish ancestry, present early in life with hepatosplenomegaly and rapid progressive deterioration of the CNS. Often the skin has a yellow–brown pigmentation, lymph nodes are enlarged, and ocular manifestations (cherry-red macula and corneal opacifications) are evident. Few children survive beyond 4 years of age.

Gaucher Disease

Gaucher disease, the most common of the lysosomal storage disorders, is inherited autosomal recessive. The gene frequency in the Jewish population is between 0.035 and 0.040. Three types represent different allelic disorders with different mutations in the structural gene of the deficient enzyme β-glucocerebrosidase (Beutler 1991; Ginns et al. 1982). In the absence of this enzyme, glucocerebroside cannot be catalytically converted into ceramide and glucose and thus accumulates in organs and tissues, particularly those of the reticuloendothelial system (RES).

The systemic result of the enzyme defect is shown in Fig. 34.6. The gene encoding acid β-glucosidase has been cloned to chromosome 1q21-q31. Diagnosis of Gaucher disease DNA analysis is shown in Table 34.11.

Table 34.10 Histochemical staining of three types of lysosomal lipidoses

	Gaucher disease	Niemann–Pick disease	Gangliosidoses GM_1 and GM_2 (types 1 and 2)
PAS	+++	0 to +	+ to +++
PAS amylase	+++	0 to +	+++
Schultz cholesterol technique	0	++	0
Oil red O	+ to ++	+++	++
Oil red O after cold acetone extraction	+ to ++	+++	++
Oil red O after hot acetone extraction	0	+++	+ to ++
Oil red O after pyrimidine extraction	0	0	0
Luxol fast blue	0	+++	++
OTAN	0	+++	++
Alcian blue	Adult 0 to + infantile ++	+	0
Acid phosphatase	++	0 to +	++
Cells involved	RE cells (neuron in infantile)	RE cells (neuron in infantile)	Neurons
Biopsy tissues of choice	Spleen, marrow	Spleen, marrow	Nerve cells

Modified from Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission
PAS periodic acid-Schiff, *OTAN* Osmium tetroxide α-naphthylamine, *RE* reticuloendothelial

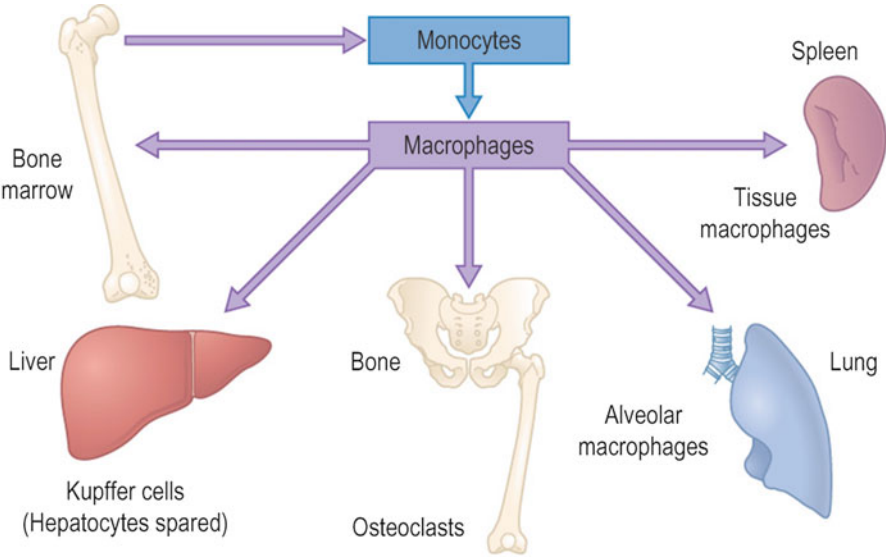

Fig. 34.6 The systemic effects of the enzymatic defect in Gaucher disease (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

Table 34.11 Diagnosis of Gaucher disease

DNA analysis has some advantages over enzymatic diagnosis
Results are qualitative rather than quantitative
Provides greater accuracy in detection of heterozygotes
Polymerase chain reaction (PCR) is the most widely used molecular
diagnostic approach used to detect Gaucher mutations
Allele-specific oligonucleotide (ASO) hybridization
Regions containing mutations are amplified via PCR
ASO probes are added and will hybridize only to complementary alleles
Mutant ASO will not hybridize to a mutated allele
Normal ASOs only hybridize to normal alleles
Serum levels of some enzymes may be elevated
Acid phosphatase
Lysosomal enzyme that may reflect overall macrophage activity
Elevation is suggestive of Gaucher disease when possibility of metastatic prostate carcinoma has been eliminated
Angiotensin-converting enzyme
Elevated plasma ferritin levels are commonly seen
Decreased plasma cholesterol levels may be seen in unsplenectomized patients

From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Mosby; 2007, with permission

Gaucher Disease Type I

Type I (non neuronopathic) is the chronic form of Gaucher disease. Clinical manifestations are highly variable. It has been diagnosed in infancy, but more commonly in later childhood and adolescence, and sometimes not until adulthood. Painless splenomegaly, thrombocytopenia, anemia, and leukopenia are the usual initial presenting features. Platelet counts may be less than 50×10^9/L without an accompanying bleeding diathesis. The liver frequently does not become significantly enlarged until later in the course of the disease. Erlenmeyer-flask deformity of the distal ends of the femur is considered diagnostic of Gaucher disease (Beautler and Grabowski 2001). Diffuse, yellow-brown skin pigmentation may involve the face and legs. Renal involvement, pulmonary hypertension, and cardiac abnormalities are less common. Patients with type I disease have normal life expectancy. A complex allele of the glucocerebrosidase gene has a milder clinical course (Zimran and Horowitz 1994).

Gaucher Disease Type II

Type II (acute neuronopathic, infantile) Gaucher disease is rare and has no ethnic predilection. It is rapidly progressive with severe neurological complications and signs of cranial-nerve nuclei and extrapyramidal-tract involvement beginning 3–6 months after birth. Although neuronal-cerebroside storage is not a feature, the brain is the site of extensive neuronal-cell death, reactive gliosis, and the perivascular accumulation of Gaucher cells. CNS deterioration is manifested by strabismus, trismus, and retroflexion of the head. Death occurs by 2 years of age (Zimran and Horowitz 1994). The condition is believed to stem from an unstable enzyme precursor.

Type III

Type III (subacute juvenile neuronopathic Swedish or Norrbottnian) has a variable age of onset but usually begins in later childhood. Characteristics include ataxia, spasticity, akinetic and myoclonic seizures, and variable degrees of dementia. Patients with types II and III share the same mutation (444 leu to pro) in the gene. The phenotypic differences are ascribed to a nonfunctional allele in type II patients.

Krabbe Disease

This autosomal recessive disorder usually presents between 3 and 6 months of age after a normal neonatal period with a rapidly progressive course. It is due to a deficiency of galactocerebrosidase activity and the accumulation of galactosylceramide in the peripheral and central nervous system. Diagnosis is made by enzyme assay of leukocytes and cultured fibroblasts; prenatal diagnosis is from assay of amniotic fluid cells or CVS.

The infantile form is rapidly progressive with spasticity and irritability progressing to hypotonia, blindness, deafness, seizures, and peripheral neuropathy. The onset is usually between 3 and 6 months of age, and death occurs by 2 years of age. The late-onset variants present in childhood and subsequently undergo diverse, progressive neuropathic complications. This type may result in sudden death early in life. The gene has been mapped to chromosome 14q24.3-32.1 and cloned (Inui et al. 1995).

The lesions of Krabbe disease are confined to the CNS and are characterized by cerebral atrophy, loss of myelin, gliosis, and presence of globoid cells (Wegner et al. 2001). Globoid cells are multinucleated, microglial macrophages distended with storage material. There is diffuse demyelination of the white matter and numerous calcifications. Intense gliosis occurs within the cortex and basal ganglia, especially around the perivascular spaces of the white matter. The perivascular spaces contain an accumulation of round mononuclear or binuclear PAS-positive globoid cells 15–20 μm in diameter. The cells are Sudan positive and glial fibrillary acidic protein (GFAP) negative. They stain strongly for *Ricinus communis* agglutinin and less strongly for peanut agglutinin and wheat-germ agglutinin. EM shows tubular structures similar to those observed in Gaucher disease.

Fabry Disease

The primary biochemical defect of Fabry disease is a deficiency of lysosomal α-galactosidase A, an enzyme that hydrolyzes ceramide to sphingosine and a free fatty acid (Brady et al. 1967; Toyooka 2011). Fabry disease is an X-linked disorder mapped to Xq22. Heterozygous female carriers have an intermediate level of enzyme activity. Glycosphingolipid, principally the trihexosylceramide-globotriaosylceramide, accumulates in all organs and tissues (Abreo et al. 1984) and may be

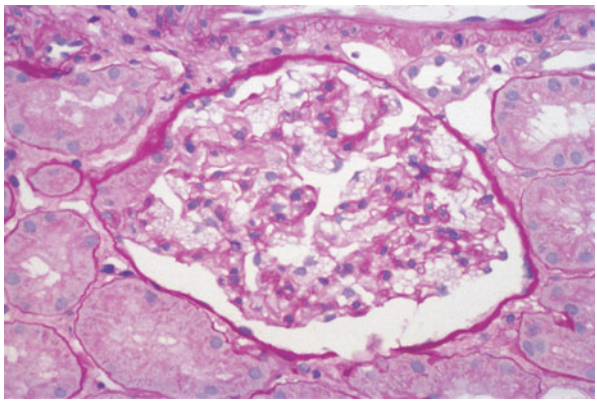

Fig. 34.7 Fabry disease. Foamy glomerular cells in kidney (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission) (Periodic acid Schiff; PAS × 100)

up to 300-fold higher than normal levels (Schibanoff et al. 1969). The greatest accumulation is observed in the kidney, lymph nodes, blood vessels, prostate, and autonomic ganglia (Fig. 34.7) (Abreo et al. 1984). Microaneurysm formation of retinal and conjunctival vessels may occur. In the skin, a transition from telangiectasia to a frank angiokeratoma is a hallmark of the disease.

The histopathologic changes frequently involve the heart, especially the myocardial cells, specialized tissues of the atrioventricular conduction system, and the valves (Schibanoff et al. 1969). Hypertrophic obstructive cardiomyopathy has been noted. The aorta may show changes suggestive of cystic medionecrosis. These cardiovascular manifestations may result in sudden death.

Gangliosidoses

GM_1 Type I Gangliosidosis

GM_1 type I gangliosidosis (generalized) is an autosomal recessive disorder that presents in early infancy with coarse facies, macroglossia, depressed nasal bridge, large ears, frontal bossing, hepatosplenomegaly, dysostosis multiplex, and rapidly progressive psychomotor deterioration with seizures and death by 2 years of age. In the brain, there is progressive atrophy with neuronal swelling, loss of neurons, and gliosis. Neurons contain sudanophilic material (ganglioside) and some PAS-positive material, whereas other viscera accumulate strongly PAS-positive material owing to the presence of mucopolysaccharides.

GM_1 Type II Gangliosidosis

GM_1 type II gangliosidosis (juvenile) usually becomes apparent at about 1 year of age and is clinically and pathologically similar to type I gangliosidosis (Gilbert et al. 1975).

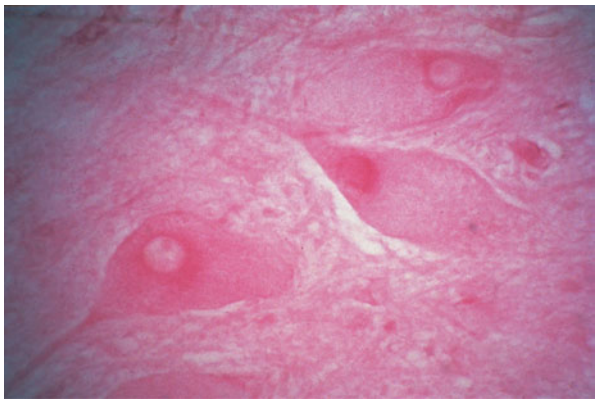

Fig. 34.8 Tay–Sachs disease (GM_2 gangliosidosis) in a brain with swollen neurons due to accumulation of gangliosides in the lysosomes (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission) (Hematoxylin and Eosin, H&E ×200)

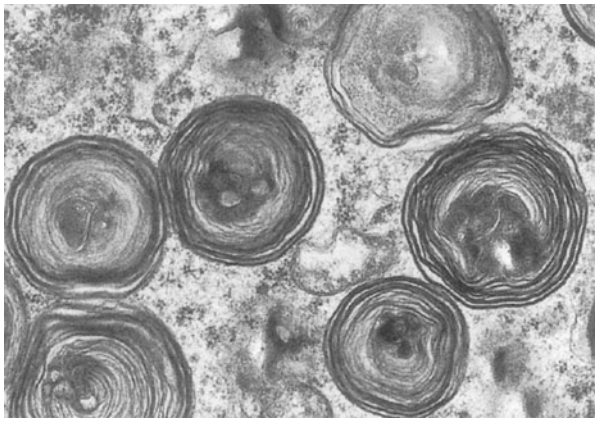

Fig. 34.9 Tay–Sachs disease. EM of characteristic membranous concentric bodies in lysosomes (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

GM_2 Type I Gangliosidosis

GM_2 type I gangliosidosis (Tay–Sachs disease) has three variants. Tay–Sachs disease and variants result from mutations of the HEXA gene, associated with deficient activity of HEXA but normal HEXB. Although normal at birth, affected infants develop rapidly progressive deterioration in the first year of life, seizures, hypotonia, blindness with cherry-red spot in the macula, and dementia and death by age 3–5 years (Sandhoff et al. 1968). In this uniformly fatal autosomal recessive disorder, gangliosides accumulate in the brain and result in the characteristic neuropathologic finding of "ballooning" of neurons with massive intralysosomal accumulation of lipophilic membranous bodies (Fig. 34.8) and membranous concentric bodies (MCBs) visible by EM (Fig. 34.9).

GM_2 Type II Gangliosidosis

GM_2 type II gangliosidosis (Sandhoff disease) features a total deficiency of β-hexosaminidase, leading to extensive neuronal and visceral storage of GM_2

gangliosides, glycolipids, glycoproteins, and oligosaccharides (Krivit et al. 1972). The pattern of inheritance is autosomal recessive with an incidence of approximately 1 in 1 million among Jewish infants in North America and about 1 in 700,000 among non-Jewish infants. The clinical course is similar to that of Tay–Sachs (Schulte 1984). The cerebrum, the cortex, and the white matter are atrophic and rubbery in consistency. The aortic and mitral-valve leaflets are thickened and distorted. There is also extraneural visceral storage in histiocytes of the spleen, lymph nodes, bone marrow, lung, gastrointestinal tract, and pancreatic acinar cells (Barness et al. 1991).

Smith–Lemli–Opitz Syndrome (SLOS)

Smith–Lemli–Opitz syndrome is an autosomal recessive disorder of multiple congenital anomalies and one of a number of malformation syndromes due to defective cholesterol biosynthesis (Porter and Herman 2011). SLOS is a true metabolic malformation syndrome (Lowry and Yong 1980). The syndrome is considered an autosomal recessive, single-gene defect. The incidence of this disease has been estimated at 1:20,000 to 1:40,000; however, Lowery et al. have suggested a minimal birth incidence of 1:20,000. Others estimate a rate as high as 1:9,000 (Lowry and Yong 1980) with carrier frequency of 1:30, but the disease prevalence may be lower because of fetal losses (Putnam et al. 2005). Plasma-cholesterol levels are markedly low, and 7-dehydrocholesterol reductase (7-DHR) activity is defective (Opitz et al. 2002). The gene is mapped to chromosome 11q12-q13.

Patients typically present with microcephaly; a narrow forehead; strabismus; ptosis; apparently low-set, posteriorly angulated ears; broad anteverted nares; micrognathia; cleft and highly arched and rugose palate; broad alveolar ridges; cleft uvula; and cataracts. Ambiguous genitalia and syndactyly are usually present with hypospadias, cryptorchidism, and frequently inguinal herniae in the male; in females, external genitalia are normal (Opitz 1999).

Metachromatic Leukodystrophy

This autosomal recessive disorder, metachromatic leukodystrophy (MLD), is due to a deficiency of arylsulfatase A, which hydrolyzes galactocerebroside sulfatide (GCS) to galactocerebroside. The incidence is estimated to be 1 in 40,000. Three phenotypes are defined; all stem from allelic mutations in the gene encoding arylsulfatase A. Genetic heterogeneity is manifested in some patients with later-onset disease which features normal activity of arylsulfatase A but decreased levels of the corresponding activator protein, saposin B. The cortex, brainstem, cerebellum, and spinal cord are affected. Significant gray-matter changes, including thalamic changes, are a recently described finding in MLD (Martin et al. 2012). A profound deficiency of arylsulfatase A occurs in all tissues from patients with the late infantile, juvenile, and adult forms of MLD. The gene maps to chromosome 22q12. Cortical atrophy of the white matter is severe and there is accumulation of

Table 34.12 Mucolipidoses (ML)

Disease	Enzyme defect or deficiency	Storage
ML I (sialidosis II)	GlcNAc	Sialyloligosaccharides
ML II (I-cell)	N-acetyl-glycosamine-1 phosphotransferase (GlcNAc-phosphotransferase)	Oligosaccharides
ML III (pseudo-Hurler)	N-acetyl-glucosamine-1 phosphotransferase (GlcNAc-phosphotransferase)	Oligosaccharides
ML IV (sialolipidosis)	Ganglioside sialidase	Gangliosides GM_3 and GD_3

Modified from Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Mosby; 2007, with permission

sulfatide in the neurons and other sites, notably in the lamina propria of the gallbladder that may become polypoid (Burgess et al. 1985), bile ducts, Kupffer cells, and renal tubular epithelial cells. Sulfatide is found in the urinary sediment. Rarely, this disorder presents in the neonatal period. In the brain, there is loss of myelin and accumulation of metachromatic material that stains brown with the cresyl-violet stain. Unexpected death in infancy may occur.

Multiple Sulfatase Deficiency (Austin Disease)

In multiple sulfatase deficiency, Hurler-type features are mild, and there is rapid psychomotor deterioration. Peripheral-nerve biopsies show brown metachromasia. Hydrocephalus present at birth, mild chondrodysplasia calcificans, and heart abnormalities may occur. Most patients die in their first decade of life.

Mucolipidoses (Oligosaccharidoses)

The mucolipidoses (MLs) are a group of recessively inherited lysosomal-storage diseases characterized by intracellular accumulation of both mucopolysaccharides and lipids in the lysosomes. There are four main groups: I, II, III, and IV (Table 34.12).

Phenotypic appearance includes coarse facial features, mental retardation, dysostosis multiplex, and lack of mucopolysaccharidurıa. Deficiency of N-acetyl neuraminidase has been identified in ML I, also called sialidosis III (Johnson et al. 1980; Aylsworth et al. 1980; Spranger et al. 1977; Spranger 1987).

Mucolipidosis I (Galactosialidosis, Sialidosis III)

A congenital form of ML I manifests with hydrops and is lethal within the first 2 years of life. A late-infantile form manifests with progressive neurological

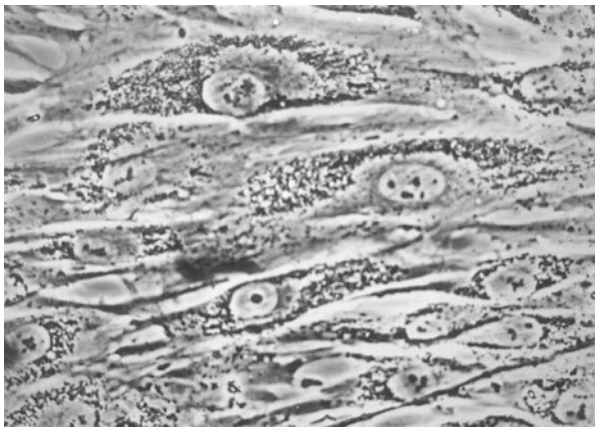

Fig. 34.10 Mucolipidosis II (MLII, I-cell disease). Cultured fibroblasts under polarized light showing coarse cytoplasmic granules (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

deterioration from the age of 6–12 months, with death in early childhood. A juvenile form presents in late infancy or early childhood. Patients with adult form survive into their fourth decade.

Mucolipidosis II (I-Cell Disease)

I-cell disease was first differentiated from the Hurler syndrome by the absence of mucopolysaccharidiuria (DeMars and LeRoy 1967). It was designated I (inclusion)-cell disease because of numerous phase-dense inclusions in the cytoplasm of cultured fibroblasts from affected individuals (Fig. 34.10).

Multiple lysosomal enzymes in ML II are deficient in cultured fibroblasts (Hickman and Neufeld 1972; Leroy et al. 1972). Mannose-6-phosphate is the recognition marker for internalization of lysosomal acid-hydrolase receptors that is absent in ML II.

ML II, like Hurler syndrome, is characterized by severe psychomotor retardation with coarse facial features (Fig. 34.11). Gingival hypertrophy is a more striking feature than in Hurler syndrome. Hepatomegaly is prominent. Lipid granulomas may be found in the lungs (Fig. 34.12a, b). Cardiomegaly, cardiac murmurs, and aortic insufficiency are common. The heart (Fig. 34.13a, b) is uniformly hypertrophied. The mitral and aortic valve leaflets are extremely thick, rigid, and retracted. Invariably patients die of cardiac complications.

The ultrastructure of myocardial cells is distorted by sarcolemmal inclusions of osmiophilic dense bodies and membranous lamellar bodies, ring-like structures, and reticulogranular deposits (Fig. 34.14a, b).

The diagnosis of ML II and ML III can be confirmed by measuring the activities of lysosomal enzymes in serum or in cultured fibroblasts. Tenfold to twentyfold increases in β-hexosaminidase, iduronate sulfatase, and arylsulfatase A are characteristic of both ML II and ML III (Kelly et al. 1975; Herd et al. 1978; Liebaers and Neufeld 1976).

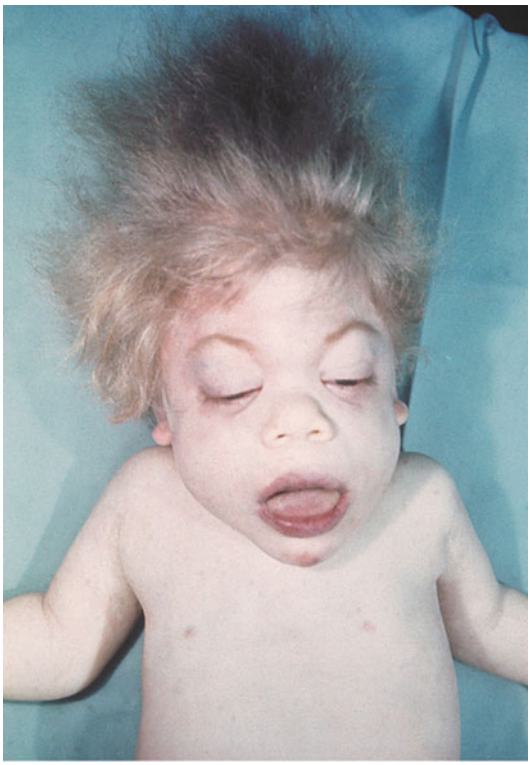

Fig. 34.11 MLII in a 5-year-old child with Hurler features and brushed out appearance of the hair (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

If death occurs after 5 years of age, the brain (Fig. 34.15) is small. The leptomeninges over the cerebral convexity are usually thickened, opaque, and gelatinous. There may be atrophy of the cerebral cortex.

Ceroid-Storage Diseases

Neuronal Ceroid Lipofuscinosis (Batten Disease)

Neuronal ceroid lipofuscinoses (NCLs) were so named because of the autofluorescent lipopigment that showed tinctorial characteristics of ceroid and lipofuscin in histological specimens (Zeman and Dyken 1969). This group of neurological disorders shares features of progressive psychomotor retardation with accumulation of large amounts of lipopigments in neural and extraneural cells. It is a progressive neurological disease (Zeman 1970). Several forms of this disorder have been described, depending on the age of onset: infantile (INCL), late infantile (LINCL), juvenile (JNCL), and adult.

NCL occurs worldwide and appears to be the most common hereditary neurodegenerative disorder in children, with an estimated incidence of 1 in 12,500 in the United States (USA). The lipopigments in NCL accumulate in

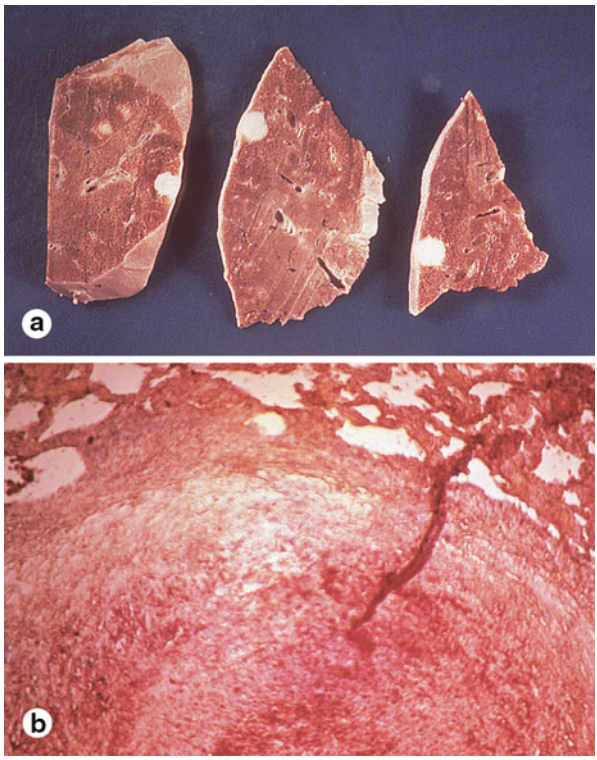

Fig. 34.12 MLII. (**a**) The lung contains lipid granulomas seen grossly. (**b**) Microscopic appearance of lipid granuloma (×100) (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission) (Hematoxylin and Eosin, H&E ×10)

the lysosomes and result from a mutation of gene CLN3, located on 16p12.1. INCL is caused by mutations of CLN1, which maps to 1p32 (Jarvela et al. 1991).

The lipopigment-containing residual bodies or cytosomes show considerable variability on EM. According to the fine structural characteristics, the cytosomes can be divided into three principal types (Table 34.13). Some of the cytosomes seem to be formed by spherical globules about 0.2–0.5 μm in diameter, called granular osmiophilic deposits (GRODs) (Fig. 34.16a). The curved profiles consist of stacks of lamellae with alternating dark and light lines about 4 μm in thickness. Each stack contains two to six pale, dark lines, and these lamellae are called cytosomes with curvilinear bodies (Fig. 34.16b) (CCBs). The third type forms structures superficially resembling fingerprints, named cytosomes with fingerprint profiles (CFPs) (Fig. 34.16c).

Carbohydrate Disorders

Galactosemia

Galactosemia is an autosomal recessive disorder with a frequency of 1 in 60,000 live births. The classic form of galactosemia is a deficiency of galactose-1-phosphate uridyltransferase (G1PUT) that results in the accumulation of galactose,

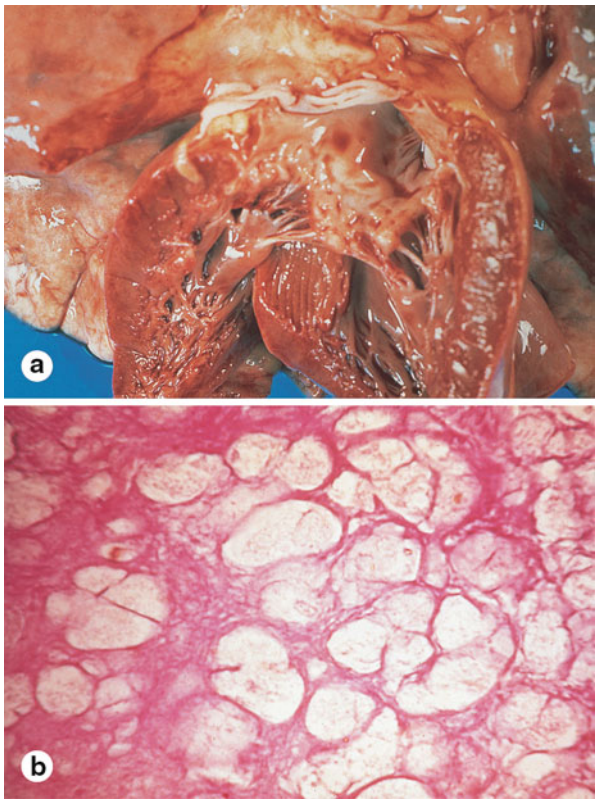

Fig. 34.13 MLII. (**a**) Gross heart: The heart valves are thickened and distorted. (**b**) Myocardial cells are distended with storage material (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission) (Hematoxylin and Eosin, H&E ×10)

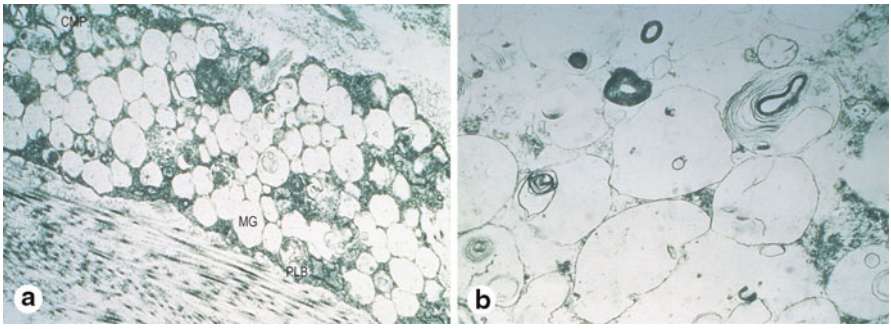

Fig. 34.14 ML II, I-cell disease. (**a**) Electron micrograph of heart valve showing vacuoles and membranogranular deposits (MG) and pleomorphic lipid bodies (PLB). (**b**) EM of renal tubular epithelial cells with large membrane-bound vacuoles containing an array of profiles with concentrically laminated bodies and stacked membranes (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

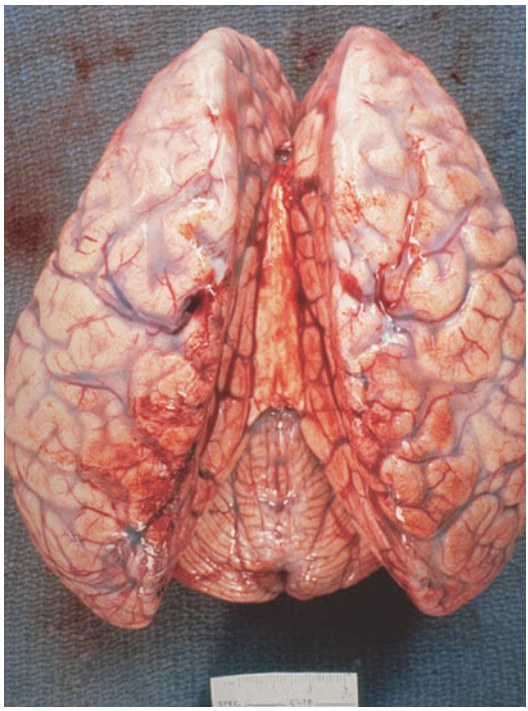

Fig. 34.15 I-cell disease. Gross brain with cortical atrophy and gelatinous exudate over the meningeal surface (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

Table 34.13 Electron-microscopic types of cytosomes in neuronal ceroid lipofuscinoses (NCL)

Cytosome disease	Abbreviation	Predominant association
Granular osmiophilic deposits	GROD	INCL
Cytosomes with curvilinear bodies	CCP	LINCL
Cytosomes with fingerprint profiles	CFP	INCL
Combination of CCB and CFP	Adult	NCL, variant types
Nonspecific electron-dense inclusions		All types

From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Mosby; 2007, with permission
INCL infantile, *LINCL* late infantile, *JNCL* juvenile NCL

galactose-1-phosphate, and galactitol in tissues. Besides red blood cells, the deficiency of the enzyme has been demonstrated in white blood cells, fibroblasts of mucosa, and liver. If the newborn infant diet includes galactose or lactose, vomiting, diarrhea, hyperbilirubinemia, hepatosplenomegaly, renal tubular dysfunction, liver failure, and cataracts develop. Newborn screening includes the test for the presence of galactose in the infant's blood. Confirmatory diagnosis is by the assay of red-cell galactose-1-phosphate uridyltransferase.

Only if the infant is receiving galactose will there be galactosuria. Reducing substances in the urine are not reactive to a glucose-specific test. Galactitol accumulation accounts for cataract formation, hepatomegaly, ascites, and mental retardation.

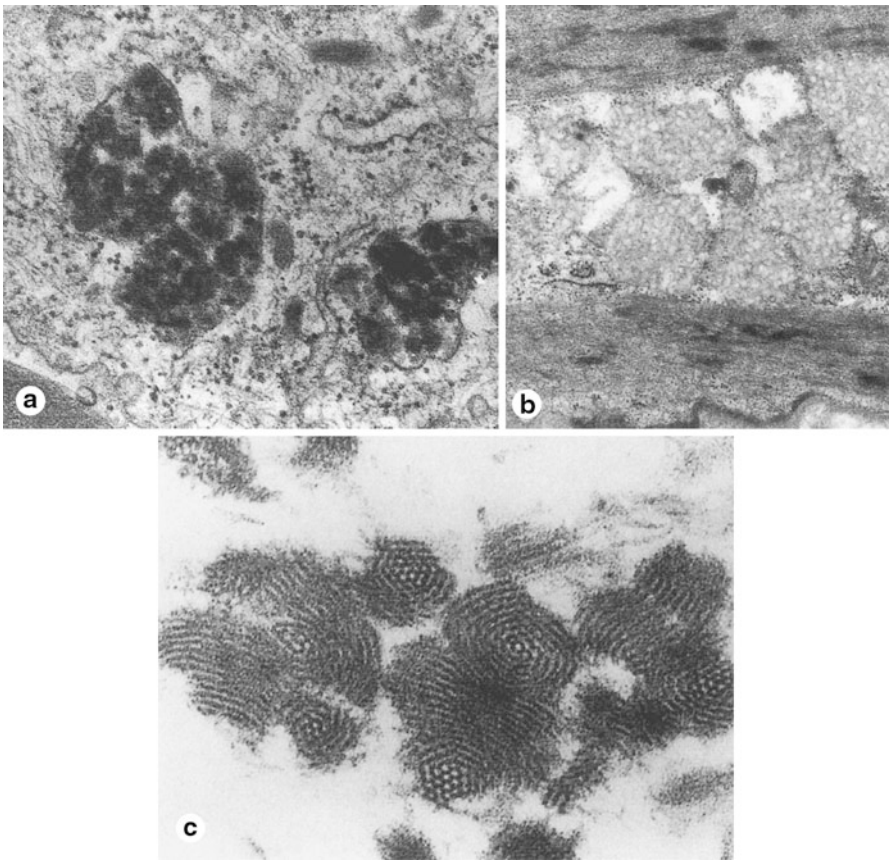

Fig. 34.16 Neuronal ceroid lipofuscinosis. EMs of (**a**) granular osmiophilic deposits, (**b**) curvilinear bodies, and (**c**) fingerprint profiles (Courtesy of Dr. Juhani Rapola)

The pathological changes are a marked steatosis of the hepatocytes and a progressive pseudoacinar change of hepatic architecture with ductular proliferation, cholestasis, focal necrosis, and finally cirrhosis (Smetana and Olen 1962). The pathological changes in galactosemia simulate those seen in hereditary fructose intolerance and tyrosinemia.

Disorders of Fructose Metabolism

Hereditary fructose intolerance (fructose-1-phosphate aldolase deficiency) and fructose-1,6-phosphatase deficiency are autosomal recessive disorders that present in the newborn or in the infant when fructose is introduced into the diet (Steinmana et al. 2001). Aldolase B is located on chromosome 9q22.3 and has been cloned and sequenced. Ominous signs of severe disease include hemorrhage with coagulopathy, metabolic acidosis, hyperinsulinemia, renal Fanconi syndrome, shock, and seizures.

Glycogen Storage Diseases

The many enzymatic steps in the synthesis and breakdown of glycogen explain the large number of glycogenoses.

Type I GSD

Type I glycogen storage disease, the classic type I glycogenosis (von Gierke disease), is due to a deficiency of glucose-6-phosphatase characterized by massive hepatomegaly, failure to thrive, severe hypoglycemia, ketosis, increased plasma lactic acid, and marked lipidemia leading to eruptive xanthomas (Hufton and Wharton 1982). Massive accumulation of glycogen in hepatocytes and in the renal tubular epithelial cells occurs.

Type II GSD

Type II (Pompe disease) is the only type in which the stored glycogen is within lysosomes. It is due to deficiency of α-1,4-glucosidase (acid maltase); it affects all tissues and is referred to as generalized glycogenosis. Functional disturbances, however, are focused on the heart and skeletal muscles with massive cardiomegaly, hypotonia, and muscle wasting. The CNS may be severely affected. Death usually results from cardiac failure before 2 years of age. Microscopic examination shows accumulation of glycogen in the liver, myocardium, skeletal muscle, vascular smooth-muscle neurons of the CNS, anterior horn cells of the spinal cord, and the stromal cells of the chorionic villi of the placenta (Bendon and Hug 1985). It is important to fix the tissues in alcohol to preserve glycogen that is demonstrated by PAS stains and digested by diastase. With formalin fixation, the hepatocytes appear empty and vacuolated and have a plant-like pattern. EM shows the glycogen in packets within the lysosomes. Other forms of glycogen storage diseases are rare.

Amino Acid Disorders

Phenylketonuria

Inherited as an autosomal recessive trait, phenylketonuria (PKU) has an incidence of 1 in 10,000 live births (Scriver and Kaufman 2001). The classic form is due to deficiency of phenylalanine hydroxylase (type I). The chromosomal region involved is 12q23.2. In the classic form, untreated infants become mentally retarded and develop seizures, a mousy odor to the urine, eczema, and impaired hair pigmentation.

Pathologically, both gray- and white-matter changes are noted (Malamud 1966), including lobar disproportion and gyral abnormalities. Demyelination and gliosis

occur in the white matter with lipid-laden macrophages. The Guthrie test, based on the requirement of phenylalanine for the growth of *Bacillus subtilis*, is a screening test in the newborn infant. Ferric chloride added to the urine in the presence of phenylalanine metabolites results in a dark green color; plasma levels of phenylalanine are increased.

Girls treated for PKU who reach reproductive age may give birth to infants with severe abnormalities, including microcephaly, low birth weight, mental and growth retardation, and congenital cardiac defects. Phenylalanine is concentrated by the placenta and may inhibit protein synthesis in fetal liver, brain, and heart (Levy et al. 1988). Failure to diagnose this disorder in the newborn may result in early unexpected death.

Hyperphenylalaninemia may also result from impaired synthesis or recycling of tetrahydrobiopterin (BH4), the cofactor in the phenylalanine, tyrosine, and tryptophan hydroxylation reactions (Mitchell et al. 2011). Analysis of a dried blood spot or urine for neopterin and biopterin, and measurement of dihydropteridine reductase activity in the dried blood spot are essential for the exact diagnosis (Blau et al. 2011).

Hereditary Tyrosinemia

Type I hereditary tyrosinemia has an incidence of 1 per 100,000–200,000, except in Quebec, Canada, where the incidence is 9 per 100,000 live births. It is an autosomal recessive disorder due to deficiency of fumarylacetoacetate hydrolase (Mitchell et al. 2001), leading to accumulation of maleylacetoacetate and fumarylacetoacetate, intermediates in tyrosine catabolism. These intermediates are natural alkylating agents with characteristics to make them candidates for carcinogenesis. They are also presumed to directly cause other cellular damage. They cannot be measured directly, but their levels are reflected in the accretion of succinylacetone. In the acute form of tyrosinemia, infants present within the first weeks of life with failure to thrive, vomiting, fever, diarrhea, hepatomegaly, and decreasing liver functions. A fishy odor may be detected. If untreated, death typically occurs at less than 2 years of age. Patients with the chronic form of tyrosinemia carry the risk of developing hepatocellular carcinoma (Weinberg et al. 1976). Infants with this disorder have increased levels of plasma methionine, prolonged prothrombin time, increased α-fetoprotein (AFP), and urinary excretion of succinylacetone and succinylacetoacetate. Prenatal detection is possible by definitive enzyme analysis of cultured amniotic fluid cells or from chorionic villus sampling (CVS). The presence of succinylacetone in amniotic fluid and high concentrations of α-fetoprotein (AFP) in cord blood of an affected newborn infant suggests that liver changes have already occurred (Hostetter et al. 1983). The major pathological changes in tyrosinemia occur in the liver and kidney. The liver is typically enlarged, yellow, firm, and nodular (Fig. 34.17a). Microscopic changes (Fig. 34.17b) include formation of areas of fibrosis alternating with nodules of regeneration or preserved parenchyma that show striking fatty metamorphosis, cholestasis, and pseudogland transformation.

Demonstration of the presence of succinylacetone on dried filter paper of samples of plasma or urine is pathognomonic.

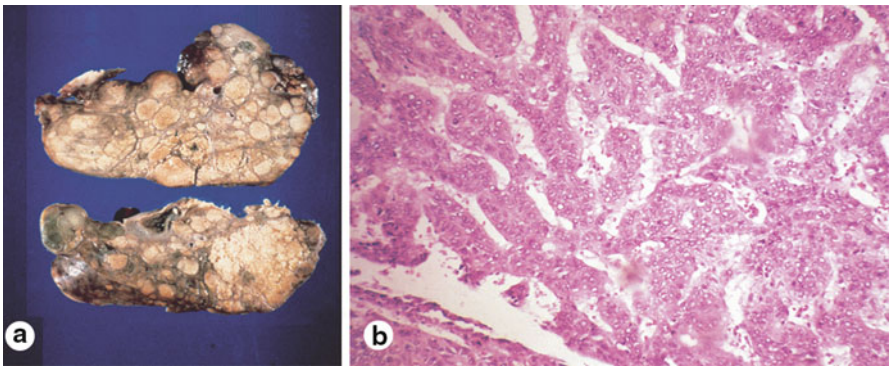

Fig. 34.17 Liver in a patient with Tyrosinemia. (**a**) Liver with micronodular cirrhosis (*above*). Nodules of hepatocellular carcinoma (*below*). (**b**) Microscopic appearance of liver showing trabecular pattern of hepatocellular carcinoma (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission) (Hematoxylin and Eosin, H&E ×20)

AFP activity is also measurable to some extent in kidney, lymphocytes, erythrocytes, fibroblasts, and chorionic tissue (Kvittingen and Brodtkorb 1986). The final diagnosis is made by enzyme determination in liver, lymphocytes, or cultured skin fibroblasts (Jakobs et al. 1990).

Alkaptonuria

Alkaptonuria is inherited as an autosomal recessive trait and is due to the accumulation of homogentisic acid, a product in the metabolism of phenylalanine and tyrosine, which in turn is due to a defect or absence of the enzyme homogentisic acid oxidase. The connective tissues have generalized pigmentation, usually gray to blue-black. Usually the deposition of pigment does not occur until the end of the first decade of life. Pigmentation is visible in the sclera, ear, cartilage, and joints; deposition of homogentisic acid results in arthritis and atherosclerosis of the aorta and coronary vessels and frequently leads to myocardial infarction (Gilbert-Barness 1990). Homogentisic acid itself is colorless, but when exposed to light, it is polymerized and results in the formation of a melanin-like pigment. Addition of Benedict solution yields a yellow-orange spot that darkens on exposure to light. Paper chromatography of the urine is a simple technique to identify homogentisic acid in urine, blood, and other tissues.

Diseases of Sulfur-Containing Amino Acid

Cystinosis

There are three forms of cystinosis which share a defect in carrier-mediated transport of cystine (Yamano et al. 1983; Nesterova and Gahl 2012). Children

with the nephropathic form of cystinosis are usually normal at birth and develop renal tubular damage similar to Fanconi urinary syndrome within the first year. Polyuria, growth failure, rickets, photophobia, and decreased pigmentation occur. Renal failure is a common cause of death that may be sudden and unexpected.

In North America, the incidence of infantile nephropathic cystinosis is approximately 1 per 100,000 to 1 per 1,000,000 births, with a carrier frequency of roughly 1 in 200 in the general population.

Untreated patients with nephropathic cystinosis usually die at about 10–12 years of age. Cystine accumulates and forms crystals within the lysosomes of most organs but particularly in tissues of the reticuloendothelial system (RES) and kidneys (Gilbert et al. 1975). Cystinosis is diagnosed by elevated cystine content of leukocytes or cultured fibroblasts. Cystine crystals are most readily seen in the cornea and bone marrow. The retina may demonstrate retinopathy with depigmentation; hypothyroidism occurs in some. Prenatal diagnosis can be performed either on cultured amniocytes following amniocentesis (Arbisser et al. 1976) or on CVS (Smith et al. 1986; Patrick et al. 1987). Diagnosis can be made at birth by measuring the cystine content of cord-blood leukocytes or of the placenta (Smith et al. 1989).

Homocystinuria

Three distinct pathophysiological mechanisms may underlie homocystinuria (HCU), an autosomal recessive disorder. Classic homocystinuria (type I) is due to a deficiency of cystathionine β-synthetase. The mutated gene is cystathionine β-synthase, located on 21q22.3. Homocystinuria is also due to defects in methylcobalamin (type II) reactions and may respond to vitamin B_{12} administration or may be due to deficiency of methylene tetrahydrofolate reductase (type III) (Beckman et al. 1987). In each type, homocysteine and other metabolites of methionine accumulate. Patients are usually tall and marfanoid and develop anterior dislocation of the optic lenses, arachnodactyly, osteoporosis, mental retardation, and thromboemboli. The vascular changes may progress to advanced arteriosclerosis.

The coronary arteries show intimal fibrosis and narrowing of the lumen and frequent thrombosis. Pulmonary vessels show similar changes. Death that may be sudden relates to vascular and myocardial complications.

Glutaric Acidemia Type I

Glutaric acidemia type I (GAI) is due to a deficiency of glutaryl-CoA dehydrogenase (GCDH). This deficiency usually presents in infancy and is characterized by acidosis and dystonia. It may simulate Huntington disease in infancy. The disease usually presents after a period of normal development with the sudden onset of hypotonia, loss of head control, seizures, opisthotonos, grimacing, fisting, tongue thrusting, rigidity, and dystonia with slow and incomplete recovery (Kimura et al. 1994; Viau et al. 2012).

Table 34.14 Branched-chain aminoacidemia

General symptoms common to all disorders
Decreased resistance to infections
Intermittent coma, Reye-like syndrome
Vomiting and failure to thrive
Hypotonia and lethargy
Hypoglycemia
Athetosis or ataxia
Peculiar odor
Myopathy
Neutropenia and thrombocytopenia
Isovaleric acidemia
Propionic acidemia
Methylmalonic acidemia
2-Methylacetoacetyl-CoA thiolase deficiency
Hypoglycemia
Maple syrup urine disease
3-Hydroxy-3-methylglutaconyl-CoA lyase deficiency
Methylmalonic acidemia
Glutaric acidemia types I and II
Carnitine deficiency
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase deficiency
Myopathy
Glycerol kinase deficiency
Carnitine deficiency
Glutaric acidemia type II

From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Mosby; 2007, with permission

Death can occur during the first decade from intercurrent illnesses or Reye-like episodes (Jamuar et al. 2012).

Diagnosis is made on the basis of increased glutaric and 3-hydroxyglutaric acids in urine and is confirmed by deficiency of GCDH in cultured fibroblasts.

Disorders of Branched-Chain Amino Acid Metabolism/Organic Acidemias

The branched-chain amino acids leucine, isoleucine, and valine are detected in excess in serum and urine in infants and children with certain organic acidemias (Sweetman and Williams 2001). Organic acidemias and organic acidurias are due to defects of amino acid or fatty acid metabolism. If symptoms begin in the neonatal period, the course may be fulminant with severe CNS dysfunction, coma, seizures, and death (Table 34.14). In older infants and children, the course

may be episodic with exacerbations following infections that may be reminiscent of Reye syndrome. Acidosis with hyperammonemia and hypoglycemia may be present.

Maple Syrup Urine Disease

This is an autosomal recessive disorder with an estimated incidence of 1 in 120,000 to 1 in 400,000 live births. In untreated infants, the disease is manifested during the first week of life with vomiting, seizures, and coma. The odor of maple syrup is detected in urine, sweat, and saliva, and the diagnosis is made by plasma amino acid analysis and urinary organic acid determinations.

Pathologically, the liver, kidney, and brain may be enlarged, and the liver contains increased amounts of glycogen. Renal cortical cysts may be present (Diezel and Martin 1964).

Spongy changes in the white matter and delayed myelination occur involving principally the pyramidal tracts of the spinal cord. Loss of myelin occurs around the dentate nucleus and within the corpus callosum and the cerebral hemispheres (Feigin et al. 1968; Riviello et al. 1991).

Isovaleric Acidemia

Isovaleric academia (IVA) is autosomal recessive and is characterized by intermittent acidosis, vomiting, ketosis, coma, and sweaty-foot odor (Duran et al. 1982). Urinary isovalerylglycine and hydroxyl isovaleric acid are elevated. Hematologic abnormalities include pancytopenia, arrested maturation of hematopoietic precursors, and thrombocytopenia (Rosenberg 1981). A chronic intermittent form of IVA is manifested during the first year of life. Pathological changes are nonspecific although hepatic steatosis and hemorrhages in the viscera, cerebellum, and cerebral ventricles may occur.

Diagnosis of isovaleric acidemia from assay of the metabolites can be confirmed by assay of fibroblasts, leukocytes, or amniocytes for a deficiency of isovaleryl-CoA dehydrogenase by either the tritium release (Hyman and Tanaka 1986) or fluorometric (Frerman and Goodman 1985; Hine et al. 1986) assays.

Propionic Acidemia

This defect is a rare autosomal recessive disorder caused by an enzyme deficiency or cofactor deficiencies of biotin propionyl-CoA carboxylase (Fenton et al. 2001). Propionyl-CoA carboxylase is composed of subunits α and β (Kalousek et al. 1980;

Gravel et al. 1980); biotin is a coenzyme that binds to subunit α, and the gene is on chromosome 13 (Lamhonwah et al. 1986). The β-subunit is on a gene on chromosome 3.

In the newborn, vomiting, respiratory distress, seizures, coma, and death may occur. Less severe forms have a later onset and may be associated with lactic acidosis, ketosis, hyperammonemia, and hypoglycemia. Blood and urine contain excessive glycines and propionate, hence the alternative name ketotic hyperglycinemia. Bone marrow depression and pancytopenia occur. The liver shows steatosis and hepatomegaly, and ultrastructurally the mitochondria may be enlarged with decreased cristae and with amorphic substance within the matrix (Fenton et al. 2001). Cerebral atrophy is noted after repeated episodes of acidosis.

Urinalysis reveals excess propionate, 3-hydroxypropionate, methylcitrate, and triglycine. Serum glycine and carnitine esters are elevated. Propionyl-CoA carboxylase is assayed in leukocytes, fibroblasts, cord-blood leukocytes, and/or amniotic fluid cells.

Urea Cycle Defects

The urea cycle involves five enzymes that are responsible for the elimination of ammonia as urea: carbamoyl phosphate synthetase I (CPS I), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (argininosuccinase, AL), and arginase. CPS I and OTC are localized in the mitochondrial matrix, whereas the other three enzymes are in the cytosol. The complete urea cycle is found only in the liver where all five enzymes are induced in the perinatal period in a coordinated manner. Induction of the urea cycle enzymes is stimulated by dietary protein and hormones such as glucagon and glucocorticoids. In extrahepatic tissues, CPS I and OTC are expressed strongly in the kidney and weakly in many other tissues (Masataka 1997). These disorders may present in the neonatal period as a catastrophic illness or later with intermittent episodes of hyperammonemia and neuropsychiatric signs.

Ornithine Transcarbamylase Deficiency

Ornithine transcarbamylase (OTC) deficiency is an X-linked recessive disorder. The gene locus has been mapped on Xp-21.1 (Fox and Rosenberg 1988). The incidence is 1 in 100,000. Two forms exist: a severe neonatal form (40 %) and a late-onset form (60 %). Hemizygous males pursue a fulminant neonatal course with hypotonia, lethargy, coma, and seizures; heterozygous females have a variable expression and may have a less severe form of the disease.

In infants, hyperammonemia and orotic aciduria are noted with reduction in plasma citrulline. The diagnosis may be made by enzyme assay of liver tissue. The pathology in neonates is nonspecific. In males, the liver is enlarged with focal cellular necrosis and steatosis. In older heterozygous females, there may be focal hepatic piecemeal necrosis, inflammation, steatosis, and fibrosis. CNS changes include spongiosis, hypomyelination, and cellular heterotopias; changes of hypoxic–ischemic injury are frequent.

Other Urea Cycle Defects

These include carbamoyl phosphate synthetase deficiency, citrullinemia, hyperornithinemia, hyperammonemia, homocitrullinuria disease, argininosuccinic aciduria, and argininemia.

Biotinidase Deficiency

Patients with this disorder are acidotic and ketotic and develop hyperammonemia, hypoglycemia, and hyperglycinemia. They may also develop seizures and become comatose (Wolf 2001; Wolf et al. 1983). A "tomcat odor" and an erythematous rash characterize this disorder. Carboxylase enzyme activities are diminished and are determined by culture of fibroblasts and amniocytes. Assay of this enzyme may be included in neonatal screening.

Purine Disorders

Adenosine deaminase deficiency (ADA) is an autosomal recessive disorder that results in reduced DNA synthesis in T- and B-cell precursors (Bluese 2001). Severe combined immunodeficiency results with multiple life-threatening infections in the first 2 years of life. Enzyme activity is depressed in erythrocytes, lymphocytes, plasma, and fibroblasts.

Lesch–Nyhan Syndrome

Lesch–Nyhan syndrome is an X-linked inherited disease due to hypoxanthine-guanine phosphoribosyltransferase deficiency which results in hyperuricemia. The gene is located on Xq26. Infants present in the first few weeks with yellow-orange crystalluria. Choreoathetosis, spasticity, and self-mutilation are common (Fig. 34.18). After several months, hyperuricemia is prominent, and gouty tophi may occur. There are forms with varying severity. Hematologic abnormalities may include megaloblastic anemia, abnormal platelet morphology, and increased peripheral blood T-cells.

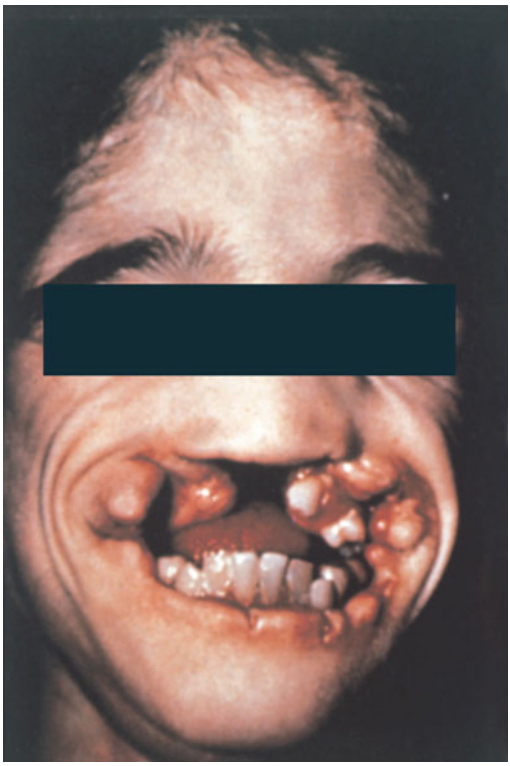

Fig. 34.18 Self-mutilation in Lesch–Nyhan syndrome (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

Pyrimidine Disorders

Orotic Aciduria

Orotic aciduria is inherited as an autosomal recessive disorder and is distinct from the orotic aciduria that accompanies disorders of the urea cycle (Becroft et al. 1986). Hereditary orotic aciduria manifests in the first year of life with hypochromic anemia, megaloblastosis, varying degrees of neutropenia and lymphopenia, immunodeficiency, and crystalluria. Defects in orotate phosphoribosyltransferase and orotidine 5-monophopshate decarboxylase are detectable in liver-biopsy specimens and in leukocytes, erythrocytes, and fibroblasts. Enzymatic diagnosis can be performed on red blood cells.

Pyrimidine 5-Nucleotidase Deficiency

In pyrimidine 5-nucleotidase deficiency, elevated pyrimidine nucleotides in the blood are associated with a non spherocytic hemolytic anemia and basophilic

stippling of the erythrocytes. The disease is inherited as an autosomal recessive disorder (Valentine et al. 1974). The gene, UMPH1, is located on 7p15-q14, and molecular diagnosis is possible (Marinaki et al. 2001). Diagnosis can also be achieved through assays of enzyme activity in erythrocytes and confirmed by measurement of the erythrocyte enzyme activity.

Fatty Acid β-Oxidation Defects

Defects of nine proteins have been identified in mitochondrial β-oxidation. These include defects of plasma-membrane carnitine transport, CPT I, CPT II, carnitine/acylcarnitine translocase, LCAD, MCAD, SCAD, 2,4-dienoyl-CoA reductase, long-chain-3-hydroxy-acyl-CoA dehydrogenase (LCHAD), and very-long-chain acyl-CoA dehydrogenase (VLCAD). The disorders of the β-oxidation pathway are characterized by skeletal and/or cardiac-muscle weakness and are all inherited as autosomal recessive. Enzyme defects can be demonstrated in fibroblasts and leukocytes.

Clinical findings of intramitochondrial fatty acid oxidation defects are shown in Table 34.15 and laboratory findings common to disorders of fatty acid oxidation in Table 34.16.

MCAD occurs in 1 in 5,000 to 10,000 live births, primarily in white children of Northern European descent. MCAD is the most important defect that may result in sudden infant death (Fig. 34.19).

Lactic Acidosis

Pyruvate Dehydrogenase Deficiency

Pyruvate dehydrogenase (PDH) is required for complete oxidation of glucose and fatty acids and provides acetyl-CoA for the citric acid cycle. Pyruvate dehydrogenase is a protein complex with three main catalytic domains: E_1, E_2, and E_3 (Robinson et al. 1987). Defects of the B_1 α-subunit are inherited in an X-linked fashion. Males with E_1 α-deficiency have a partial deficiency; females may carry a more severe mutation. A defect of pyruvate dehydrogenase results in a variable phenotype, including lactic acidosis in the early neonatal period, ataxia and developmental delay in infancy (Robinson et al. 1987; Stansbie et al. 1986).

Mitochondrial Disorders

A disease caused by abnormal mitochondrial energy production was first described in 1962 (Luft et al. 1962). Mitochondria are present in all eukaryotic cells dependent on aerobic metabolism and generate most of the cellular ATP. They also regulate cytoplasmic calcium levels. By electron microscopy,

Table 34.15 Clinical findings in intramitochondrial fatty acid oxidation defects

Medium-chain-acyl-CoA dehydrogenase deficiency
1. Reye-like or sudden infant death syndrome (SIDS)-like symptoms with hypoketotic hypoglycemia secondary to lack of oral intake, usually within the first 2 years of life
2. Ammonia and liver enzymes (may or may not be elevated)
3. Possible mild hepatomegaly because of fat accumulation in hepatocytes
4. Increased levels of urinary N-hexanoylglycine, 3-phenylpropionyl glycine, and suberylglycine during episode
5. Elevated C_6–C_{12} dicarboxylic acids in urine during episode
6. Acylcarnitine profiles also reflect increased medium-chain fatty acid CoA thioesters during episode
7. Increased octanoyl carnitine after 100 mg/kg of oral carnitine intake during asymptomatic period
Short-chain acyl-CoA dehydrogenase deficiency
1. Reye-like symptoms (acute)
2. Failure to thrive and muscle weakness chronically
3. Lipid in muscle and liver tissue (triglyceride)
4. Low muscle carnitine with low-normal plasma carnitine levels
Long-chain acyl-CoA dehydrogenase deficiency
1. Reye-like or SIDS-like symptoms
2. Hypoketotic hypoglycemia, hepatomegaly, cardiomegaly, and hypotonia usually presenting between 2 and 4 months of age
3. Possible muscle cramps and myoglobinuria in chronic disease
4. Possible failure to thrive
5. Hepatomegaly with or without elevated hepatocellular enzyme or ammonia level
6. Fatty liver with low carnitine levels
7. Low plasma carnitine with high esterification
Carnitine palmitoyltransferase deficiency
1. Seizures and coma from fasting hypoglycemia and hypoketonemia
2. Normal liver tests and ammonia level
3. Normal carnitine levels
4. Fatty liver but no accumulation of triglycerides in muscle tissue
Systemic carnitine deficiency
1. Recurrent episodes of Reye-like or SIDS-like symptoms during infancy or early childhood
2. Muscle weakness progressing to atrophy
3. Eventual development of cardiomyopathy with abnormal echocardiogram
4. Fatty liver
5. Low serum carnitine levels with disproportionately high urine levels

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mitochondria show a smooth, spherical outer membrane and an inner membrane with numerous infoldings, known as cristae. The cristae are usually perpendicular to the long axis of a mitochondria. The membranes divide the contents of mitochondria into separated compartments, each harboring specific biochemical structures for transportation and processing of chemical compounds. The outer

Table 34.16 Laboratory findings common to disorders of fatty acid oxidation

Hypoglycemia
Hypoketosis (negative or 1+ urine ketones)
Elevated plasma FFA
Plasma FFA > β-hydroxybutyrate
Acidosis
Mild to moderate
Increase lactate (especially in LCHAD deficiency)
Mild to moderate increase in AST and ALT usually without hyperbilirubinemia
PT, PTT normal or mildly elevated
Elevated CPK
Cardiac and skeletal muscle
Marked with episodic muscle weakness
Rhabdomyolysis, myoglobinuria
Mild elevation of ammonia
Marked hyperuricemia
Low plasma carnitine (except in CPT I deficiency)
Elevated acylcarnitine (except in CPT I deficiency)
Specific accumulating acylcarnitines

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FFA free fatty acids, *LCHAD* long-chain 3-hydroxyacyl-CoA dehydrogenase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PT* prothrombin time, *PTT* partial thromboplastin time, *CPK* creatine phosphokinase, *CPT* carnitine palmitoyltransferase

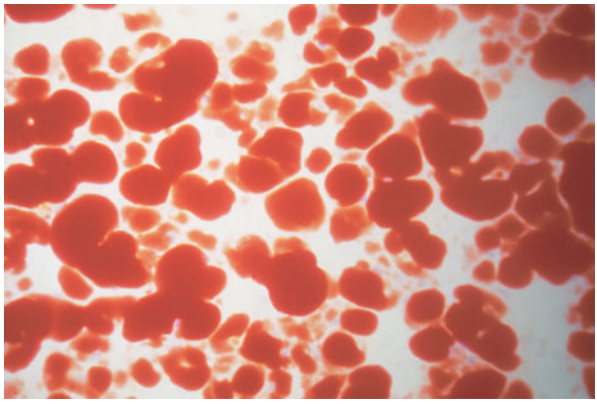

Fig. 34.19 Medium-chain acyl-dehydrogenase deficiency (MCAD) liver showing marked fat (oil red O stain ×100) (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

membrane is permeable to many small molecules and contains receptors for transporting macromolecules from the cytosol to the inner parts of the mitochondrion. The inner membrane is impermeable and contains special transporters for small molecules, controlled by several specific translocase systems. Four complexes of the electron-transport chain are embedded in the inner membrane.

The mitochondrial matrix contains many enzymes, including those of the citric acid (Krebs) cycle, fatty acid oxidation pathways, and many others. The mitochondrial genome and its protein-synthetic machinery for mitochondrially coded polypeptides are also confined to the matrix.

Mitochondrial Genome

The mtDNA of all cells has its origin in the unfertilized ovum. mtDNA is inherited exclusively from the mother (Giles et al. 1980). Maternal or cytoplasmic inheritance has several unique features differing from Mendelian traits (Wallace 1992). When mutant mtDNA is present in the ovum, it is transmitted to all offspring, resulting in larger numbers of affected individuals than in autosomal dominant traits.

Mitochondrial Diseases

Inherited defects in mitochondrial diseases are known for each of the main biochemical sets of reactions in the mitochondria, most of which are inherited as autosomal recessive.

The contemporary classification (De Vivo 1993) is based on the biochemical defects linked with the molecular genetic findings of the patients. All disorders caused by mtDNA defects and intergenomic signaling defects impair respiratory chain and/or oxidative phosphorylation.

Pathological Changes of Mitochondrial Diseases

The morphological changes associated with mitochondrial dysfunction are divided into two groups: (1) abnormalities associated with altered number and structure of the mitochondria and (2) secondary degenerative and destructive changes due to impaired function of the mitochondria.

EM reveals a number of mitochondrial alterations in mitochondriopathies. The number and size of the mitochondria are often increased. Giant mitochondria with concentric tubular, reticular, lamellar, or otherwise dissociated cristae are characteristic. The mitochondrial matrix may be swollen and contain large, spherical dense bodies, vacuoles, or crystals. The rectangular crystals are often arranged in blocks of parallel crystals with a “parking lot” configuration (Stadhouders and Sengers 1987). They contain proteins; at least two different types of crystals are known.

Light microscopic and EM investigation of suspected mitochondrial disorders show changes confined to defects of the respiratory chain of oxidation–phosphorylation coupling but not disorders of substrate utilization (DiMauro et al. 1990). Several examples of disorders of oxidative phosphorylation have no morphological mitochondrial changes. On the other hand, ragged-red fibers

(RRFs) and accompanying EM findings are occasionally seen in a small proportion of muscle fibers in neuromuscular disorders other than mitochondriopathies. Zidovudine, a drug used to treat AIDS, causes myopathy with RRFs (Arnaudo et al. 1991). Absent or weak histochemical cytochrome oxidase (COX) activity is seen in some, but not all, mitochondrial disorders due to complex IV defects. Moderately increased fat droplets and glycogen are often seen in association with RRFs, but extensive fatty infiltration of the muscle and liver is more characteristic of carnitine-transport defects and impaired fatty acid oxidation (Hale and Bennett 1992).

Leigh Syndrome

Leigh syndrome (subacute necrotizing encephalomyelopathy) (SNE) is an encephalopathy of infancy. Four major causes have been well established: (1) pyruvate dehydrogenase deficiency transmitted as autosomal recessive or an X-linked recessive, depending on the subunit affected: (2) COX deficiency inherited as an autosomal recessive; (3) pyruvate carboxylase deficiency; and (4) maternally inherited point mutation at nt 8993 in the ATPase 6 gene of mtDNA. Beside the CNS, heart involvement has been described in all four forms and consists of hypertrophic cardiomyopathy with electrocardiographic evidence of concentric left-ventricular hypertrophy (Rutledge et al. 1982; Servidei and DiMauro 1994).

A distinctive pattern of destructive brain lesions is seen in mitochondriopathies caused by deletions and point mutations of the mtDNA and includes Kearns–Sayre syndrome, myopathy, encephalopathy, lactic acidosis, neurological weakness, ataxia, retinitis pigmentosa (NARP), Leber hereditary optic neuropathy (LHON), stroke (MELAS), and myoclonic epilepsy, ragged-red fibers (MERRF) syndromes (Muller-Hocker et al. 1993; Van Hove et al. 1994; Tritscher et al. 1991).

Barth Syndrome

Barth syndrome is a congenital dilated cardiomyopathy and mitochondrial myopathy with growth retardation. Mitochondria are abnormal, and there is neutropenia. This genetic defect has been mapped to chromosome Xq28 and involves mutation of the TAZ (G4.5) gene that encodes the tafazzin protein. Seventy-three different disease-causing mutations have been identified (Gonzalez 2005). Diagnostically important laboratory findings include 3-methylglutaconic aciduria and acidemia, increased urinary excretion of citric acid-cycle intermediates and 2-ethylhydracrylic acid, hypocholesterolemia, low levels of tetralinoleoyl cardiolipin in muscle, platelets and cultured fibroblasts, and mutation of Xq28-linked G4.5 (TAZ1) gene. Sudden death is usually secondary to cardiac complications.

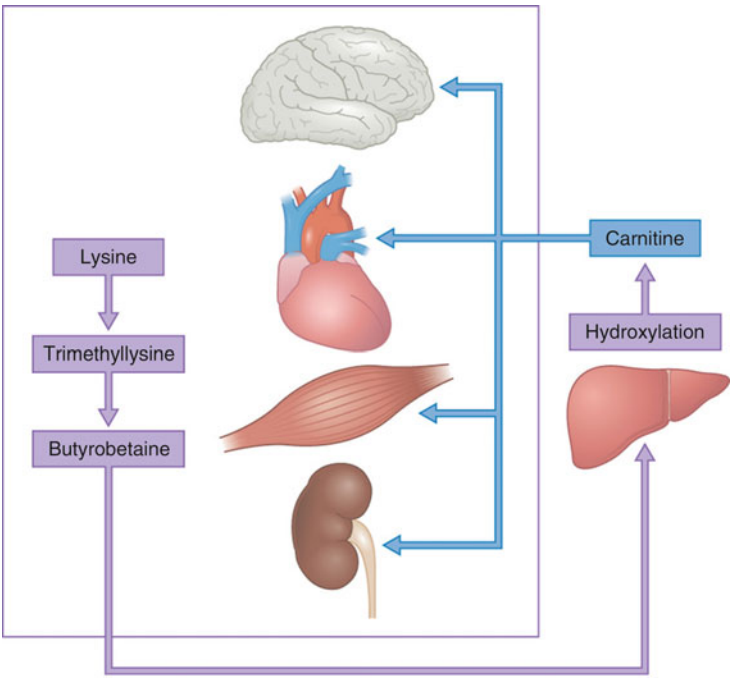

Fig. 34.20 Transport of carnitine (From Gilbert-Barness E. editor. Potter's pathology of the fetus, infant, and child. 2nd ed., Elsevier; 2007, with permission)

Carnitine Deficiency

Carnitine deficiency is transmitted as an autosomal recessive trait and results in a defect in fatty acid transport across the inner mitochondrial membrane. Carnitine is synthesized from peptide-bound lysine to trimethyllysine and further to α-butyrobetaine (Fig. 34.20). Carnitine also regulates the intramitochondrial CoA/acetyl-CoA ratio. Fatty acids are transported to the liver and other tissues and form acyl-CoA esters. Primary carnitine deficiency is classified into myopathic, systemic, and mixed forms (Rebouche and Paulson 1986). The myopathic form is manifested as progressive skeletal muscle weakness. Serum carnitine is normal, but muscle carnitine is low. Systemic carnitine deficiency is characterized by low serum and tissue carnitine concentrations. Abnormality of the CoA/acetyl-CoA ratio results in accumulation of acetyl-CoA compounds. The gene maps to chromosome 5q31.2-32. Clinical features of carnitine deficiency are shown in Table 34.17.

Lipid accumulates in the skeletal muscle in type I myocytes, the liver, and frequently the cardiac muscle cells (Gilbert 1985). EM demonstrates abnormal mitochondria. The pathological features of carnitine deficiency are summarized in Table 34.18. Diagnosis is readily made by plasma carnitine levels or muscle biopsy. Secondary carnitine deficiency may be associated with varied defects of intermediary metabolism.

Table 34.17 Clinical features of carnitine deficiency

	MCD	SCD	MxCD
Average age of onset (years)	15	3–5	4–5
Familial occurrence	+	+	+
Progressive weakness	Common	Frequent	Frequent
Encephalopathy	–	+	+
Cardiomyopathy	Rare	+	+
Respiratory symptoms	+	Rare	Rare
Myoglobinuria	+	–	+
Peripheral neuropathy	+	–	+
Serum carnitine	Normal	Decreased	Decreased
Increased serum CK	Usual	Usual	Usual
Lipid storage in muscle	+	+	+
Abnormal EMG	+	+	+
Response to carnitine	Usually good	Variable	Variable

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MCD myopathic carnitine deficiency, *SCD* systemic carnitine deficiency, *MxCD* mixed carnitine deficiency, *CK* creatine kinase, *EMG* electromyogram

Table 34.18 Pathologic features of systemic carnitine deficiency

Heart
Gross: usually cardiomegaly, biventricular hypertrophy, mild endocardial fibrosis
Microscopic: myocardial fibers containing vacuoles of lipid (stains positively for neutral lipid)
EM: disruption of myofibrils by accumulation of frequently bizarrely shaped mitochondria; disrupted and twisted mitochondrial cristae with electron-dense inclusions
Liver
Microscopic: extensive fatty metamorphosis (microsteatosis)
EM: proliferation of endoplasmic reticulum and increased numbers of peroxisomes, lipid vacuoles
Skeletal muscles
Microscopic: accumulation of lipid droplets (type I fibers); positive neutral lipid (oil red O, Sudan black B, Nile blue sulfate); type I fibers, granular appearance with subsarcolemmal basophilic staining (ragged-red fibers with Gomori trichrome stain)
EM: lipid vacuoles without limiting membrane adjacent to mitochondria; alteration of mitochondria-indistinct or concentric cristae, dense or paracentric inclusions

Carnitine Palmitoyltransferase Deficiency

Carnitine palmitoyltransferase (CPT) deficiency results in two different clinical variants: one with hepatic (CPT I) and one with muscular symptoms (CPT II).

CPT I is important in the transfer of long-chain fatty acids into mitochondria where all the enzymes for β-oxidation are located. This enzyme is present in the outer mitochondrial membrane. CPT II is present on the inner mitochondrial membrane and catalyzes the regeneration of carnitine and the long-chain fatty-acyl-CoA when they undergo β-oxidation.

CPT I Deficiency

The clinical presentation is characterized by coma, seizures, hepatomegaly, and hypoketotic hypoglycemia following fasting, a viral infection, or diarrhea. There is no evidence of chronic muscle weakness, and cardiomyopathy has not been noted. The onset is between 8 and 18 months of age.

High plasma-carnitine levels (both total and free) distinguish CPT I deficiency from the other known carnitine defects.

The definitive diagnosis of CPT I deficiency is made by measuring enzyme activity in fibroblasts, leukocytes, or solid tissues.

CPT II Deficiency

Neonatal onset of lethal multiorgan dysfunction with dysmorphic features, cardiomyopathy, and cystic dysplasia of the kidney has been described in CPT II deficiency. A late-onset form is more benign with myopathy.

Peroxisomal Disorders

Except for type I hyperoxaluria, all peroxisomal disorders can be identified prenatally in the first or second trimester of pregnancy by measurement of very long chain fatty acids (VLCFAs), bile-acid intermediates, and assays of plasmalogen synthesis (Beard et al. 1986) in cultured amniocytes or in cultured chorionic villus cells (Poll-The and Saudubray 1996).

Zellweger Syndrome

Zellweger syndrome is inherited as autosomal recessive. Newborn infants have a typical phenotype with high forehead, upwardly slanting palpebral fissures, hypoplastic supraorbital ridges, epicanthal folds, micrognathia, severe weakness and hypotonia, seizures, and ocular abnormalities including cataracts, glaucoma, corneal clouding, Brushfield spots, pigmentary retinopathy, and optic-nerve dysplasia. Infants rarely live more than a few months with liver and renal involvement. Sudden death may occur.

Neonatal Adrenoleukodystrophy

Neonatal adrenoleukodystrophy (NALD) is a slightly less severe illness than Zellweger syndrome, and the dysmorphic features are less striking. Peroxisomes in liver or cultured skin fibroblasts (Vamecq et al. 1986) are diminished in number, and VLCFA accumulation is less than in Zellweger syndrome. NALD shows the same biochemical abnormalities as Zellweger syndrome.

X-Linked Adrenoleukodystrophy

The basic defect in X-linked adrenoleukodystrophy (ALD) is a specific impairment in the capacity to degrade VLCFAs (Zellweger 1987). The adrenal glands are small. The cells in the adrenal cortex, particularly the zona fasciculata, contain cytoplasmic lipid inclusions with a characteristic lamellar structure seen in the ultrastructure.

Hyperpipecolic Acidemia

The clinical features of hyperpipecolic academia closely resemble those of Zellweger syndrome, with hepatomegaly, hypotonia, eye changes, and excretion of pipecolic acid, but is less severe. EM shows peroxisomes in the liver, suggesting a functional disorder of the peroxisome (Brul et al. 1988). Complementation studies suggest that hyperpipecolic academia is allelic with one form of Zellweger syndrome and with infantile Refsum syndrome.

Hyperoxaluria, Primary Oxalosis

Patients have a deficiency of the enzyme alanine–glyoxylate aminotransferase that catalyzes the conversion of glyoxylate to glycine. This reaction results in the accumulation of glyoxylate, which is converted to oxalic acid. The enzyme is in the peroxisome (Danpure and Jennings 1986). Diagnosis depends on demonstration of excessive quantities of glyoxylate, oxalate, and glycolic acid in the urine. Hepatic and renal failure occurs.

Classic Refsum Disease

Classic Refsum disease is autosomal recessive with an isolated defect of phytanic acid oxidation. Manifestations include retinitis pigmentosa, hearing loss, peripheral neuropathy, and cerebellar ataxia. Cardiac arrhythmias or conduction defects may occur when phytanic acid levels are very high.

Rhizomelic Chondrodysplasia Punctata

Rhizomelic chondrodysplasia punctata (RCDP) is autosomal recessive and differs from the single enzyme disorders. In RCDP, there is a profound defect in plasmalogen synthesis. RCDP is characterized by stippled foci of calcification within the hyaline cartilage and is associated with dwarfing and multiple malformations as well as contractures of vertebral bodies. Coronal clefts are occupied by cartilage and are due to an embryonic arrest. Short stature affects the

proximal parts of the extremities (rhizomelia). Metaphyseal cupping, disturbed ossification, cataracts, microcephaly, severe mental retardation, and ichthyosiform erythroderma are present.

Diagnostic Findings of Peroxisomal Disorders

Increased levels of very-long-chain saturated fatty acids are in the plasma, red blood cells, and/or cultured skin in peroxisomal disorders. Saturated VLCFAs are elevated in the peroxisomal disorders (Goebel and Schulz 1979), except in RCDP. Diminished levels of plasmalogen represent the most striking single abnormality in RCDP (Wanders and Skjeldal 2001). Elevated pipecolic acid levels in the plasma are present in nearly all patients with disorders of peroxisomes. Elevated levels of plasma phytanic acid are the prime and characteristic abnormality in Refsum disease (Wanders and Skjeldal 2001). EM shows absent and abnormal peroxisomes in liver-biopsy specimens.

Disorders of Metal Metabolism

Neonatal Iron-Storage Disease (Neonatal Hemochromatosis)

Neonatal iron-storage disease or neonatal hemochromatosis is clinically and pathologically defined by severe liver disease of intrauterine onset associated with extrahepatic siderosis that spares the reticuloendothelial system (Knisely 1990; Knisely et al. 1987; Silver et al. 1987; Witzleben and Uri 1989). Attempts to identify a primary disorder of iron handling have not been successful. Infants with neonatal hemochromatosis may be stillborn or born prematurely. Oligohydramnios may be present, and placental edema or polyhydramnios may occur. Infants with neonatal hemochromatosis exhibit hypoglycemia, hypoalbuminemia, edema, and frequently a hemorrhagic diathesis with or without evidence of fibrinogen consumption or thrombocytopenia, anemia, and acanthocytosis. Hyperbilirubinemia develops during the first few days after birth. Transaminase activities are usually low, and serum concentrations of AFP are high.

The presence of hyperferritinemia supports the diagnosis of neonatal hemochromatosis. Cholestasis and giant-cell transformation are found in all cases. Iron accumulation is massive in liver cells with lesser quantities in biliary epithelium and Kupffer cells. Diffuse interacinar fibrosis, cholangiolar proliferation, and cirrhosis may be present at birth (Silver et al. 1992; Hoogstraten et al. 1990). Hyperplasia and hypertrophy of islets of Langerhans are constant findings. Extrahepatic sites for iron accumulation include pancreatic acinar and islet cells, renal tubules, the adrenal cortex, and the thyroid follicular epithelium. The RES is spared. Ultrastructurally, hemosiderin accumulates in lysosomes within hepatocytes and to a lesser extent in Kupffer cells. Electron-dense masses and membranous arrays are observed in the lysosomes (Phillips et al. 1987).

Wilson Disease

Wilson disease is an inborn error of copper metabolism with an autosomal recessive pattern of inheritance. Levels of hepatic copper are elevated, and liver and serum ceruloplasmin are decreased, although in some cases the serum ceruloplasmin values may be normal. Serum-copper levels are usually low, and copper excretion in the urine is increased. Incorporation of radioactive copper into ceruloplasmin is considered a reliable test for Wilson disease. The gene ATP7B maps to chromosome 13q14.3 (Chelly and Monaco 1993). The Wilson disease gene product is a copper-binding P-type ATPase protein homologous to the Menkes disease gene (Bonilla and Schotland 1970). In Wilson disease, there is a reduction in the rate of incorporation of copper into ceruloplasmin and a reduction in biliary excretion of copper.

Acute hepatitis and hepatic failure may be presenting features in the very young patient. Hemolytic anemia, CNS signs, and Kayser–Fleischer rings develop during the course of the disease.

In the precirrhotic stage of Wilson disease, the changes resemble a chronic, active hepatitis with focal necrosis, scattered acidophilic bodies, and moderate-to-marked steatosis (Scheinberg and Sternlieb 1984). Glycogenated nuclei in periportal hepatocytes are a typical finding. Kupffer cells are hypertrophied and may contain hemosiderin. In later stages, periportal fibrosis, portal inflammation, and finally cirrhosis develop.

The ultrastructural changes are pathognomonic (Phillips et al. 1987). The mitochondria show marked pleomorphism, widened intracristal spaces, and microcytes at the tips of the cristae. Copper deposits are extremely electron dense.

A major copper-binding protein in Wilson disease is metallothionein (Nartey et al. 1987). It has been suggested that the liver damage in Wilson disease may be due to the toxic ionic form of copper which saturates the binding sites of metallothionein (Schilsky et al. 1994).

Menkes Syndrome

Inherited as an X-linked recessive disorder of copper metabolism, Menkes kinky hair syndrome is characterized by a defect in intestinal copper absorption resulting in low serum level of copper and ceruloplasmin in affected male infants (Danks et al. 1972; Kaler 1994). Copper is bound intracellularly in excess to metallothionein. The gene, ATP7A, maps to Xq21-q13. The phenotype is characterized by a sparse, steel wool appearance of the hair, which is coarse and brittle (pili torti), with pudgy cheeks, skeletal changes including Wormian bones, and metaphyseal widening. Progressive neurological deterioration leads to death in infancy.

Cystic Fibrosis

Cystic fibrosis is a common metabolic disorder inherited as autosomal recessive and characterized by steatorrhea and malnutrition resulting from pancreatic

Table 34.19 Classification and characteristics of congenital porphyrias

Metabolites present in excess					
Disease	**Inheritance**	**Enzyme defect**	**Urine**	**Feces**	**Erythroid cells**
Congenital erythropoietic porphyria	AR	Uroporphyrinogen I synthetase and uroporphyrinogen III cosynthetase	Uroporphyrin I ++++ Coproporphyrin I +++	Coproporphyrin I ++++ Uroporphyrin I ++	Uroporphyrin I ++++ Coproporphyrin ++
Congenital erythropoietic Protoporphyria	AD	Ferrochelatase	Normal	Protoporphyrin ++++ Coproporphyrin ++	Protoporphyrin ++++ Coproporphyrin + Coproporphyrin III ++++
Intermittent acute porphyria	AD	Uroporphyrinogen I synthetase	δ-Aminolevulinic acid ++++ Porphobilinogen ++++	Normal	Normal
Hereditary coproporphyria	AD	Coproporphyrinogen synthetase	Coproporphyrin III +++	Coproporphyrin III +++ Protoporphyria +	Normal
Variegate porphyria	AD	Protoporphyrinogen oxidase	δ-Aminolevulinic acid ++ Porphobilinogen ++	X-porphyrin ++++ Protoporphyrin ++++ Coproporphyrin ++++	Normal
Porphyria cutanea tarda	AD	Uroporphyrinogen decarboxylase	Uroporphyrin I and III ++++	Protoporphyrin N to ++ Coproporphyrin N to ++	Normal

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exocrine insufficiency, severe pulmonary disease, and disturbances in sweat- and mucus-secreting glands. In whites, it is estimated to occur in 1 in 2,000 and 1 in 3,000 live-born infants with equal sex occurrence.

The defect is identified as a mutation of the cystic-fibrosis transmembrane-regulator (CFTR) gene on chromosome 7 (Riordan et al. 1989). The most common mutation results in a protein defective in phenylalanine at position 508, referred to as ΔF508; more than 400 other mutations have been identified.

The pathology has been extensively reviewed (Oppenheimer and Esterly 1975). It may present in the perinatal period as a meconium ileus, in which meconium is so viscous that it results in intestinal obstruction and even rupture in the fetus or newborn leading to meconium peritonitis. The pancreas in severe cases contains dilated and cystic ducts filled with inspissated secretions. The acini may be completely destroyed by fibrosis, and the islets are usually intact. Nasal polyps, salivary glands, duodenum, small bowel, and appendix are the sites of accumulation of eosinophilic secretions. The lung presents a wide spectrum of changes. Grossly, zones of emphysema alternate with areas of atelectasis, depending on whether the obstruction by viscous secretions has been partial or complete. Secondary infection is usually due to *Staphylococcus aureus* or *Pseudomonas aeruginosa* and leads to bronchiectasis. In long-standing cases in which vitamin A deficiency and infection coexist, there is often squamous metaplasia of the tracheobronchial mucosa. At the time of death, the entire tracheobronchial tree is usually filled with dense purulent material. In 90 % of the cases, this yields a pure bacterial culture. In the liver, focal biliary cirrhosis occurs in 10 % of infants up to 3 months of age and in 25 % over 1 year of age (Farrell et al. 1993). Myocardial lesions have been related to mitochondrial deficiency secondary to malabsorption. The gallbladder and the cystic duct may be filled with mucus. Patients usually die from respiratory insufficiency or, in some cases, from heat intolerance during the summer months.

Porphyrias

Porphyrias are due to error in heme synthesis (Anderson et al. 2001). They have variable forms of inheritance and are classified according to the site of their main effect as either erythroid or hepatic types (Table 34.19). Sudden death has been reported to occur, particularly during an acute episode of acute intermittent porphyria.

Conclusion

Pediatric metabolic diseases can have a wide range of clinical presentations including a mixture of neuromuscular disorders and failure to thrive. These diseases may have acute exacerbations precipitated by infections and may cause sudden unexpected death, thus coming to the attention of the forensic pathologist.

Definitive diagnosis of a metabolic disease usually requires specific biochemical, genetic, and enzymological testing, as the histological findings are often nonspecific. This necessitates sampling of blood and various fresh tissues at the time of autopsy, including a postmortem skin or fascia sample for fibroblast cultures. As metabolic diseases are inheritable diseases, the diagnosis of a metabolic disease at autopsy has widespread implications for the entire family, including potential future pregnancies.

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The Disabled Child

35

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Contents

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Abstract

Infants and children may suffer from a wide variety of inherited, congenital, and acquired conditions that can result in significant physical and mental disabilities. Although there is a certain degree of overlap in the issues that are encountered with developmentally normal children, the recurrent problems that are encountered in this group of special children warrants separate consideration. Both the underlying disorder and the associated manifestations may lead to complications that require careful forensic assessment. Questions may also arise concerning the quality of care or the adequacy of medical diagnosis and treatment. In this chapter, an approach to children either with a history of developmental abnormalities or with dysmorphic features first identified at autopsy that may be linked to mental and physical delay will be outlined. In addition, some of the particular features of specific conditions will be reviewed.

Introduction

The number of childhood conditions associated with developmental delays is vast and covered in depth in standard pediatric and pediatric forensic textbooks. Selected conditions, particularly those with neurological manifestations or with identified chromosomal abnormalities may present challenges in the investigation of forensic cases such as with the assessment of morphological lesions that may be encountered at autopsy and the possible range of mechanisms that may result in a lethal outcome.

Generally speaking, sudden death in developmentally delayed children is often associated with epilepsy or with syndromic congenital cardiovascular conditions. These conditions are discussed in greater detail below in descriptions of specific entities. However on occasion, causes and mechanisms of death may not be clearly discernable. For example, severely intellectually impaired children may have recurrent and sometimes lethal asphyxial events that are caused by subtle autonomic instability or suffer nutritional deprivation with superimposed sepsis. Infections may be exacerbated by physical factors such as severe kyphoscoliosis, which may restrict lung expansion, or by certain medications that may cause respiratory depression (Carter and Jancar 1984). The disabled child may also be the victim of abuse and neglect, pertinent findings often overshadowed by the inherent pathological conditions. On the other hand, the disabled child may present with injuries or morbid conditions that are secondary to the inherent disorder and that are easily mistaken for maltreatment.

Central Nervous System Conditions

Structural and Developmental Abnormalities

Determining the mechanism of sudden death may be difficult in infants and children who have stable structural defects of the brain such as microcephaly, hydrocephalus, pachygyria, micropolygyria, or holoprosencephaly (Speights and Bauserman 1991).

However, such defects may be associated with other congenital anomalies. Children with Arnold-Chiari malformation have maldevelopment and downward displacement of portions of the medulla and cerebellum into the cervical spinal canal. This is associated with an increased incidence of sleep apnea and sudden death from brainstem compression (Byard 1996). In addition to natural diseases, the possibility of accidental or inflicted injury must be considered in children with neurodevelopmental delays as they often require a high level of supportive care, are poor historians, and may not be able to protect themselves or fend off an assailant.

Cerebral Palsy

Cerebral palsy is not so much a specific diagnosis but a clinical term used for a group of nonprogressive motor disorders arising from a malfunction of the brain rather than the spinal cord or muscles (Badawi et al. 1998). Children with cerebral palsy have a reduced life expectancy associated with aspiration of gastric contents and bacterial pneumonia (Hutton et al. 1994; Norman et al. 1990). These problems arise because of dysphagia, shallow respirations, disturbances of cough or gag reflexes, and immunological deficiencies (Eyman et al. 1990, 1993). Such secondary problems are worse in children with the greatest intellectual and motor disabilities (Blair et al. 2001).

At autopsy, acute pathological changes may not be detected as defective autonomic control or epilepsy can predispose to unexpected cardiopulmonary arrest. Rarely repetitive abnormal head movements may cause vertebral artery dissection with resultant subarachnoid hemorrhage (Ganesan et al. 2002). These children and adolescents are also at an increased risk of traumatic deaths from motor-vehicle impacts and drowning (Strauss et al. 1999).

Hydrocephalus

Hydrocephalus refers to the situation where there is accumulation of cerebrospinal fluid (CSF) within the ventricles of the brain. It may be congenital, associated with spina bifida or Dandy-Walker syndrome, or it may result from an acquired obstruction of the cerebrospinal-fluid drainage channels due to infection, hemorrhage, or tumor. Shunting of cerebrospinal fluid into either the atrium of the heart or the peritoneal cavity is a standard treatment for obstructive hydrocephalus and may be associated with unexpected death due to acute shunt obstruction or disconnection of one of the component parts (Staal et al. 1987). Antemortem symptoms may be quite variable (Tomlinson and Sugarman 1995), but a history of headaches can be significant. Shunt blockage may not necessarily be demonstrable at autopsy.

Another problem that may arise from ventriculoatrial shunts is pulmonary thromboembolism arising from thrombi that develop around the intravascular/cardiac tip of the catheter. Thrombi are initiated by contact of blood with the thrombogenic catheter tip or with areas of denuded endothelial lining (David and Andrew 1993). Indwelling shunt catheters may also predispose to sepsis or to

pulmonary hypertension, the latter associated with sudden collapse and/or death particularly during cardiac catheterization (Byard 1996; Fuster et al. 1984). Sepsis may also be a feature of ventriculoperitoneal catheters if the tip has perforated the intestine (Byard et al. 2001).

Epilepsy

Epilepsy is a finding in certain developmentally delayed children and is characterized by episodic seizures which may be associated with sudden unexpected death (Byard 2010). The children who are at highest risk are those with polytherapy-refractory epilepsy, cerebral palsy, and mental retardation (Forsgren et al. 2005).

Sudden unexpected death in epilepsy or SUDEP has been defined as "sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus where necropsy examination does not reveal a toxicological or anatomical cause for death" (Nashef and Brown 1996). It has also been referred to as a category of death in people with epilepsy occurring in the absence of a known structural cause of death, and that is most likely heterogeneous with regard to mechanisms and circumstances (Nashef et al. 2012). Although it is a significant problem in general epileptic populations, the diagnosis of SUDEP cannot be applied in cases where an underlying disease or syndrome is present with structural abnormalities of the brain.

The mechanism of death in epilepsy is continually debated with possibilities such as asphyxia, including suffocation from soft bedding, pulmonary edema, and cardiac arrhythmias. Possible mechanisms have been classified into the following groups: (i) sympathetic-induced cardiac arrhythmia, (ii) parasympathetic-induced bradycardia/asystole, (iii) apnea/respiratory failure, (iv) a combination of arrhythmia and apnea, and (v) neurogenic pulmonary edema with cardiac failure (Leestma 1988). There is an association of sudden death with sleep, possibly associated with a reduction in seizure threshold (Schwender and Troncoso 1986). It is most likely that autonomic nervous-system instability occurs in these children during a seizure with cardiac tachyarrhythmias, atrioventricular block, bradyarrhythmias, ventricular fibrillation, and asystole (Akalin et al. 2003). An alternative possibility to also consider is that an underlying cardiac arrhythmia has caused cerebral hypoxia which has in turn initiated a seizure. Such children may have had automatic cardioverter–defibrillators implanted (Campbell 2005).

At the death scene there may be no evidence of disturbed bedding or urinary or fecal incontinence, and the autopsy findings may be similarly unhelpful. Bite marks of the tongue may occur but are neither specific nor diagnostic for epilepsy (Fig. 35.1a, b). Of note, many decedents show fixed anterior lividity with congestion and petechiae/ecchymoses of the face, anterior neck, and upper chest, indicating death in a facedown position (Byard et al. 2010). There may be froth in the airways from neurogenic pulmonary edema. Aspiration of food or foreign material is not usually found. If so, the prescribed diet type, e.g., mechanical or pureed, should be investigated.

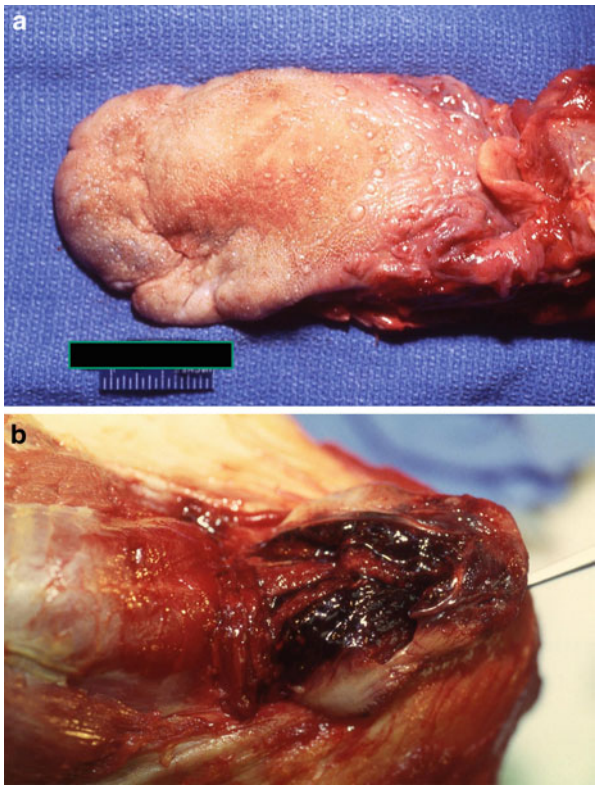

Fig. 35.1 (**a**, **b**) Tongue of an epileptic is deformed by multiple scars secondary to seizures and tongue biting. Acute hemorrhage in the tongue of an individual who died of status epilepticus

In developmentally delayed children, preexisting malformations of the brain or neuronal depopulation and gliosis of the hippocampus secondary to previous hypoxic episodes may be evidenced. Acute lesions are usually not present.

Toxicology should be performed in all cases to determine whether care has been taken to ensure that medication has been adequate and appropriate. The finding of therapeutic levels of anticonvulsant drugs does not, however, preclude the occurrence of sudden death by seizure (Schwender and Troncoso 1986).

While children with a range of central nervous system conditions may be at increased risk of sudden death from epilepsy, autopsy findings are often absent. The diagnosis becomes one of exclusion, relying on clinicopathological correlation, past medical history, a reliable description of the fatal episode, and the absence of other lethal natural or unnatural conditions.

Chromosomal Abnormalities

A number of disorders that were originally described as syndromes because of the regular occurrence of the same set of features have now been shown to be caused by specific chromosomal abnormalities. Many of these are associated with intellectual impairment,

Fig. 35.2 A girl with Turner syndrome demonstrating morbid obesity

physical diseases, and sudden, unexpected death. The identification of particular chromosomal disorders may assist in understanding the clinical manifestations and also in determining the possible risks of sudden death in family members (Fig. 35.2).

Down Syndrome (Trisomy 21)

Down syndrome is the most common chromosomal abnormality associated with intellectual impairment. Caused by an additional copy of the proximal part of chromosome 21q22, affected children have intelligence quotients (IQs) ranging from 20 to 85 (Byard 2007). As the diagnosis of Down syndrome has usually been made prior to autopsy, the major focus will be on establishing the cause of death.

Affected children have a short stature and typical facial features. They have a rounded face with an open mouth and protruding tongue. The teeth may be malformed, maloccluded, absent, or small with occasional supernumerary teeth. The nasal bones are hypoplastic with flattening of the nasal bridge. The palpebral fissures are upwardly slanting with bilateral epicanthic folds. The head is often small and round with a flattened occiput and sloping forehead. Brushfield spots and cataracts may be found in the eyes, and the ears may be small and folded. The genitalia in males may be small with hypospadias and cryptorchidism. The hands tend to be short and broad with a single flexion crease in 20 % of individuals. A prominent space may be present between the big and index toes (Byard 2007). Atlantoaxial instability with malformation of the odontoid process is reported in Down syndrome. As this can cause acute compression of the upper cervical cord, lethal respiratory arrest may occur (Alvarez and Rubin 1986; Hungerford et al. 1981; Parfenchuck et al. 1994). Trauma or activities that result in extreme or repeated neck flexion are risks for these patients. The whiplash, or flexion–extension, neck movement in a motor-vehicle collision can be fatal. Risky recreational activities include diving, swimming the butterfly stroke, trampolining, tumbling, and contact sports. Interestingly, epilepsy is not common in Down syndrome and there is no increased incidence of hydrocephalus (Hunter 2001; Scholl et al. 1982).

Children with Down syndrome are at increased risk of unexpected death associated with a wide range of congenital cardiac defects that include endocardial-cushion defects, ventricular and atrial septal defects, tetralogy of Fallot, and aortic-arch hypoplasia. Pulmonary hypertension and right-ventricular hypertrophy may develop if reversal of blood flow across septal defects/shunts occurs (Ferrans and Boyce 1983). Other cardiovascular abnormalities that may be found at autopsy include a single ventricle, coarctation of the aorta, anomalous pulmonary veins, pulmonary valve stenosis, mitral stenosis, cor triatriatum, and right-ventricular hypoplasia. Rarely pulmonary or coronary artery embolism may arise from thrombi associated with congenital cardiac defects (Stahl et al. 1995).

Other problems associated with early death are upper-airway compromise from stenosing lesions such as choanal stenosis, macroglossia, subglottic stenosis, and enlargement of the tonsils, adenoids, and lingual tonsils. Additional malformations associated with morbidity and mortality include midface hypoplasia, subglottic stenosis, laryngomalacia, tracheomalacia, bronchomalacia, and congenital malformations of the larynx, trachea, and bronchi (Bertrand et al. 2003; Rohde et al. 2005; Jacobs et al. 1996).

Gastrointestinal-tract malformations include tracheoesophageal fistula/esophageal stenosis/atresia, pyloric stenosis, duodenal atresia/obstruction, hypoplasia of the small intestine, malrotation, Hirschsprung disease, imperforate anus, annular pancreas, and bile-duct atresia (Buchin et al. 1986; Frid et al. 1999; Scholl et al. 1982). Deaths from malnutrition in Down syndrome are less common nowadays with improvements in institutional care and in clinical management (Byard 2007).

Children with Down syndrome have an increased rate of lethal infections and so full microbiological workup is advisable. The predisposition to lethal infections arises from a variety of factors including congenital heart disease, abnormal pulmonary vasculature, and reduced mobility. In addition, these children may have abnormal immunological function with defects in cytokine production; in B, T, and natural killer cell function; in immunoglobulin levels; and in phagocytic and chemotactic responses (Tolksdorf and Wiedemann 1981; Gatenby et al. 2003). Young Down syndrome children have an increased incidence of acute myeloid leukemia (AML) and other hematopoietic malignancies (Creutzig et al. 1996; Fryers 1986; Izraeli 2003; Scholl et al. 1982) that may initiate bleeding abnormalities with intracranial hemorrhage.

Systemic Manifestations

Cardiovascular

A number of congenital cardiac defects are inherited, and some may be associated with syndromes having physical and mental disabilities. The most recognized of these would be Down syndrome where congenital cardiac defects are present in 40–50 % of cases. As noted above, the most common findings in this syndrome are

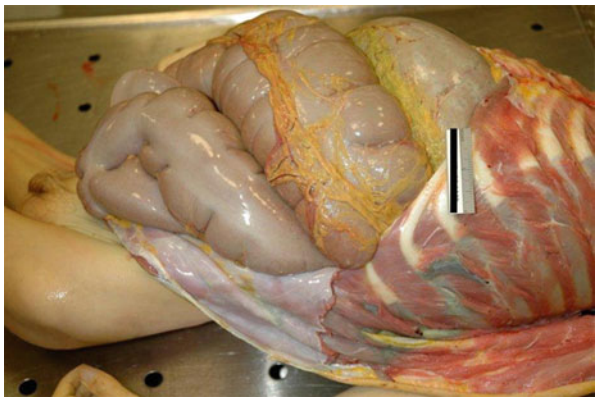

Fig. 35.3 A child with cerebral palsy had constipation, fecal impaction, and megacolon

atrioventricular canal and perimembranous ventricular septal defects. In addition there may be atrial septal defects, tetralogy of Fallot, isolated patent ductus arteriosus, and aortic-arch hypoplasia (Marino et al. 1990).

In any child with developmental anomalies, the autopsy must be conducted as if there are going to be complex cardiovascular anomalies present, so that a measured and stepwise dissection of the heart, lungs, and major vessels can be conducted. Failure to adopt this approach may result in the situation of a complex congenital cardiac defect only being identified once the heart has been removed from the body, effectively precluding an accurate assessment of vascular attachments and organ relationships.

Gastrointestinal

A number of gastrointestinal conditions may be found in disabled children resulting in anorexia, vomiting, abdominal distension, or prolonged constipation, including fecal impaction. Reasons for the increased incidence of constipation in this patient population include immobilization, soft diet, poor fluid intake, multiple medications, and neuromuscular disorders of elimination (Kozma and Mason 2003) (Fig. 35.3). However, the manifestations of acute gastrointestinal conditions may be masked by inherent problems with communication. Lethal volvulus may occur when hypotonia has predisposed to constipation and the intestine has twisted on a redundant mesocolon. In other children, acute colonic dilatation may develop spontaneously. Pseudo-obstruction may also be encountered in these individuals. Rarely, significant upper-gastrointestinal hemorrhage may be caused by severe reflux esophagitis, and lethal acute gastric dilation and rupture may follow air swallowing with inadequate gastric emptying (Byard and Couper 2001). Congenital defects of the mesocolon resulting in herniation with lethal intestinal infarction/obstruction may occur in children at all levels of development but are generally easier to detect clinically in mentally normal children who can more clearly vocalize their discomfort.

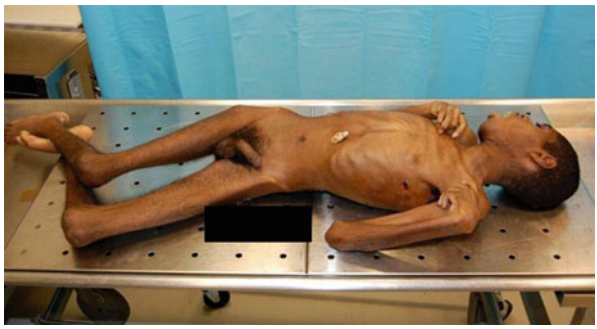

Fig. 35.4 An immobile cerebral palsy patient required a gastric feeding tube for adequate nutrition. However, note that he is very thin with contractures and muscular atrophy, common findings in these patients

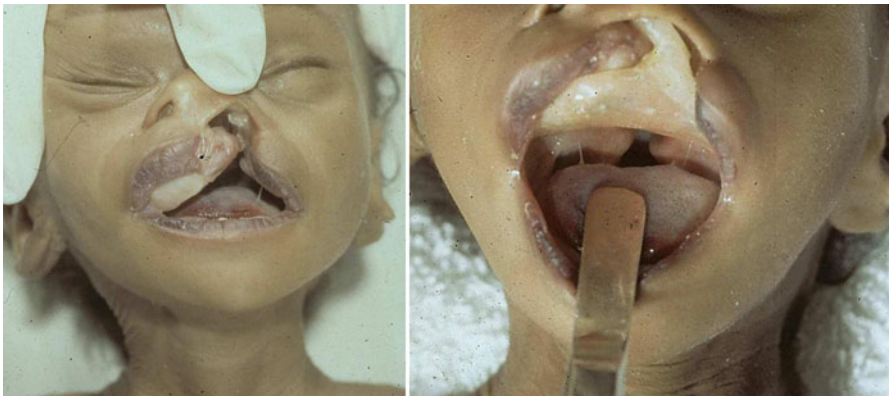

Fig. 35.5 A girl with cleft lip and palate died of malnutrition secondary to poor feeding (Image courtesy of Kara Ross MD)

Feeding problems and eating disorders are not uncommonly encountered in the disabled child. Children with severe intellectual impairment may be significantly underweight, well below the 3rd percentile of growth parameters. Problems with ensuring an adequate caloric intake in the face of esophageal dysmotility and swallowing problems with recurrent aspiration of gastric contents into the upper airways and lungs may necessitate the insertion of a gastrostomy feeding tube (Fig. 35.4). Bulimia and pica can result in excessive amounts of food or a range of often bizarre materials including soil, button batteries, screws, and toys being ingested. Such ingestion may cause acute upper-airway obstruction, aspiration into the airways, or gastrointestinal perforation with resultant sepsis (Jancar and Speller 1994). Food may also be inadequately masticated due to a lack of understanding of normal chewing and swallowing processes, sometimes compounded by carious or inadequate dentition (Byard 1996). The recommended diet necessary for the individual may not be instituted resulting in dysphagia and aspiration. Other reasons for dysphagia include decreased saliva secretion, oromotor discoordination, poor cough and gag reflex, cleft lip and palate, and pocketing of food (Fig. 35.5). Episodes of difficult feedings and recurrent

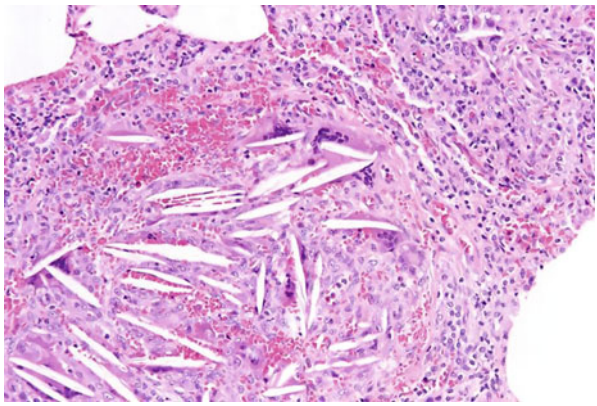

Fig. 35.6 Microscopic section of the lung from an individual with poor oromotor skills and dysphagia shows features of chronic aspiration typified by granulomas with foreign body giant cells and cholesterol clefts (Hematoxylin and Eosin, H&E ×40)

aspiration pneumonia may be noted on history. Histological examination of the lungs can reveal scarring, foreign-body giant cells, and polarizable foreign material, evidence of previous episodes (Fig. 35.6).

Oropharyngeal

In addition to the aforementioned dysphagia, disabled children often present with other oral manifestations of their disease. Some have self-destructive chewing behavior resulting in severe lesions of the lips and tongue. Periodontal disease is prevalent due to decreased saliva, special diets, inability to perform dental hygiene, behavior preventing adequate hygiene by the caretaker, medications, and malocclusions Figs. 35.7a, b and 35.8

Respiratory

In addition to aspiration, aspiration pneumonia, and gastroesophageal reflux, the disabled child may have other respiratory difficulties. Poor coughing and swallowing reflexes combined with an abnormal chest shape due to severe kyphoscoliosis and reduced muscle bulk can predispose to the accumulation of mucoid secretions within the lungs. Such accumulations with mucus pooling are prime areas for bacterial growth. Some of these children require ongoing chest physiotherapy with postural drainage because of the ever present risk of pneumonia. Compounding these risk factors, syndromes such as trisomy 21 are being associated with impaired immunological responses increasing the risk of lethal bacterial infection.

Skin

Disabled children often have chronic skin conditions. These conditions may be inherent to the disease such as lower-extremity edema and ulcerations, eczema, and

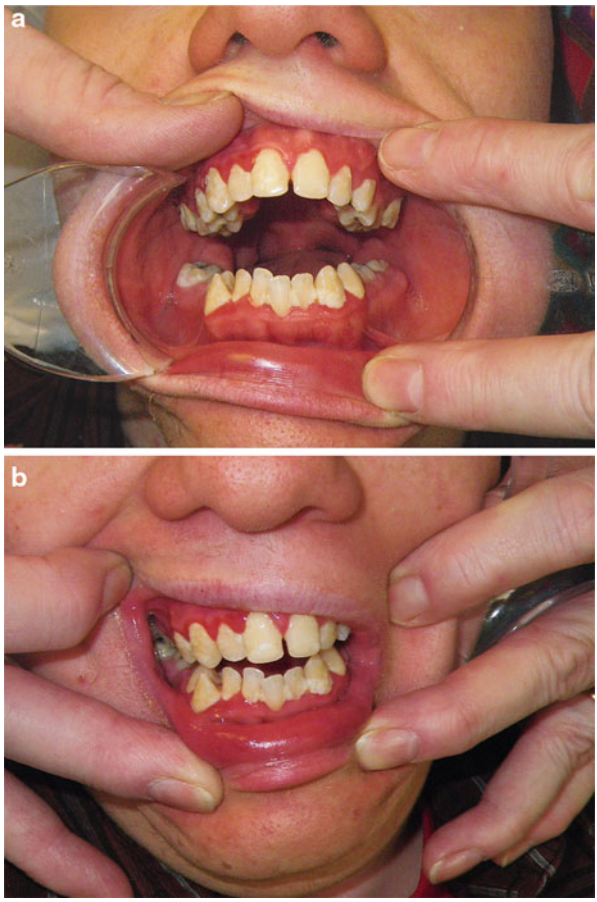

Fig. 35.7 (**a**, **b**) An autistic adolescent teen has numerous restorations, plaque on the teeth, and periodontal disease (Image courtesy of Paige J. Collins DDS)

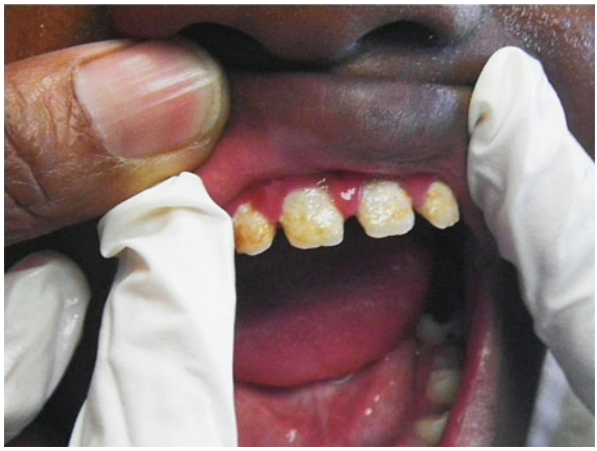

Fig. 35.8 A teen with Down syndrome has plaque build-up and periodontal disease (Image courtesy of Paige J. Collins DDS)

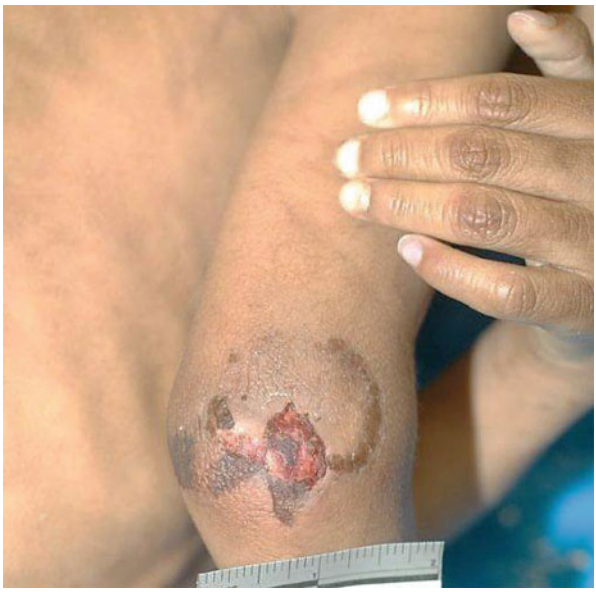

Fig. 35.9 Pressure abrasions and eschars on the elbow secondary to immobilization

autoimmunity. Self-destructive skin picking can result in ulcerations and infections. Prolonged immobilization and restraints can cause abrasions, chronic lichenification, or pressure ulcerations (Figs. 35.9 and 35.10a, b). Incontinence enhances skin breakdown and increases the chance of secondary infections. Infections can also be identified at PEG and tracheostomy sites. An abnormal immunological system will also predispose the disabled child to infections.

Skeletal

Many disabled children have skeletal-system abnormalities and/or are predisposed to skeletal pathology (Fig. 35.11a, b). Contractures and muscular atrophy are common features of cerebral palsy (Fig. 35.12). Osteopenia and osteoporosis are due to decreased vitamin D, hypogonadism, special diets (such as ketogenic), decreased mobility, and medications (Fig. 35.13). Joint hypermobility and arthropathy are characteristics of several disorders including Down syndrome. These abnormal changes in the skeletal system result in fractures, dislocations, and subluxations.

Infectious

Abnormal immunological function can result in infections and occult sepsis, particularly in the more profoundly disabled children (O'Brien et al. 1991). As noted above, reduced respiratory excursion with impaired neuromuscular control of

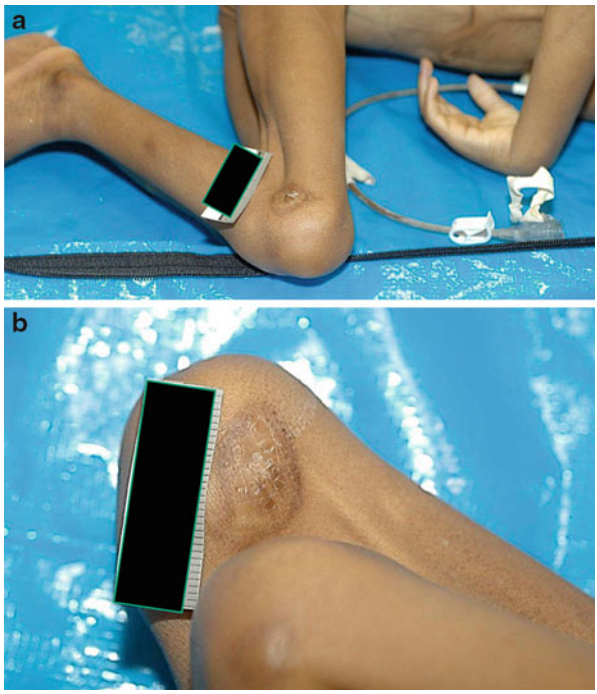

Fig. 35.10 (**a**, **b**) Chronic lichenification of the lateral and medial aspects of the knees secondary to prolonged immobilization

swallowing provides the basis for this increased susceptibility and repeated episodes of pneumonia. Given the significant physical problems that many of these children have, it is a testament to the quality of care that survival for decades may occur. In less well-cared for and/or immobile children, infected pressure sores act as a portal for bacterial entry. Fungal infections are also more common in these children as compared to nondisabled children. At autopsy, blood cultures should be performed, evidence of pressure sore medical treatment documented, sections taken for histology, and pressure sore sections taken for microbiology culture.

Metabolic

A heterogeneous group of over 400 disorders exists resulting from inborn errors of metabolism, a number of which may cause unexpected death in affected children (see ▶ Chap. 34, "Pediatric Metabolic Diseases"). Such diseases include disorders of fatty acid oxidation and carbohydrate, amino acid, urea cycle, and organic acid metabolism. Such deaths most often result from seizures, acute encephalopathy, and cardiac disease (Dionisi-Vici et al. 2002). Affected children may be hypotonic with failure to thrive and exhibit psychomotor delay, unusual odors, vomiting, and diarrhea. There may be a family history of an inherited metabolic disorder or previous infant or childhood deaths, as inheritance is usually autosomal recessive

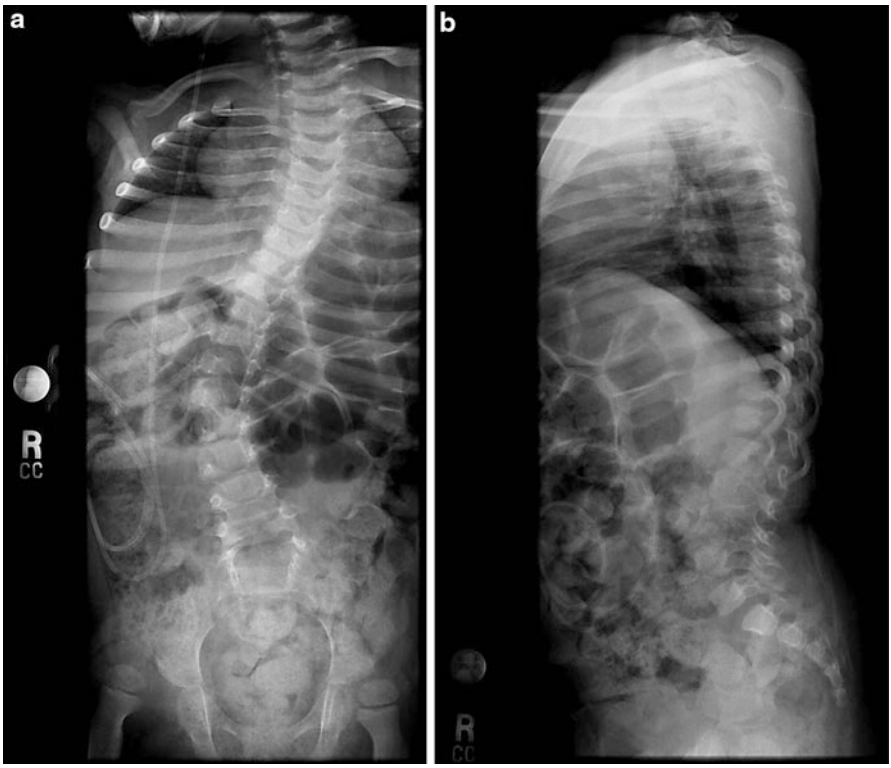

Fig. 35.11 Frontal radiograph of a 5-year-old boy with Chiari II malformation shows the absence of spinous processes in the lower lumbosacral region with widened pedicles due to the meningomyelocele (**a**). Lateral radiograph (**b**)

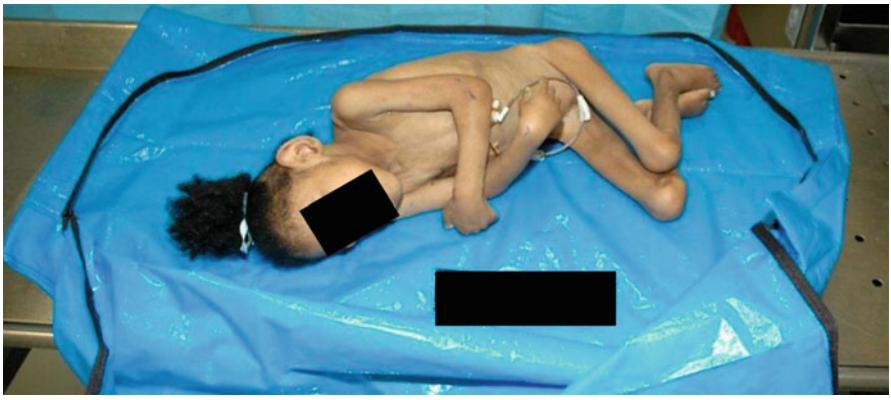

Fig. 35.12 An immobile child with cerebral palsy has a gastric feeding tube, decreased body mass, muscular atrophy, and contractures

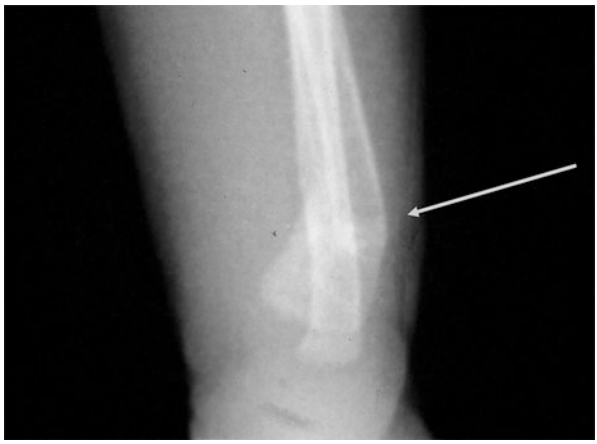

Fig. 35.13 Fracture secondary to demineralization (*arrow*)

or X-linked. While a diagnosis may have been established in older children, it may be unrecognized at the time of autopsy in the very young.

At autopsy the findings may be quite nonspecific and so the diagnosis will depend on metabolic testing of blood or tissues for the most common conditions such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. In this disorder of β-oxidation of fatty acids, the most common mutation (in nearly 89 % of cases) involves an A-to-G nucleotide replacement at position 985, resulting in a substitution of glutamate for lysine at position 329 of the MCAD precursor protein (Gregersen et al. 2000). Features at autopsy that suggest an underlying metabolic defect include cardiomegaly with fatty change in the liver, heart, smooth and skeletal muscles, and renal tubules.

Certain conditions such as homocystinuria, a heterogeneous metabolic disorder caused by a deficiency in cystathionine synthase, may have particular findings at autopsy that should raise suspicions as to the diagnosis. Affected children have variable degrees of intellectual impairment and cardiovascular disease, with a high rate of thromboembolism due to shedding of the endothelium with exposure of subepithelial collagen. This may result in fatal cerebral infarcts (Harker et al. 1974; Schwab et al. 1987).

Overall, it is most likely that 1–5 % of cases of sudden infant and early childhood death are caused by metabolic disorders.

Scenarios with Injuries to the Disabled Child

Accidental Injuries

A number of difficulties may arise in children with physical and mental disabilities that predispose them to having accidents. Lack of understanding of the dangers of particular situations, for example, traffic on a busy road, may put

them at risk, as may playing at the edge of waterways or attempting to swim in unsafe conditions. Positional asphyxia is a problem that may occur in any individual with significant psychomotor impairment due to the inability of the affected person to self-extricate from unsafe situations (Byard et al. 2008). For this reason sleeping accidents where children have asphyxiated in unsafe sleeping environments occur at older ages in children with disabilities than in other children (Amanuel and Byard 2000).

Disabled children with abnormal gait, ataxia, and poor mobilization are more prone to minor and major accidental trauma. Increased fracture incidence is seen with increased mobility. Even minor trauma can be fatal in certain children due to the aforementioned systemic abnormalities.

Certain conditions may predispose to drowning, for example, Angelman, or "happy puppet," syndrome which is characterized by a fascination for water. The other features of the syndrome of mental retardation, ataxia, and poor coordination may add to the risk of drowning (Herbst and Byard 2012; Didden et al. 2008). Bathing in hot water may rarely induce reflex epilepsy (Ìncecik et al. 2004) increasing the risk of drowning. In fact, it has been shown that more than 10 % of children who have drowned may have an underlying predisposing condition such as epilepsy (Smith et al. 1991). The range of lethal accidental injuries that may be encountered in the nondisabled child is discussed elsewhere in the text.

Inflicted Injuries

The disabled child is known to be at an increased risk of maltreatment, and children with disabilities have been found to be 3–4 times more likely to be maltreated than their nondisabled peers (Hibbard and Desch 2007; Sullivan and Knutson 1998). Children with disabilities are vulnerable to abuse and neglect because of their cognitive level and inability to relate the history, inability to defend themselves, and dependency requiring a high level of supportive care. In addition to sustaining physical abuse, these children may suffer neglect consisting of starvation/malnutrition/dehydration or medical neglect such as generalized sepsis from infected pressure sores or untreated pneumonia. All of these conditions are discussed in greater detail elsewhere in the text.

Certain special conditions may involve self-infliction of injuries or have a predisposition to injury. A classical example of the former is Lesch-Nyhan syndrome, an X-linked disorder of purine metabolism characterized by mental retardation, choreoathetosis, and spasticity. The self-mutilation involves biting of the fingers, lips, and tongue. Sudden and unexpected death in these children is due to central apnea, aspiration, or high cervical spinal cord damage (Neychev and Jinnah 2006). However, the physical findings of self-injury can be dramatic and potentially overshadow the natural disease components. Osteoporosis from disuse atrophy can result in fractures of long bones in children with cerebral palsy, often associated with only minor trauma (Lingam and Joester 1994). Down syndrome individuals have tendencies to lower-extremity fracture.

Sexual abuse should always be considered in the vulnerable, disabled victim. Besides the tendency for certain disabled patients to be labeled as "hypersexual," these individuals are also targets for control and manipulation by perpetrators and caretakers. A careful history and physical examination with procurement of specimens for forensic analysis is often positive.

Bruises

As fractures increase with increasing age and mobility, the number of bruises also increase. The incidence of bruising is a function of mobility and coordination. The suspicious areas for bruises, i.e., worrisome for inflicted trauma, parallel those of the nondisabled child. These include the ears, chin, neck, chest, abdomen, pelvis, and buttocks. However, there are certain situations in which one may see truncal bruises. These are when a disabled child requires increased transfers or assistance with moving (Goldberg et al. 2009). Traumatic transfers result in more prevalent bruising as the child increases in weight. Bruises on the feet are also more common if the disabled child is in a wheelchair or has increased transfers/assistance with moving. The incidence of bruises also increases with a decrease in muscle tone. Orthotics is not associated with an increase in bruising and may even be associated with decreased injury as they may provide a protective barrier.

An Autopsy Approach

The autopsy approach to a child with a history of developmental delay or with dysmorphic features noted at autopsy requires a careful combination of both pediatric and forensic skills. The following two major issues arise: establishing the nature of the underlying condition (or confirming the clinical diagnosis/assessment) and determining the cause, mechanism, and manner of death.

Establishing the nature of the underlying condition may not be necessary in many cases where there has been considerable medical contact over a number of years. In such cases, the purpose of the autopsy is not only to confirm the clinical findings but to search for any subtle manifestations of the disorder and in particular for any unexpected or untoward illnesses that may have been preventable or at least treatable. The most important step prior to undertaking the autopsy is to request a full set of medical records from the local children's hospital where it is quite likely that the child may have been extensively investigated and treated. The contact details of treating doctors will also be available from these records that will have observation charts, staff statements, and medication regimes. Any records from social services should also be sought. An additional step that the authors find very useful is to discuss complex cases with a clinical geneticist or senior pediatrician. Other specialists who may be of great assistance in specific cases include neurologists, neuropathologists, cardiologists, pediatric infectious disease, and metabolic physicians. In the best-case scenario, they will have personally treated the child,

know of the condition, or be able to do a search of clinical computer databases looking for any linkage of various autopsy findings.

Whether the underlying condition has been identified or not, a requirement in all cases will be to establish the cause, potential mechanism, and manner of death and to decide whether or not these were associated with the underlying syndrome and treatment or were coincidental (Byard 2007). Ancillary studies include sterile skin and fresh tissues for cytogenetic and molecular studies, blood and/or filter-paper blood spots for metabolic testing, peripheral blood for toxicology, vitreous humor for chemistry and metabolic analyses, microbiological studies, and full-body radiographs.

Conclusion

The autopsy investigation of disabled children can be extremely difficult due to the complexity and rarity of many of the entities. The subtlety and nonspecificity of findings may be an issue, and forensic pathologists often feel uncomfortable in dealing with such cases. The key to succeeding with these children is to consult widely and to obtain as much information as possible before performing the autopsy. Thus, when a suspected case is encountered, a detailed family and medical history is the required starting point. All this may involve is a telephone call to the nearest pediatric tertiary center which may also initiate consultation with a medical geneticist/senior pediatrician. Once the process begins, the careful external examination with photographic documentation of positive and negative findings should be augmented by a skeletal survey. The internal examination should be similarly carefully documented. Sampling of body fluids and tissues can be guided by established protocols or by direct consultation with the local pediatric hospital.

In cases where a diagnosis has not been made prior to autopsy referral of the family for medical assessment/medical genetics, follow-up is advisable. Unfortunately, this is with the recognition that the usefulness of genetic counseling may be limited by the increasing complexity of the genetic profiles of many of these conditions. Specifically, a number of heritable conditions involve numerous mutations in large or multiple genes, and families may have unique mutations of completely uncertain significance. Despite these drawbacks, the proper investigation of these cases usually requires the integration of the pathology findings with quite diverse clinical information, and so the pathologist can often achieve the best outcome by coordinating a number of specialists from diverse fields.

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Abstract

This chapter details pediatric anthropology and odontology. Because definitions of "a child" vary in the literature, the chapter commences with a discussion about terminology and outlines the age ranges used by the authors. A brief summary is provided of situations where the expertise of a forensic anthropologist and/or odontologist may be required. This may be in estimating the age of living individuals in clinical cases, assessing alleged bite marks, and examining and analyzing juvenile skeletal remains to assist with identification of the individual and provide descriptions and interpretations about dental and skeletal traumatic injuries.

The accuracy and precision with which the forensic anthropologist and odontologist can identify an unknown individual from their skeletal and/or dental remains depends not only on the preservation of the remains but also on available comparative standards. Therefore, reference collections and population-specific standards are discussed. Preservation is then considered as a variable that may influence the study of juvenile remains.

The role of the forensic anthropologist is to differentiate between human and nonhuman skeletal remains, develop a biological profile (ancestry, sex, age, and stature), and assess changes in the skeleton which may be evidence of disease and/or trauma. Each of these analyses is considered in detail highlighting the advantages and limitations of the methods used when dealing with juvenile remains. A number of case studies are provided that illustrate examples of applications of forensic anthropology and odontology.

Introduction: Definitions and Terminology

The aim of this chapter is to provide a comprehensive review of the role of forensic anthropology and odontology in pediatric cases. Pediatrics is the branch of medicine concerned with child health. However, there is much debate in the anthropological literature about how to define "a child," with cultural, psychological, anthropological, and biological factors all influencing discussions (Ingvarsson-Sundström 2003; Lewis 2007; Rogers 2009; Rosen 2007). According to the Convention of the Rights of the Child, Article 1, a child is a person under 18 years of age. While a "child" has legally been defined as an individual less than 18 years of age, there is a range of terms used by forensic and biological anthropologists and forensic odontologists when dealing with the human remains of individuals who have not reached maturity. Such terms include non adult, subadult, fetus, stillborn, neonate, perinate, infant, child, juvenile, adolescent, and immature. Unfortunately, terminology in the literature is not always consistent: age ranges ascribed to each term differ between practitioners. For example, an infant has been described as being between 0 and 3 years by some (White and Folkens 2005) and birth and 1 year of age by others (Ingvarsson-Sundström 2003; Lewis 2007).

In this chapter, "juvenile" will be used as an umbrella term to describe those individuals up to the age of 18 years. Specific age groups will be described as follows:

Fetus	9 weeks to before birth
Infant	0– <2 years
Child	2–12 years
Adolescent	13– <18 years

These age ranges were defined by Australian forensic anthropology and odontology practitioners following a Medical Sciences Scientific Advisory Group (Donlon 2009) critical-issues workshop on age estimation held in Adelaide, Australia, in 2010. It is, however, recognized that the medical profession describes perinatal death as stillbirths, defined by some as >24 weeks gestation (Hill 2004) and others as after 20 completed weeks of gestational age (Zegers-Hochschild et al. 2009) and within the first week of life; neonatal death = <28 days; and infant death = <1 year of life (Hill 2004).

Studying the Juvenile Skeleton and Dentition

Although most forensic anthropology and odontology practitioners will see relatively few cases involving juvenile skeletonized remains (see below for a discussion on number of cases), it is vital for practitioners to be familiar with the relevant anatomy. Although reference teaching specimens are rare, there are a number of excellent textbooks devoted to juvenile skeletal and dental anatomy (Scheuer and Black 2000a, 2004; Schaefer et al. 2009; Baker et al. 2005) as well as casts of skeletons of infants (newborn, 0.5–1.5 years, and 1–2 years), children (7.5–8.5 years), and adolescents (15–18 years). Dental development casts are also available (www.francecasts.com/home; http://www.boneclones.com/ko-247-set.htm).

Applications of Anthropology and/or Odontology

Clinical Cases

A forensic odontologist and/or anthropologist may be required to provide an opinion on clinical cases (Black et al. 2010). For example, it may be necessary to establish the age of the perpetrator of a crime in order to determine whether the person is classified as an adult and therefore to deliver the appropriate sentence. Clinical age assessments may also be required in cases of adoption, illegal immigration, and refugee claims (Hardy 2007; Nuzzolese and Di Vella 2008; Schmidt et al. 2007). In other contexts the age of individuals is critical in cases where children have allegedly been recruited into armies, and those responsible are being

charged with war crimes (Rosen 2007). In such cases, age estimation may be undertaken following a radiological examination of dental and skeletal development (Schmeling et al. 2001, 2003).

Bite Marks

A forensic odontologist may be involved in the examination and assessment of alleged bite marks on the living or the deceased (Hill 2000; Rothwell 1995). Bruise patterns may be uninterrupted arch forms; partial (Fig. 36.1), single (Fig. 36.2), or multiple bites (Fig. 36.3); and faded or old healed bite wounds.

If such bruise patterns are found, the following questions need to be asked:

- Is it a bite mark?
- Is it human or nonhuman (animal) in origin? (Murmann et al. 2006)
- Was the mark made by an adult or child?
- If it is a human bite mark, was it caused by the upper or lower arch?
- Are there any features in the pattern which may connect the bite to a perpetrator?

A human bite mark will typically be oval or semilunar in appearance with two arches opposing each other (Fig. 36.4). Usually only six anterior upper and lower teeth are involved. The upper and lower dental arch features an alignment of individual contusions, abrasions, and lacerations that approximate the size, shape, and alignment of the teeth. The maxillary (upper) arch generally produces the larger area of bruising. An adult bite mark will have an approximate width of 3.5–4.5 cm representing the inter canine distance. In comparison, a bite mark made by an infant will have a width generally less than 3 cm.

Protocols for Collection of Bite-Mark Evidence

The sooner the injury pattern is recognized as a human bite mark and reported, the better the evidence collection will be. For legal reasons all evidentiary material gathered must be catalogued with a unique number and date attributable to the case being investigated. All suspected human bite marks must be photographed. A series of close-up images of the bite mark should be taken with the ABFO No2 scale in position. All bite-mark injuries should be swabbed for possible DNA evidence. The evidence containers should be stored at−20° C until processed. The presence of a bite mark indicates violence. Evidence of bite-mark injuries may have civil (abuse, assault, battery) and/or criminal (rape/murder) implications.

Juvenile Skeletal Remains

While there has been discussion and examination of archeological human juvenile remains (Baker et al. 2005; Chamberlain 2000; Cohen and Rutter 2007; Hillson 2009; Lewis 2007; Scott 1999; Sofaer Derevenski 1997), forensic cases involving

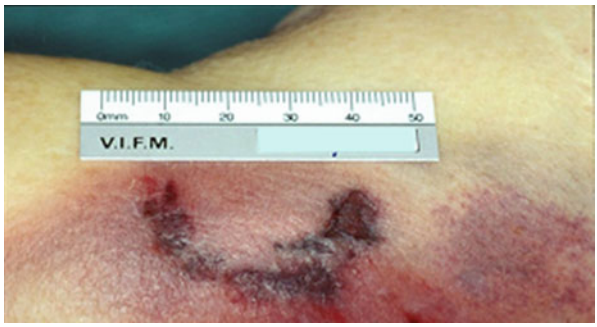


Fig. 36.1 Partial bite mark

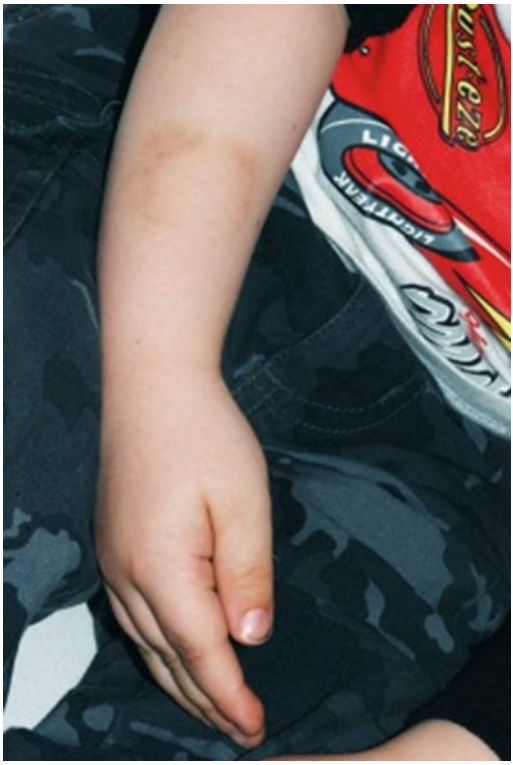


Fig. 36.2 Single bite mark

the skeletal/and or dental remains of children are less reported (Weaver 1998). In both archeological and forensic cases, it has been argued that poor preservation is a major limiting factor in case load (see below). Rather than a question of preservation, it is more likely that there are simply fewer cases for the forensic anthropologist and/or odontologist which involve the skeletonized remains of juveniles.

In cases involving a deceased juvenile (e.g., following abuse, trauma, accident, suicide, neglect, or a war crime investigation), an anthropologist and/or odontologist

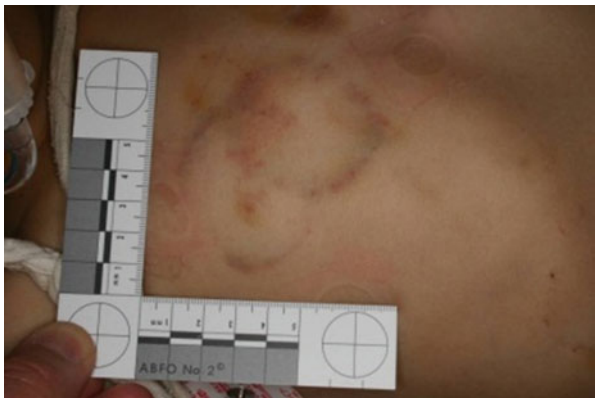


Fig. 36.3 Multiple bite marks

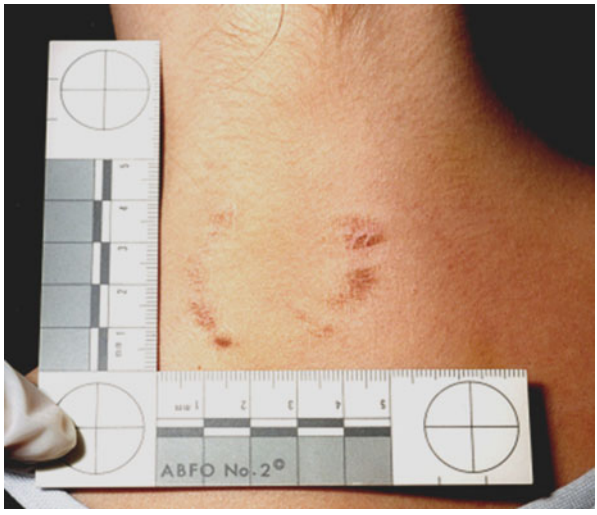


Fig. 36.4 Adult human bite mark

may assist with identification of the individual and provide descriptions and interpretations of dental and skeletal traumatic injuries (Lewis and Rutty 2003).

Age estimations of deceased juveniles (see below) may be useful in a number of scenarios such as homicide cases (Steadman et al. 2009) and multiple disaster incidents. The forensic odontologists and/or anthropologists can also assist where age estimations are pivotal in differentiating fragmented and commingled remains. For example, in the 2009 Australian (Victorian) bushfires, one scene involved the death of two juveniles. Due to the fragmentation and commingling of the remains, it was impossible to visually distinguish between the individuals. Examination of computed tomography (CT) images of the dentition of the deceased individuals enabled forensic odontologists to provide age estimations which facilitated identification of the children (Bassed and Hill 2010). However, positive identification of juveniles based on a dental examination may not always be possible because in

many cases children seldom see a dentist on a regular basis. Dental records may not exist or they may have insufficient information for identification to be made (Lewis 2007).

Age estimations are also important in confirming or denying the veracity of statements of events. There are cases involving the recovery of juvenile remains where parents claim the fetus miscarried or that the infant died immediately after birth. Estimating the age at death in such cases is paramount in determining whether the child died around the time of birth or lived for some time after birth. The age estimation obviously has serious ramifications for the parents in terms of accusations made about their actions leading up to the infant's death (Case Study 1).

Case Study 1

Background

A 19-year-old woman spent the night with her partner. During the night the woman felt unwell and suffered what she described to her partner as stomach cramps. She was left alone for several hours and eventually informed her partner that she had delivered a stillborn female baby in his absence. Allegedly, the partner had not been aware that his partner was pregnant, and the woman did not want to tell her parents of the situation.

The couple wrapped the infant in a towel, placed it in a plastic bag, and buried it in a tree plantation. The partner described the baby as being well formed and about the size of a "normal" newborn baby. Three years later, the man returned to the plantation. He dug up the bag, placed the bundle in a plastic bag, and kept it in his car until handing it to the police.

The bag was examined and remains consisting of a fully skeletonized human neonate were recovered. The majority of the skeletal elements were present apart from the bones of the hands, feet, three ribs, and some of the epiphyses. Despite many of the elements having dirt adherent to their surface and roots growing through foramina, they were well preserved.

Based on measurements of the diaphyses of the majority of long bones (Ubelaker 1989), the individual was aged between 0 days (i.e., newborn) and 6 months of age. While some tooth cusps had been lost postmortem, others were observed in situ in the left and right mandibular crypts. Detailed radiographic assessment of the crown formation of these deciduous molar cusps (Moorrees et al. 1963a, b) supported the skeletal age estimation but suggested that the child was closer to newborn than 6 months in age.

Of interest, however, was the fact that although the skeletal (diaphyses) and dental age estimates were consistent, the vertebral analysis provided different evidence. At birth each thoracic vertebra is represented by three bony masses. Posterior fusion of the laminae commences in the thoracic and lumbar regions at around 1 year of age (Scheuer and Black 2000a; Kósa and Castellana 2005). Yet in this individual, fusion in some thoracic vertebrae was complete,

suggesting an age greater than 12 months. While in this instance the difference between the observed fusion and published standards was assumed to represent individual variation, the case highlights the need for additional research investigating the relationship between skeletal and dental development (Hillson 2009).

Reference Collections and Population-Specific Standards

The accuracy and precision with which the forensic anthropologist and odontologist can identify an unknown individual from their skeletal and/or dental remains depends not only on the preservation of the remains but also on available comparative standards. Precision refers to a measurement that is highly repeatable. Although a measurement of, for example, a long bone to estimate age may be repeatable (and therefore precise and reliable), it can still be a poor representation of age and, therefore, inaccurate (Komar and Buikstra 2008).

To derive unknown parameters such as ancestry, sex, age, and stature, anthropologists and odontologists proceed by comparing the unknown skeletal/dental remains with the equivalent information obtained from individuals whose ancestry, sex, age, and stature are documented. The majority of standards used by forensic anthropologists and odontologists today have been developed from data based on measurements collected either from archeological collections where age and sex are known (Molleson and Cox 1993) or from anatomical samples (e.g., The Huntington Collection, the Terry Collection, the Hamann-Todd Collection, and the Dart Collection) where independent records of these biological attributes exist (Hunt and Albanese 2005; Skeletal Collections Database; Scheuer and Black 2000a; Saunders and de Vito 1991).

One of the most complete studies of fetal growth and development was undertaken in the 1960s and 1970s based on a Hungarian sample of 138 babies who were stillborn or who died soon after birth (Fazekas and Kosa 1978). Measurements of both long and irregular bones (skull and pelvis) were taken in order to correlate length with gestational age. In other studies aging criteria have been developed using radiographic data from North American populations (Hoffman 1979; Maresh and Deming 1939; Sherwood et al. 2000; Weaver 1998). While reference collections of juveniles of known age and sex exist (Alemán et al. 2012), practical and ethical issues have called into question undertaking research involving invasive procedures on deceased juveniles or taking radiographs of healthy children (Ramsthaler et al. 2009) to further understand skeletal and dental development (Hillson 2009). However, the increased application of CT scanning as part of the normal autopsy process has meant that noninvasive research on skeletal and dental development of juveniles is possible (Grabherr et al. 2009; Graham et al. 2010; Pommier et al. 2009). Such research will aid in the development of standards based on contemporary populations.

Acknowledgment of the importance of incorporating individual variation into standards has grown (e.g., in some cases skeletal elements may fuse earlier or later

Table 36.1 Values for estimating age (in years) from permanent mandibular (lower tooth) formation as developed by Moorrees et al. (1963a) and refined by Smith (1991)

	Ci	Cco	Coc	$Cr^{1/2}$	$Cr^{3/4}$	Crc	Ri	Rcl	$R^{1/4}$	$R^{1/2}$	$R^{2/3}$	$R^{3/4}$	Rc	$A^{1/2}$	Ac
Males															
I1	-	-	-	-	-	-	-	-	-	5.6	6.2	6.7	7.3	7.9	-
I2	-	-	-	-	-	-	-	-	5.8	6.6	7.2	7.7	8.3	8.9	-
C	0.6	1.0	1.7	2.5	3.4	4.4	5.2	-	6.9-	8.8	-	9.9	11.0	12.4	-
Pm1	2.1	2.6	3.3	4.1	4.9	5.6	6.4	-	7.8	9.3	-	10.2	11.2	12.7	-
Pm2	3.2	3.9	4.5	5.0	5.8	6.6	7.3	-	8.6	10.1	-	11.2	12.2	13.5	-
M1	0.1	0.4	0.8	1.3	1.9	2.5	3.2	4.1	4.9	5.5	-	6.1	7.0	8.5	-
M2	3.8	4.3	4.9	5.4	6.1	6.8	7.6	8.7	9.8	10.6	-	11.4	12.3	13.9	-
M3	9.5	10.0	10.6	11.3	11.8	12.4	13.2	14.1	14.8	15.6	-	16.4	17.5	19.1	-
Females															
I1	-	-	-	-	-	-	-	-	4.8	5.4	5.9	6.4	7.0	7.5	-
I2	-	-	-	-	-	-	-	-	5.0	5.6	6.2	7.0	7.9	8.3	-
C	0.6	1.0	1.6	2.5	3.5	4.3	5.0	-	6.2	7.7	-	8.6	9.4	10.6	-
Pm1	2.0	2.5	3.2	4.0	4.7	5.4	6.1	-	7.4	8.7	-	9.6	10.5	11.6	-
Pm2	3.3	3.9	4.5	5.1	5.8	6.5	7.2	-	8.2	9.4	-	10.3	11.3	12.8	-
M1	0.2	0.5	0.9	1.3	1.8	2.4	3.1	4.0	4.8	5.4	-	5.8	6.5	7.9	-
M2	3.6	4.0	4.5	5.1	5.8	6.6	7.3	8.4	9.5	10.3	-	11.0	11.8	13.5	-
M3	9.9	10.4	11.0	11.5	12.0	12.6	13.2	14.1	15.2	16.2	-	16.9	17.7	19.5	-

I1 first incisor, ***I2*** second incisor, ***C*** canine, ***Pm1*** first premolar, ***Pm2*** second premolar, ***M1*** first molar, ***M2*** second molar, ***M3*** third molar

than the age outlined in established standards). In addition, the importance of population-specific studies is also now well recognized. Some studies evaluate the applicability of "traditional" techniques for a specific population (Australia – Blenkin and Evans 2010; Turkey – Celikoglu et al. 2010; Hoppa and Fitzgerald 2005; Schaefer and Black 2005). Other research is aimed at developing new population-specific standards for the skeletal and dental assessment of juveniles from different geographic areas (Table 36.1). For an excellent summary of these studies see Lewis and Flavel 2006. Related questions about the "...requirement to establish the degree to which accuracy is compromised when the more general model is applied" (Komar and Buikstra 2008) have also been raised (Chaillet et al. 2005) but are yet to be addressed.

Taphonomy Issues: Preservation of Juvenile Skeletal Remains

It has been argued that a juvenile will decompose at a faster rate than an adult (Morton and Lord 2002) and that juvenile human skeletal remains do not survive as well as those of adults (Buckberry 2000). While the bones of juveniles are not as well mineralized as those of adults, rates of decomposition and preservation are affected by a number of intrinsic and extrinsic factors including age at death,

trauma to the body, whether the individual is clothed, type of clothing worn (cotton, nylon, etc.), whether the body is buried or dumped, the time of year (weather), and the geography of the dump/burial site.

Despite a widespread belief that juvenile human skeletal remains do not survive as well as those of adults (Guy et al. 1997), there are numerous collections of archeological juvenile human skeletal remains from around the world (Lewis 2007, see Table 36.2 for a summary of sites where large numbers of juvenile skeletal remains have been recovered). It has been suggested that the belief that juvenile bones do not survive is more probably related to the fact that although some bones (e.g., cranial remains) are fragile, the small bones are more likely not to be recognized and therefore not collected (Lewis 2007). The importance of working with a forensic anthropologist with knowledge and expertise in developmental anatomy is vital when dealing with cases potentially involving the recovery of juvenile bones.

Differentiating Human from Nonhuman Skeletal and Dental Remains

The importance of having a good understanding of comparative anatomy is highlighted when faced with differentiating human from nonhuman juvenile (and adult) skeletal and dental remains. Differentiation may be required in domestic case work and/or disaster victim identification scenarios (Lain et al. 2010). Although potentially similar in length, morphological differences exist between human and nonhuman skeletal remains that make differentiating small nonhuman (animal) and human juvenile bones possible. The most important distinguishing feature for differentiation is the presence/absence of epiphyses (Byers 2005). However, the size and number of skeletal elements will depend on the relative age of the child: for example, the juvenile skeleton may consist of 156 recognizable bone elements at birth but 332 at approximately 6 years of age (Lewis 2007).

Developing a Biological Profile: Ancestry, Sex, Age, and Stature

One of the main roles of the forensic anthropologist is to develop a biological profile from the recovered skeletal elements in order to narrow the search for possible identifications. When analyzing adult remains, an anthropologist will typically estimate the ancestry before determining sex and estimating age. This order of analysis is adhered to because morphological features used to comment on ancestry may also be features used to determine sex. For example, a robust glabella typically indicates that the sex of an individual is male. However, the morphology of the glabella in Indigenous Australian Aboriginal people is noticeably prominent in both men and women. Thus, the use of the glabella to determine sex will therefore be relative.

Table 36.2 Summary of skeletal and dental pathology

Condition	Appearance	Comment	References
Nonspecific infections			
Periostitis (new bone formation)	Disorganized and porous bone (woven bone indicative of an active phase of infection); Remodeled new bone layer: evidence of an infection that is healed	Diagnosis on long bones is problematic in juvenile remains due to the fact that normal growth of long bones involves the deposition of immature disorganized bone on the cortical surface	Lewis (2007)
Osteomyelitis (Fig. 36.13)	Shedding of the periosteum causes the creation of a new sheath of bone (involucrum – Fig. 36.14). Bacteria within the medullary cavity results in necrosis of the original cortex (sequestrum) which is drained through a sinus (cloaca) (Fig. 36.13)	All three features must be present to make a diagnosis of osteomyelitis; May be seen as part of fungal infections, tuberculosis, sickle-cell anemia, congenital syphilis, chickenpox, typhoid fever, smallpox	Lewis (2007); Schmitt and Glorion (2004)
Specific infections			
Tuberculosis	In addition to the lungs, lymph nodes, skin, and intestines, in some cases the bones and joints are affected. Skeletal tuberculosis lesions are characterized by minimal bone formation (involucrum) and necrosis (sequestrum) and marked osteoporosis		Hayes (1961); Lewis (2007); Santos and Roberts (2001)
Congenital syphilis	Lesions are usually symmetrical and affect multiple bones, with circumferential profuse new bone formation, which may also involve the calvarium, mimicking porotic hyperostosis; Dental changes include incisors that are small and notched (Hutchinson incisor) and hypoplastic first molars (mulberry or Fournier molars) (Fig. 36.15)		Caffey (1939); Genc and Ledger (2005). Lewis (2007); Vargov and Horáčková (2010)
Leprosy	Rhinomaxillary changes; lesions on the lower legs, hands, and feet	Children rarely present with the most deliberating form of the disease (lepromatous leprosy)	Lewis (2002)

(*continued*)

Table 36.2 (continued)

Condition	Appearance	Comment	References
Metabolic disorders			
Infantile scurvy (vitamin C deficiency)	Fractures of the cortical bone at the metaphysis; hemorrhage showing in the orbits; pitting and new bone formation on the cranium (Fig. 36.16a and b) (vault, greater wing of sphenoid, orbital roof, orbital aspect of the zygomatic bone, posterior aspect of the maxilla, internal aspect of zygomatic bone, infraorbital foramen, palate, mandible (coronoid process) and scapula and long bones)	Ascorbic acid deficiency affects the collagen matrix often resulting in trauma to weakened bone and vessels; associated with anemia	Lewis (2007); Maat (2004); Ortner and Ericksen (1997)
Rickets and osteomalacia (vitamin D deficiency)	Bending of the diaphysis of the lower extremities (Fig. 36.17) and club-shaped widening of the metaphyseal ends	Associated with anemia	Baroncelli et al. (2000); Lewis (2007); Ortner and Mays (1998)
Hematopoietic disease			
Anemia	Cribra orbitalia, porotic hyperostosis	Cribra orbitalia and porotic hyperostosis are not pathognomonic of iron deficiency anemia and are also seen in congenital forms of anemia. Also associated with rickets and scurvy	Dallman et al. (1980); Hershkovitz et al. (1997); Lewis (2007); Lewis (2012).
Joint disease			
Juvenile rheumatoid arthritis (Still disease)	Chronic arthritis: inflammatory joint involvement		Rothschild et al. (1997); Cassidy et al. (1986)
Tumors			
Neoplasms	Varying		Alt et al. (2002)
Dental disease			
Enamel defects (e.g., enamel hypoplasia – Fig. 36.18) and dental decay	Same as adults		Hillson and Bond (1997)

In cases involving juveniles, estimations of ancestry, sex, and stature are limited up to 18 years of age. Estimation of age is considered the most reliable of all the assessments used to develop a biological profile for juveniles (Saunders 2000).

Estimation of Age at Death

Age can be defined as the uninterrupted process of normal development that leads to a progressive decline in physiological function and ultimately to death. However, there are different measurements of age: chronological age, measured by accepted calendar dating; social age which reflects the normative behavior that is culturally imposed upon particular age groups; and physiological age, a medical construct that estimates levels of functional ability or impairment.

Forensic anthropologists and odontologists record changes of physiological (i.e., biological) age as opposed to chronological age or age at death in years. Physiological age will not be the same as chronological age due to the variation in the rate of maturation (Introna and Campobasso 2006). Physiological change (i.e., maturation, degeneration, and remodeling) is not linear and constant in comparison with chronological age which is both (Angel et al. 1986). However, attempts are made to correlate physiological and chronological age.

Estimating the age of an individual from skeletal remains is based on the premise that osseous tissue undergoes a predictable and patterned sequence of changes throughout the life of the individual and that this change can be quantified and accurately correlated with calendar age. Age estimates are reached by comparing skeletal and/or dental data from a deceased individual with information on patterns of growth and maturation collected from individuals of known age (Schultz 1923). Depending on the condition and preservation of the skeletal remains, age estimation may involve macroscopic, microscopic, and/or radiographic examination of a number of areas of the body that are known to alter with age at a particular rate. Age estimation of juveniles is based, in order of precision, "on dental development, epiphyseal closure, and diaphyseal length" (Hoppa and Fitzgerald 2005). While dental development provides the most accurate age estimation (Ubelaker 1989), the relative completeness and preservation of the human remains as well as the general age of the skeleton (e.g., fetal, infant, child, or adolescent) in each specific case will dictate which method can realistically be employed.

Dental Development: Calcification and Eruption

The most accurate method for estimating the age of juvenile remains is an assessment of dental development, specifically calcification of the crowns and roots of developing teeth and/or eruption pattern of the teeth. Teeth not only survive extremes of heat, burial, and other physical–chemical challenges better than bone, but they also develop "over almost the whole of the juvenile age range starting in the embryonic period and nearing completion during the late adolescent and early adult period" (Scheuer and Black 2000b).

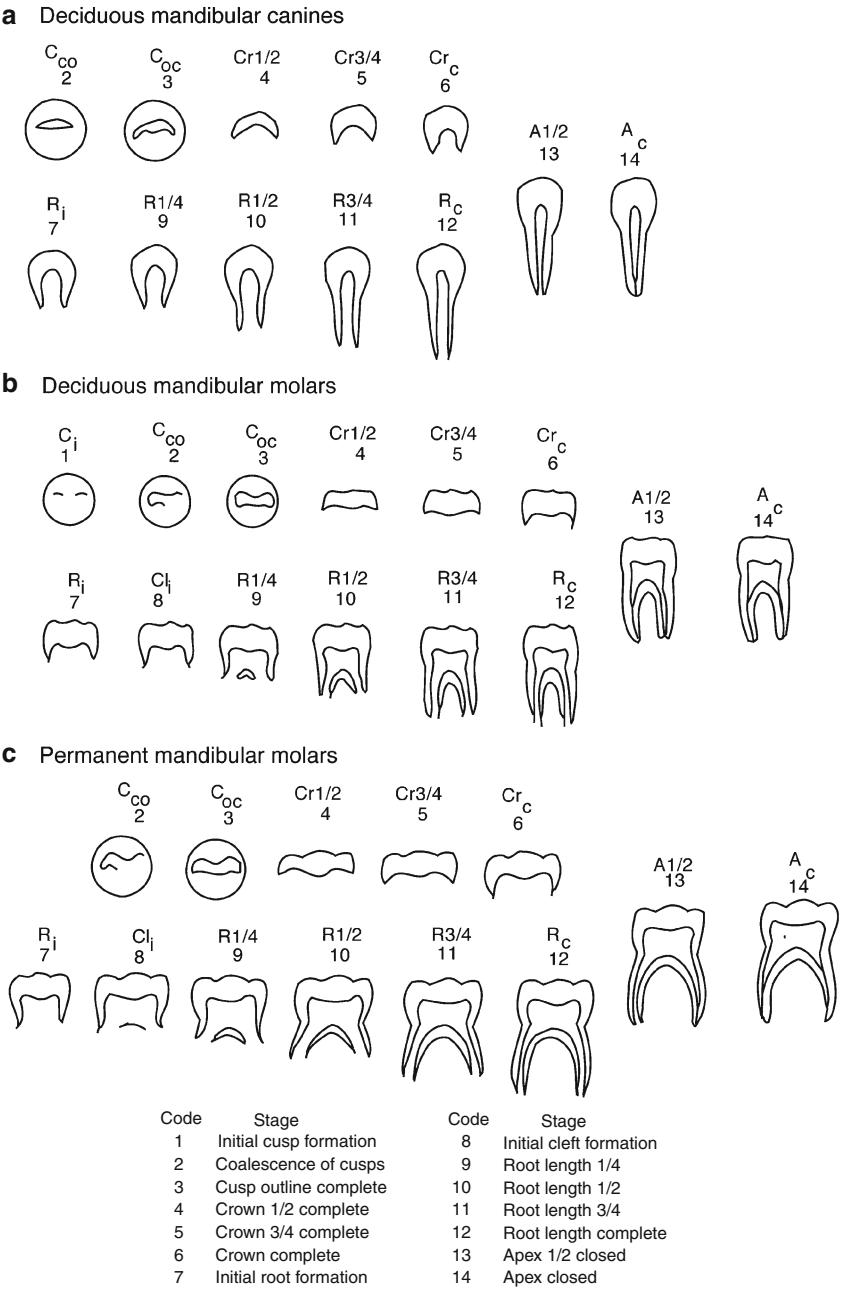
The stages of development of the dentition, from initial deposition of enamel in cusp formation to the apical closure of the root structures, have been studied for all deciduous and permanent teeth. These stages have then been equated to a known chronological age. Studies have also examined the relationship between chronological age and the eruption sequence of emerging teeth. The timing of the emergence of dentition as well as variations in timing have been documented by many researchers. The most widely used methods for providing a dental age estimate include those developed by Moorrees et al. (1963a, b), which were subsequently reworked by Smith (1991), Demirjian (1978), and Schour and Massler (1941).

Moorrees, Fanning, and Hunt examined radiographs of Ohio children from a range of socioeconomic backgrounds to derive mean age of attainment for 14 dental developmental stages of deciduous (1963a) and permanent teeth (1963b) (Fig. 36.5). Smith (1991) subsequently reworked the data developed by Moorrees and colleagues (Table 36.1). She recommended making an independent observation of each tooth and then averaging mean values representing the midpoint between the beginning and end of the stage of development. While the Moorrees, Fanning, and Hunt method has been shown to provide an estimate within 2 months of age (Komar and Buikstra 2008), more recent research which assessed the accuracy of age estimation based on the Moorrees, Fanning, and Hunt method but using CT imaging techniques showed that chronological-age estimates were systematically underestimated (Graham et al. 2010).

Demirjian (1978) developed an eight-stage system for measuring dental maturity based on a longitudinal study of children from Montreal. Despite being used for age estimation, it has been argued that the Demirjian model is not really appropriate for such estimations "because it does not allow for missing teeth" (Hillson 1996). Demirjian's (1978) method has been tested on different populations and shows a mean accuracy of ± 2.15 years for children aged 2–18 years (Chaillet et al. 2005).

Schour and Massler (1940a, b, 1941) developed a visual aid for examining the formation and eruption of deciduous and permanent dentition. However, the data used to develop the diagram was based on a relatively small number of terminally ill children whose dental development may have been affected by their condition. The data were revised by Ubelaker (1978) based on analysis of remains of Indigenous Native Americans but are widely referred to as a standard (Fig. 36.6).

Another approach to estimating dental age has been developed using measurements of teeth (dental metrics) (Liversidge et al. 1993) where the length of the tooth is correlated with known age. A comprehensive review of all aging methods involving dental development is provided by Hillson (1996) and Blenkin (2009). Many of these methods have been tested on historical archeological populations which include the remains of juveniles of known age. Such research is aimed at investigating the relationship between physiological and chronological age (Bowman et al. 1992) and whether patterns in aging have changed over time. The research results illustrate that dental calcification and eruption were similar to modern populations (Hoppa and Fitzgerald 2005).



Code	Stage	Code	Stage
1	Initial cusp formation	8	Initial cleft formation
2	Coalescence of cusps	9	Root length 1/4
3	Cusp outline complete	10	Root length 1/2
4	Crown 1/2 complete	11	Root length 3/4
5	Crown 3/4 complete	12	Root length complete
6	Crown complete	13	Apex 1/2 closed
7	Initial root formation	14	Apex closed

Fig. 36.5 Stages of formation for the crown, root, and apex of (**a**) deciduous mandibular canines, (**b**) deciduous mandibular molars, and (**c**) permanent mandibular molars. The code used by Moorrees et al. (1963a) appears above the numerical code for each stage (Buikstra and Ubelaker 1994) (Reproduced with kind permission from Arkansas Archaeological Survey)

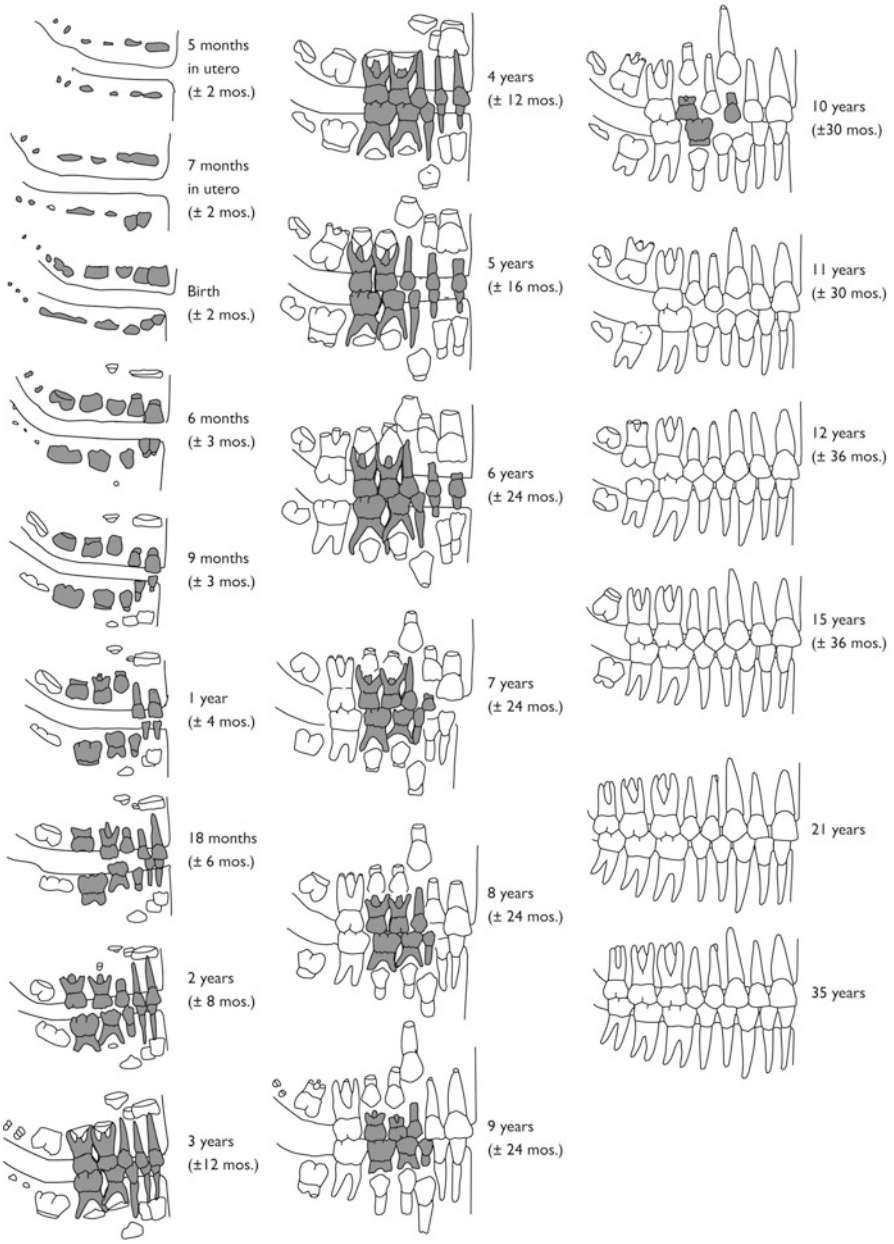


Fig. 36.6 Sequence of formation and eruption of teeth among Indigenous Americans (Buikstra and Ubelaker 1994) (Reproduced with kind permission from Arkansas Archaeological Survey)

It has been recognized that "different methods may produce different age estimates from the same material" (Hillson 1996). Consequently it is vital to assess the population upon which standards were developed before applying a single method (Case Study 2). An age estimation based upon several techniques is probably more appropriate. Ongoing research is being undertaken to understand the ways in which methods developed on one population are relevant for a geographically different population (Blenkin and Evans 2010; Celikoglu et al. 2010).

Case Study 2

On January 1, 1998, the body of an infant male was recovered from a dam in rural Victoria, Australia. Based on the circumstances of the disappearance, associated clothing, and DNA testing, the individual was identified as 14-month-old male who had been reported missing to the local police authorities six and a half months earlier on the June 15, 1997.

The de facto father of the infant was eventually charged with the murder of the boy. As part of the defense brief, it was postulated that the individual may have been abducted on the night of his reported disappearance and kept alive for months before finally being killed and disposed of in the dam. If this scenario was true, the de facto father could not have committed the crime, since he had been held in custody during this time.

Assistance was requested from a forensic odontologist to estimate the age of the infant when he died: the question was asked whether it was possible to determine if the infant was 14 months old (killed immediately after being abducted) or up to 20 months old (kept alive for some time prior to being killed). Periapical radiographs of the mandibular dentition and an occlusal radiograph of the upper anterior dentition were taken to estimate the radiographic development of the dentition and the stage of calcification and apical-root closure of the teeth (Fig. 36.7). These results were then compared to published dental literature relating to age estimation.

A number of limitations became apparent: research on age estimations of infants had focused on populations from the United States (USA), Canada, and Europe. The applicability of such research in an Australian context could not be demonstrated. The sample size of infants used in the research models was often small (41 children – Gustafson and Koch 1974). The small sample size had the potential to lead to possible statistical errors in the interpretation of results. Further, the published literature described the developmental stages of the dentition of infants in sequences of three, six and nine months. There was no literature which described the developmental stages month by month. It was therefore difficult to assign an exact month to the stage of development observed from the postmortem radiographs of infant X. Also, the published literature was relatively out of date, meaning it was difficult to determine the applicability of the techniques for a modern population.

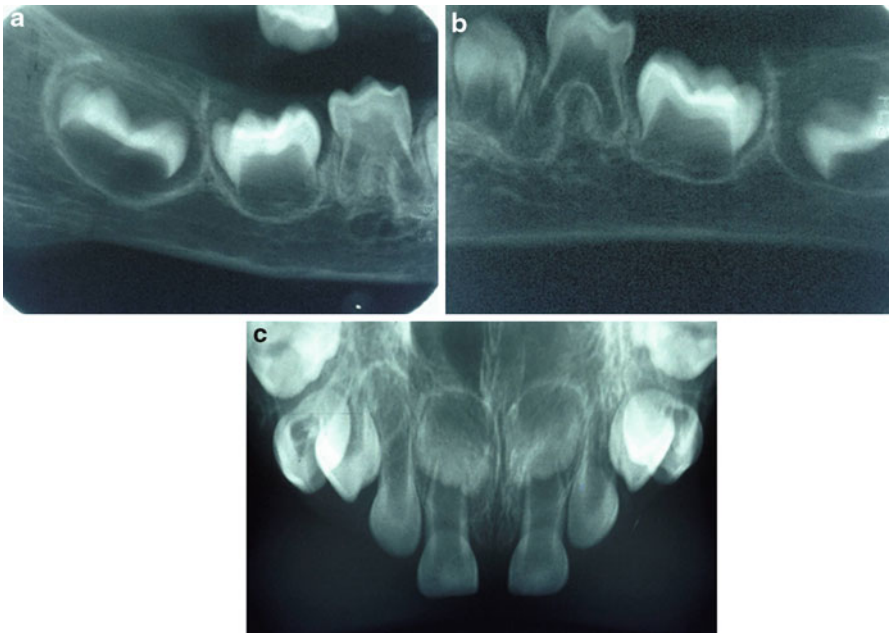


Fig. 36.7 Postmortem radiographs of the deceased infant. (**a**) Right mandible – first permanent molar crown cusps fused; second deciduous molar crown complete; first deciduous molar crown complete; root formation commenced. (**b**) Left mandible – first permanent molar crown cusps fused; second deciduous molar crown complete; first deciduous molar crown complete, root formation commenced; deciduous canine crown complete, initial root formation. (**c**) Maxilla – deciduous left and right central incisors erupted, root incomplete, and apices open; deciduous left and right lateral incisors unerupted, crown complete, root ½ formed; deciduous canines, first and second deciduous molars visible; left and right permanent incisors, crown fused

The forensic odontologist submitted a report which stated: "[U]sing a combination of published dental literature relating to radiographic developmental results and developmental survey data, I conclude that the dental age of the remains is between 12 and 16 months." While this conclusion was never tested in court, this case highlights the need to undertake detailed population-specific research on contemporary populations of juveniles.

Depending on preservation and the recovery of postmortem material, there may be cases where an age estimate cannot be provided using the dentition. Consequently, it is important to be aware of other methods that can be employed.

Phases of Bone Development

A technique employed by forensic anthropologists to estimate age involves assessing the stages of bone development: the appearance and growth of ossification centers followed by assessment of the order and timing of final fusion of the centers.

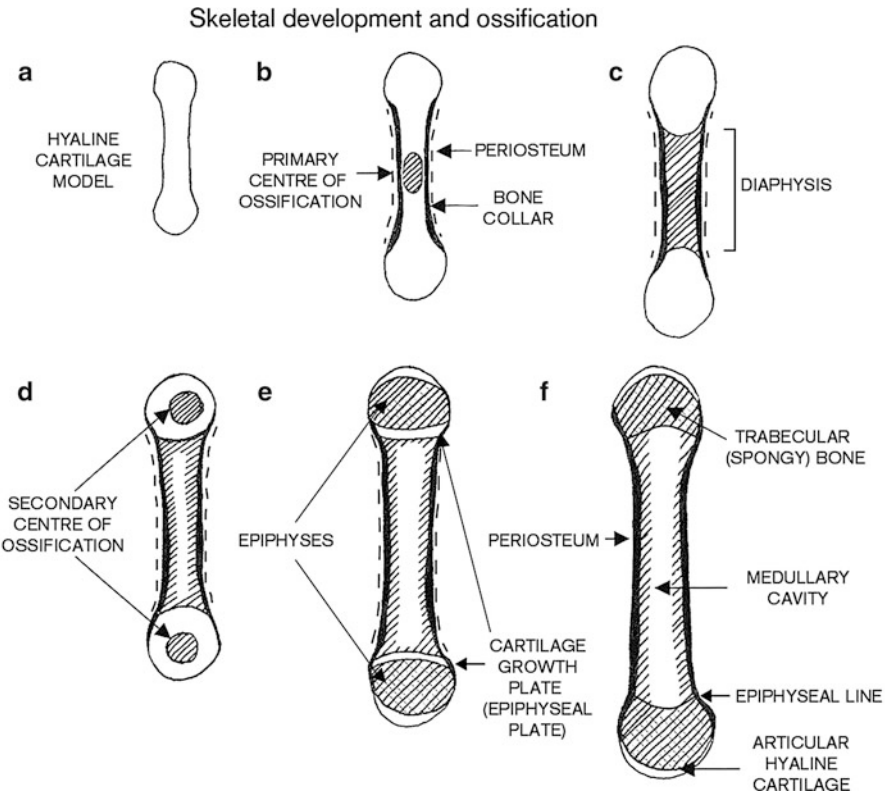


Fig. 36.8 Schematic diagram illustrating bone growth and the primary and secondary ossification centers (After Carola et al. 1992 and Lewis 2007, Fig. 4.1)

Appearance and Growth of Ossification Centers

The development of bone (osteogenesis) normally commences within the embryonic "connective tissue precursor at a constant locus, which is known as the primary centre and this expands until the cartilaginous precursor is totally replaced by bone" (Scheuer and Black 2000b) (Fig. 36.8). With the exception of some bones such as the carpals and tarsals where the initial site of ossification (primary center) occurs after birth, the majority of primary centers occur during the fetal period.

In principle, an assessment of the stage of development of ossification centers may be a reliable indicator for estimating age. However, by the 11th prenatal week, there are approximately 800 centers of bone growth, the "bony pieces" of the skeleton. Thus, the number, small size, and fragility of most of these bony structures may make recovery difficult (Byers 2005). In addition, most ossification centers do not have a distinctive morphology and can only be identified by their

anatomical position, necessitating preservation of soft tissue (Scheuer and Black 2000b). By about halfway through the development of the fetus, the ossification centers of most bones will have increased in size and therefore become recognizable to a point that they are useful for age estimations. These centers unite as the fetus grows, and at birth, there are about 450 centers (Scheuer and Black 2000a).

Fusion of Ossification Centers

Secondary centers typically appear after primary centers and can "coalesce quickly with the primary centre or develop as separate elements known as epiphyses" (Baker et al. 2005). The final phase of bone development is the fusion between one or more primary centers or between a primary center and its secondary center (Fig. 36.8). Information on the timing of the union of epiphyses is more frequently used for age estimation than data on the appearance of ossification centers. The fusion of primary centers such as those in the skull (Fig. 36.9), pelvis, atlas, and axis may be useful in aging individuals less than 10 years of age. The size and closure of the various cranial fontanelles may assist in broad-scale aging: for example, disregarding any disease process, the closure of any of the fontanelles indicates that the individual is no longer a fetus or a neonate but is significantly older.

It has also been stated that "the closure of the metopic suture on the frontal bone may distinguish a neonate from a fetus" (Weaver 1998). However, caution must be taken given that studies have shown that complete closure of the metopic suture can occur within the first year of life (e.g., 3–9 months) (Vu et al. 2001) but with normal variation may vary from birth to 8 years of age (Bademci et al. 2007).

The majority of long bones and many irregular bones develop epiphyses. While the primary centers for most bones form prior to birth, most (but not all) secondary centers appear after birth. Following the fusion of the primary centers of ossification, bone growth commences by the deposition of osseous material at the "roughened, porous, usually irregular end of an immature long bones' metaphysis" (primary center of ossification) (White 1991). Over time the epiphyses ossify within the cartilaginous joint area. There are numerous epiphyses in the human skeleton (Fig. 36.10) which have predicted age ranges at which they unite (Fig. 36.11).

Data relating to the ages at which primary and secondary ossification centers appear, develop, and fuse for each of the skeletal elements have been collected and standards developed. These standards provide reference material when dealing with individuals of unknown age. The process of ossification and epiphyseal union begins approximately 2 years earlier in females than in males. This subsequently leads to a shorter period of growth in females and is responsible for their smaller adult size. Population-specific studies undertaken on different ancestral groups, for example, using Mexican American and African males (Crowder and Austin 2005), Bosnian males (Schaefer and Black 2005), and Portuguese males and females (Coqueugniot and Weaver 2007) show considerable variation in the timing of ossification and epiphyseal fusion (Komar and Buikstra 2008).

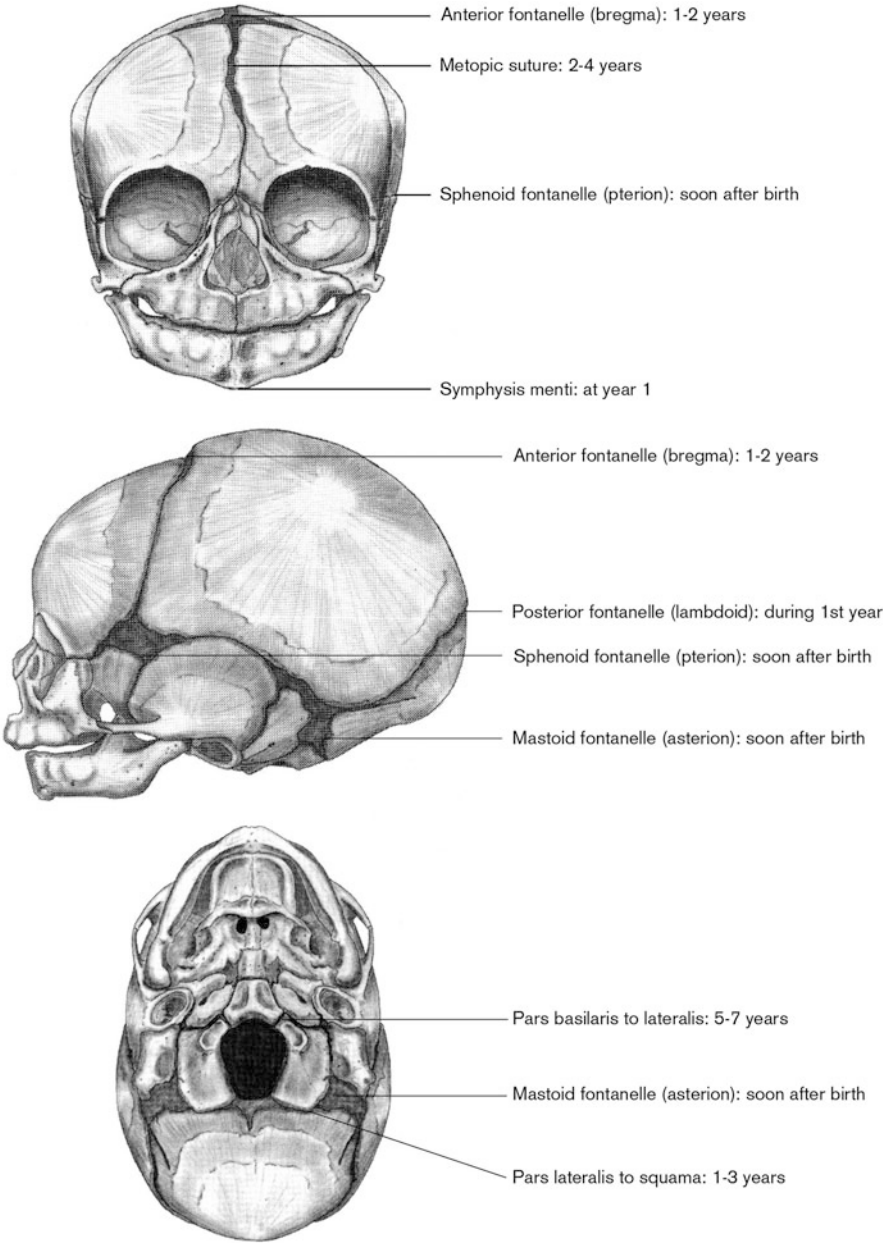


Fig. 36.9 Location and timing of complete fusion of fontanelles and sutures of the skull (After Scheuer and Black 2000a, Fig. 5.12) (Reproduced with kind permission from Elsevier publishers)

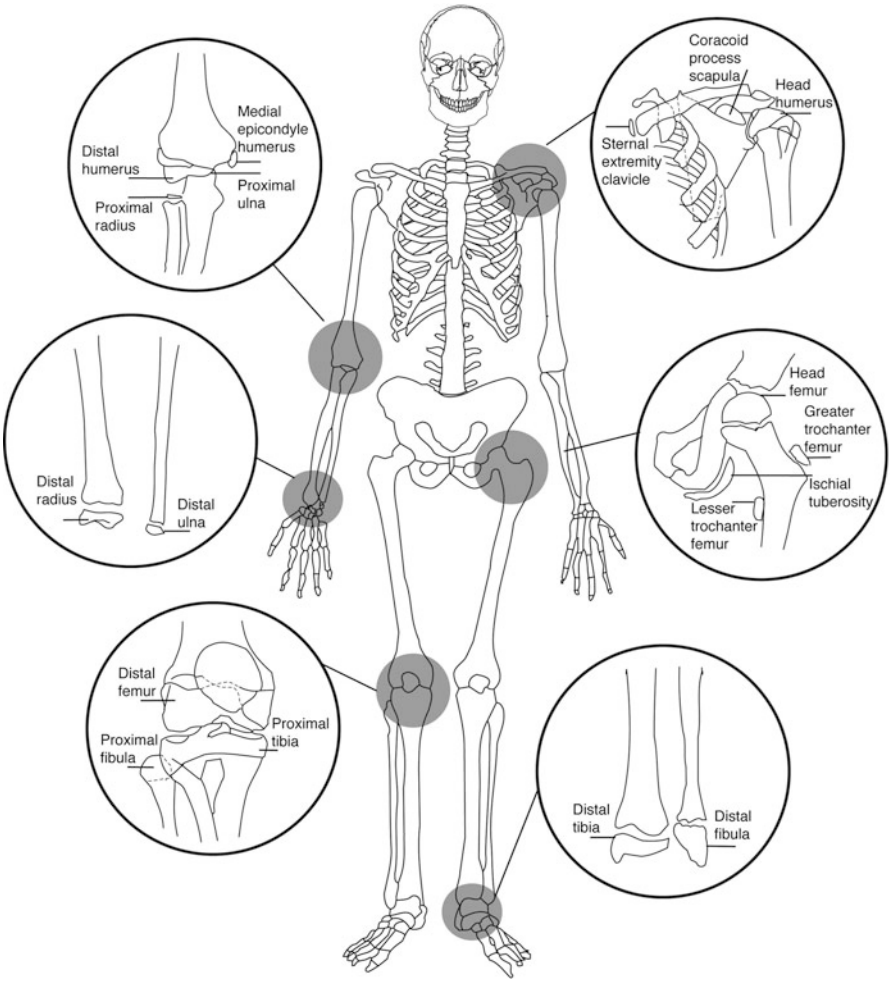


Fig. 36.10 Location of some of the epiphyses (Buikstra and Ubelaker 1994) (Reproduced with kind permission from Arkansas Archaeological Survey)

The appearance of ossification centers and the beginning of epiphyseal union occur in a sequence. For example, the order of epiphyseal union commences with the elbow and concludes with the shoulder (Fig. 36.12). There are numerous studies which document variations of this sequence (Schaefer and Black 2007; White and Folkens 2005; Buikstra and Ubelaker 1994) with mnemonics to aid memorization of the order (Barron and Branfoot 2003). A detailed summary of the age (or age range) at which ossification and fusion commences and concludes for each skeletal element is provided by Scheuer and Black (2000a) and Schaefer et al. (2009).

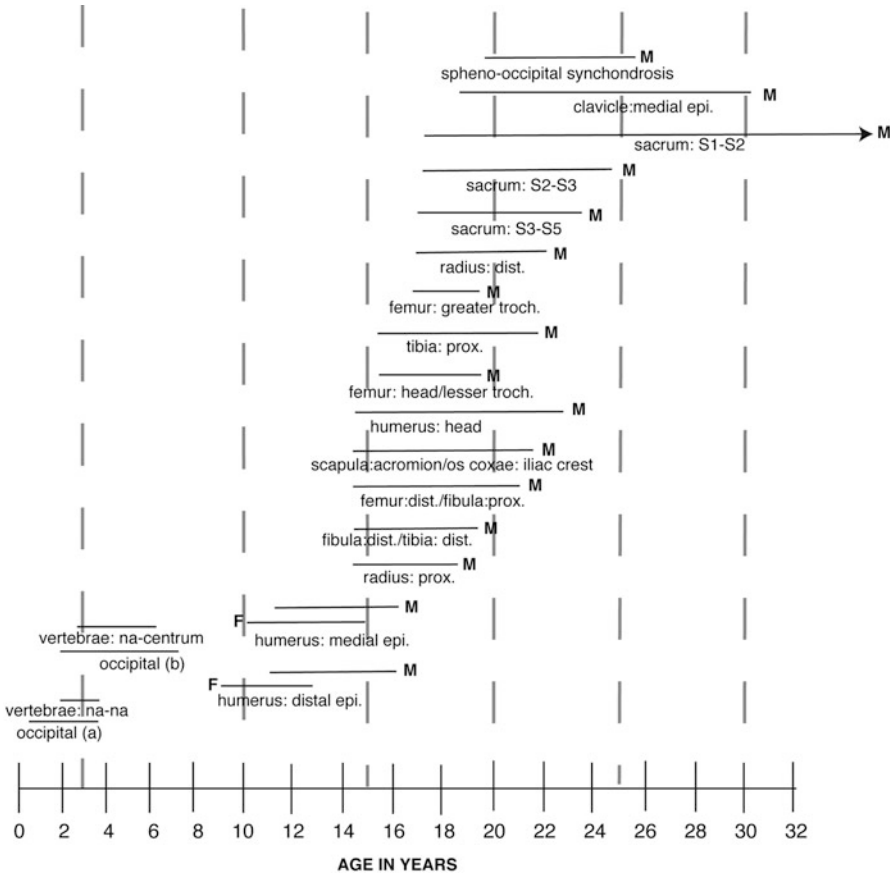


Fig. 36.11 Timing of the fusion of epiphyses for various human osteological elements. Horizontal bars indicate the period during which union/fusion is occurring. Male and female data (Buikstra and Ubelaker 1994) (Reproduced with kind permission from Arkansas Archaeological Survey)

Measurement of Bone Size and Length

In situations where the dentition has not been recovered (e.g., in cases involving very young infants or fetal remains), estimation of age at death can be attempted through the metric assessment of bone size and length (Scheuer and Black 2000a).

As with all mammals, the development of human bone length occurs through centers of ossification and epiphyses. The rate of skeletal growth is most rapid during the fetal and early postnatal period. It has been shown that there is a linear correlation between diaphyseal length and the age of the juvenile which becomes a less reliable estimator of age after birth.

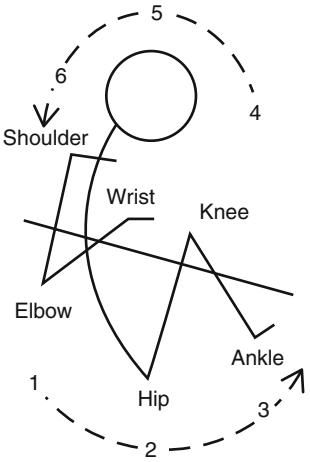


Fig. 36.12 Schematic representation illustrating the sequence of epiphyseal union (After Stewart 1979)

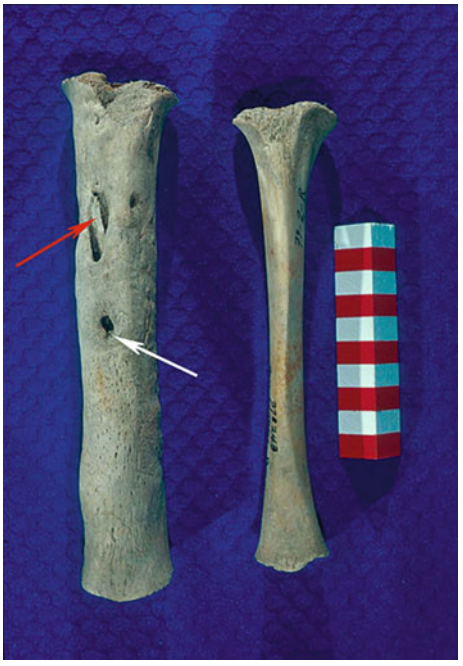


Fig. 36.13 Anterior view of left and right tibiae of a child of approximately 9 years of age. Right tibia is normal. Left tibia has osteomyelitis – note the sequestrum (*red arrow*) and cloaca (*white arrow*) (Photograph from the research slide collection of Donald J. Ortner. Reproduced with kind permission from Department of Anthropology, Smithsonian Institution, Washington, DC)

Forensic anthropologists use a technique in which a measurement of diaphyseal length is compared to the data on bone lengths of individuals of known age (Ubelaker 1989). While population-specific age changes have been identified (Hoffman 1979; Johnstone 1962), "differences in age-specific bone lengths are seen between modern and ancient populations" (Chamberlain 1994) highlighting

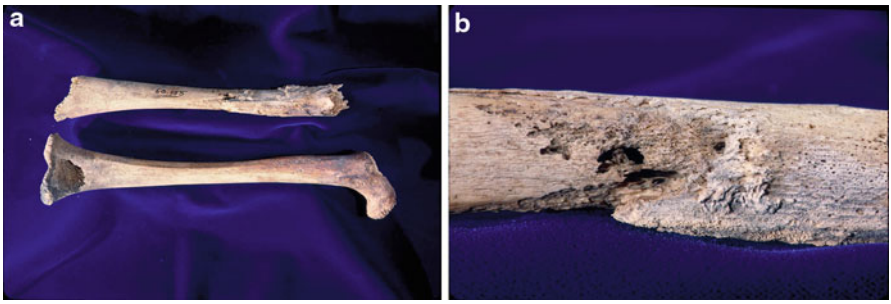


Fig. 36.14 Posterior view of left and right femora of a child of approximately 8 years of age. Left femur is normal. Right femur has osteomyelitis – note the involucrum (detailed image) (Photographs from the research slide collection of Donald J. Ortner. Reproduced with kind permission from Department of Anthropology, Smithsonian Institution, Washington, DC)

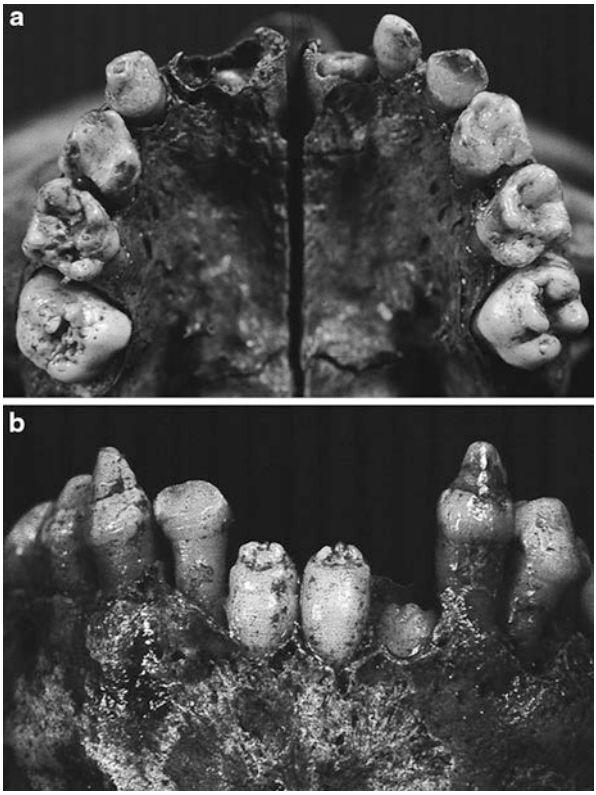


Fig. 36.15 (**a**) Enamel hypoplasia and mulberry molars in the maxillary dentition; (**b**) enamel hypoplasia and Hutchinson incisors. Dental lesions suggestive of congenital syphilis in 7-year-old child (After Lambert 2006) (Photographs reproduced with kind permission from Patricia Lambert)

the effects lifestyle and diet (nutrition) have on growth and therefore aging (Weaver 1998).

Unlike dental development which is strongly controlled by genetic rather than environmental factors (Smith 1991; Ubelaker 1989), it has been argued that

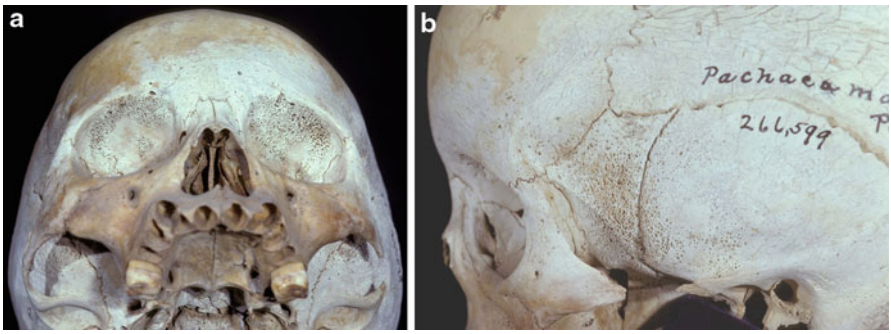


Fig. 36.16 Cranium of an 8-year-old child. View of (**a**) orbits and (**b**) left lateral cranium showing porous bone reaction indicative of scurvy (Photographs from the research slide collection of Donald J. Ortner. Reproduced with kind permission from Department of Anthropology, Smithsonian Institution, Washington, DC)

retarded bone growth results predominantly from poor maternal nutrition in the prenatal period and is not strongly affected by malnutrition of the baby itself after birth (Mays 1998; Scheuer et al. 1980). However, postnatal nutrition is certainly among a number of factors such as nutrition, socioeconomic status, urbanization, migration, physical activity, physiological stress, climate, exposure to lead, intestinal parasites, and noise pollution that have all been shown to affect bone growth (Lewis 2007).

Histological Analyses

Although less commonly used, histomorphology (traditionally used for estimating the age of adults) has been assessed for its utility in estimating the ages of juveniles. Using the rib cortex of individuals aged from 2 to 21 years, a series of developmental changes in the bone microstructure were identified that can be used to estimate age within four phases: phase 1, <5 years; phase 2, 5–9 years; phase 3, 10–17 years; and phase 4, 18–21 years (Streeter 2010). While it is argued that such techniques are useful when dealing with incomplete or commingled remains, the method has yet to be tested on individuals of known age. Such techniques are obviously destructive and require specific additional expertise. Further, due to remodeling which occurs in the growing skeleton, bone turnover is usually seen as too complex to be used for age estimations.

Estimation of Ancestry

Anthropological estimations of ancestry in adults are often seen as controversial (Tattersall 2004) because of the subjective nature of the morphological features used in the assessments. Further, in many instances an individual cannot be fitted neatly into one of the three traditional "racial" groups (Caucasoid, Negroid, and Mongoloid). Estimating ancestry based on juvenile skeletal remains is problematic

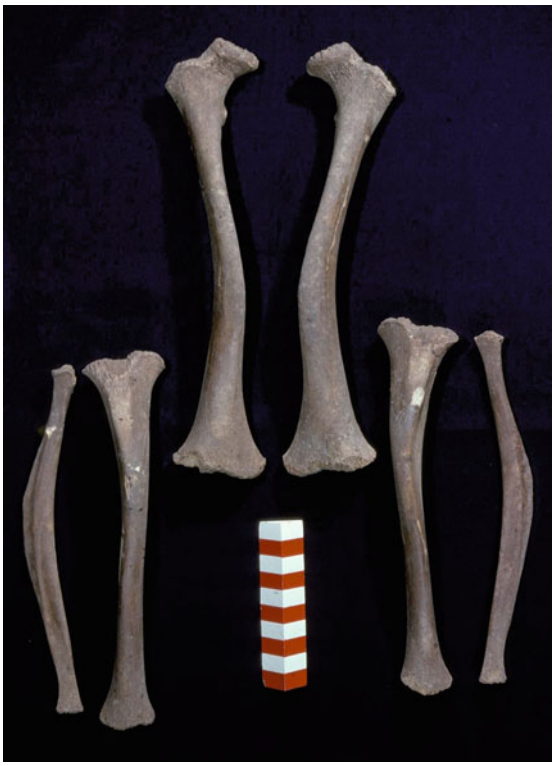


Fig. 36.17 Abnormal bowing of the femora and tibiae of a child (approximately 7 years old) indicative of rickets (Photograph from the research slide collection of Donald J. Ortner. Reproduced with kind permission from Department of Anthropology, Smithsonian Institution, Washington, DC)

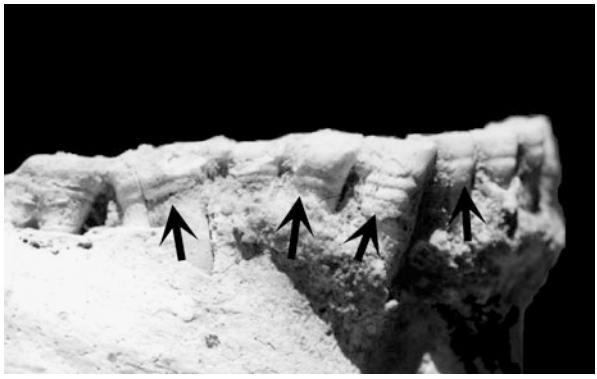


Fig. 36.18 Example of enamel hypoplasia, right adult mandible (*arrows*)

(Lewis 2007) even though ongoing research is being undertaken to test different methods (Buck and Strand Vidarsdottir 2004; Schmeling et al. 2000). Despite Kerley's claim that "race determination is usually possible in subadult skeletons" (1976), even if specific criteria could be agreed upon, many of the metric and nonmetric traits used to assess ancestry are affected by age. While Weaver stated that "many of the cranial non-metric traits that are used to infer biological affinity

[ancestry] simply would not yet have developed in fetuses and neonates" (1998), other research suggests that some cranial morphological differences between African- and European-derived fetuses can be identified (Weinberg et al. 2002).

Ancestral cranial traits observed in adults are thought by some researchers to be visible as early as 5 or 6 years of age (Tobias 1958). Such claims have been tested by research which compared juvenile remains from South Africa with those of infants of Caucasoid ancestry (Steyn and Henneberg 1997). While the study demonstrated differences between the two ancestral groups, the conclusions must be treated with caution: not only were the sample sizes small resulting in the pooling of males and females, but the South African population was an archeological collection of juvenile remains which means the ancestry was assumed (Lewis 2007).

Perhaps more useful in the estimation of ancestry of deceased juveniles is the study of the dental morphology. For example, shovel-shaped deciduous and permanent incisors are seen more frequently in individuals of Mongoloid ancestry (90 %) than individuals of Caucasoid or Negroid ancestry (15 %) (Devoto et al. 1968).

To summarize, estimation of ancestry may be problematic when dealing with adult human skeletal remains and will be more limited in cases of juvenile remains because of the influence age has on diagnostic features. In the absence of further research, it is not possible to confidently estimate ancestry of juveniles. Variables such as condition and preservation of the skeletal elements will also impact the practitioner's ability to comment on this.

Determination of Sex

> *The ability to determine the sex in the skeletons of children may be quite limited, and such determinations are often quite unreliable*. (Kerley 1976)

The biological sex (as opposed to the cultural construct of gender) of adult skeletal remains is ideally determined following an assessment of skull and pelvis morphology. Because sexual differentiation is understood to commence around the eighth (Komar and Buikstra 2008) to tenth fetal week (Weaver 1989), research has been undertaken to investigate the possibility of estimating the sex of a person from juvenile skeletal remains (Schutkowski 1993). Such research has focused on discriminant functions based on measurements of the long bone lengths (Choi and Trotter 1970); the morphology of the pelvis (Lewis 2007) specifically the ilia (Weaver 1990; Wilson et al. 2008); the fetal sciatic notch (Holocomb and Konigsberg 1995) and the auricular surface (Mittler and Sheridan 1992); the mandible (Loth and Henneberg 2001; Scheuer 2002; Franklin et al. 2006) and the size of dentition (Lewis 2007; Mays 1998; Żądzińska et al. 2008); as well as the cranial base (basicranium) (Veroni et al. 2010).

In most cases, the degree of sexual dimorphism in the skeleton is not pronounced enough to facilitate accurate methods for determining the sex of juvenile individuals, particularly for forensic cases (Hoppa and Fitzgerald 2005; Weaver 1998). Most methods fail to yield an accuracy level of 70 % (as opposed to

98–100 % achieved with techniques used to estimate the sex of adult remains) and therefore are seldom employed (Komar and Buikstra 2008; Lewis 2007). Despite acknowledged difficulties in estimating the sex from juvenile remains, research continues to be undertaken to examine, measure, and quantify the relationship between skeletal and dental morphology and sex in juveniles (Cardoso 2010).

The utility of DNA in determining the sex of juvenile skeletal remains has also been investigated. Successful results have been achieved for relatively recent cases in the coronial context (e.g., 16 years) (Yamamoto et al. 1998) as well as archeological remains greater than 1,000 years old (Stone et al. 1996). Variables such as cost and time and the fact that the process is destructive remain limiting factors in the application of DNA to determining the sex of juvenile remains.

In summary, the ability to determine the sex of an individual when dealing with juvenile skeletal remains should be assessed on a case-by-case basis taking into account the condition and preservation of the remains. In the absence of DNA analyses, morphological assessments will produce limited results because differences in the sexes are not obvious until after puberty.

Estimation of Stature

Stature estimates of unidentified adults are commonly achieved by measuring the long bones, the results of which are then used in formulae for height prediction derived from the measurements of individuals of known height. Similar methods are available for estimating stature (and body mass – Robbins et al. 2010) from juvenile bones (Telkka et al. 1962; Himes et al. 1977; Feldesman 1992; Ruff 2007). Based on equations developed from modern European Americans, it has been suggested that juvenile stature using long bone measurement is more reliable for younger ages (4–6 and 7–9 years) than estimates of older ages (13–15 and 16–17 years) (Sutphin and Ross 2011). However, the exact contributions of the cartilaginous growth plates to length and standing height are unknown due to individual variation, thus hindering height estimations for juveniles (Lewis 2007).

Skeletal and Dental Pathology

> *If we run over the various regions of the body, the brain, heart, lungs, lymphatic glands and so on, few, and those but minor, differences can be pointed out between the products of disease in the child and of the same in an adult. Some diseases are more common at one time of life than at the other; but should they overstep the limit of age usual to them, they appear in their old form, or with but slight modifications. . . . . The bones form the most notable exception to this rule*. (Goodhart and Still 1925)

There are a number of pathological conditions that may be identified through examination of juvenile remains. These include specific infections (leprosy, syphilis, rheumatoid arthritis, neoplasia), nonspecific infections (periostitis, osteitis, and

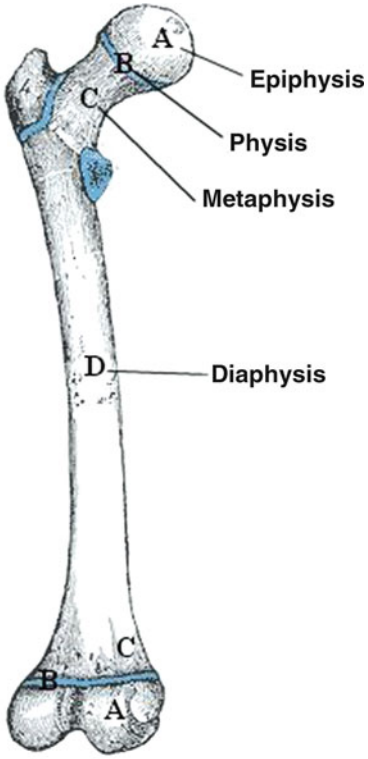


Fig. 36.19 Features of growing tubular bones (After Glencross and Stuart-Macadam 2000)

osteomyelitis), indicators of stress (e.g., enamel hypoplasia, Harris lines), trauma, metabolic diseases, and nutritional deficiencies (e.g., vitamin-D deficiencies may result in rickets or marked bowing of the long bones) and congenital conditions (Table 36.2).

The diagnosis of disease in cases of juvenile remains is influenced not only by preservation but also by the differences in mechanical properties between juvenile and adult bones (Currey and Butler 1975). The physiological and mechanical properties associated with epiphyses, physes, metaphyses, and diaphyses (Fig. 36.19) mean that juveniles are prone to particular diseases and injuries (Glencross and Stuart-Macadam 2000). For example, the rapid turnover of bone in a juvenile "means certain conditions such as rickets become more apparent as large quantities of structurally inferior new bone quickly replace the previous ossified cortex" (Glencross and Stuart-Macadam 2000); the widespread distribution of hemopoietic marrow, for example, allows for "greater dissemination of infections throughout the skeletal system" (Glencross and Stuart-Macadam 2000) and the loosely attached periosteum which is more easily stripped away from the cortex potentially leads to more obvious and widespread involvement of the bone surface

(Glencross and Stuart-Macadam 2000). However, when interpreting lesions on juvenile skeletal remains, it must be remembered that the individual was significantly immunologically compromised to develop the condition but robust enough to survive the disease into its chronic stages (Ortner 1991).

There are numerous studies describing bony changes recorded from archeological juvenile skeletal remains that have been interpreted as evidence of disease (Buckley 2000; Lewis 2000). Publications include reports of case studies giving evidence of a specific disease in an individual (multiple-bone tuberculosis in a child – Dabernat and Crubézy 2010; an unusual osteitic reaction in a young child – Anderson and Carter 1995; evidence of scurvy in infancy – Ortner and Ericksen 1997) as well as population studies that look at the prevalence of disease as a means of understanding the epidemiology of disease in the past (Lewis 2000) (nutritional stress in juveniles in Egypt – Wheeler 2012; evidence of genetic anemia in Romano-British juvenile populations – Lewis 2012).

It is vital that all skeletal and/or dental defects are fully described prior to providing an interpretation of their possible meaning. All skeletal alterations that may be pathological and/or traumatic in origin must be described in terms of location on the body and physical manifestation. This includes descriptions of

- Position in relation to anatomical landmarks
- Abnormality of shape
- Abnormality of size: bone loss, bone formation

Where possible, differential diagnoses should be provided and become particularly important in cases where preservation is poor and/or there is limited contextual information. For example, a partial cranium was recovered from a site in Uzbekistan dating to the fourth–third century BC. There was an unusual aperture observed at the bregma. While the morphology of the defect indicated this was not a postmortem lesion, interpretation of the disease or trauma process was limited as there was no associated postcranial skeleton. Therefore, a range of differential diagnoses were provided including congenital developmental defect (failure of the sutures at the bregma to fuse), a meningocele (in which the young age of the child prevented a bony ridge developing), cranium bifidum occultum, or a congenital inclusion cyst (Blau 2005).

Skeletal and Dental Trauma

Evidence of various forms of skeletal trauma in juveniles has been recorded in the archeological record (Brickley 2005; Glencross and Stuart-Macadam 2000). However, interpretation about the meaning of such trauma in terms of skeletal patterning and circumstances is drawn from information obtained from studies of clinical cases of childhood trauma (Lewis 2007; Mandelstam et al. 2003). "A major deterrent to childhood trauma studies has been the view that evidence of healed childhood injuries will be completely erased by skeletal remodeling during growth" (Glencross and Stuart-Macadam 2000).

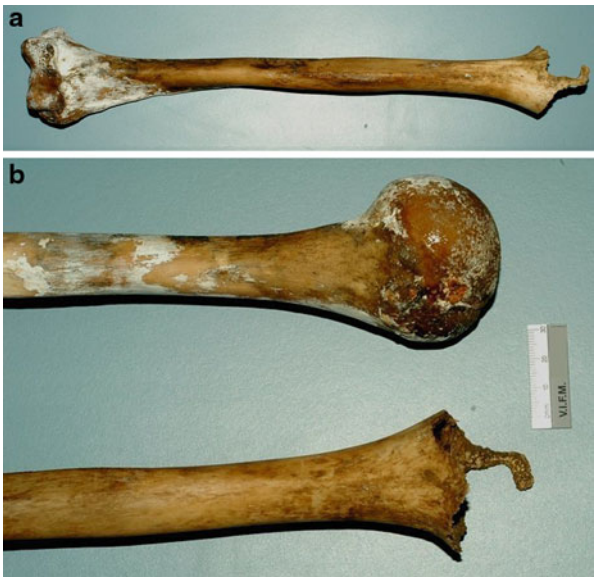


Fig. 36.20 (**a**) Adult left humerus illustrating animal scavenging of the head; (**b**) Close-up of right (*normal*) and left humeral (*scavenged*) heads (Photographs courtesy of the Victorian Institute of Forensic Medicine [VIFM])

In the clinical literature, the frequencies of specific injuries according to age are well summarized (Maguire 2010; Glencross and Stuart-Macadam 2000). In many cases injuries sustained by juveniles are separated into pre- and post-ambulatory injuries because it is argued that "[C]hildren who are not yet walking are far less likely to sustain accidental long-bone fractures" (Maguire 2010). It is also important to be aware of other disease processes (e.g., osteogenesis imperfecta or metabolic diseases) that may predispose juveniles to bone trauma.

Following a description of the location, shape, and size of possible traumatic injuries, it is the role of the forensic anthropologist to comment on evidence of repair and, where possible, on the timing of the trauma. This may be

- Antemortem: usually shows signs of healing
- Perimortem: sharp fracture margins, radiating fracture lines, straight fracture lines, fractures tend to be oblique; color of fractured edges same as surrounding bone
- Postmortem damage: animal activity (Fig. 36.20), natural actions (e.g., freezing, fluvial action, abrasion, sun bleaching, and root damage), marine exposure (e.g., bleaching, loss of bone cortex, algae or barnacles deposited), human actions (e.g., excavation techniques, trophy or souvenir remains, attempts to remove identifying features by acid or other means, religious/cultural activity such as "skull-cap bowls")

In most cases where juvenile skeletal remains are recovered, a significant amount of time has passed since burial/dumping of the body has occurred (Steadman et al. 2009). Differentiating peri- from postmortem trauma in such cases is paramount (Ubelaker and Montaperto 2011).

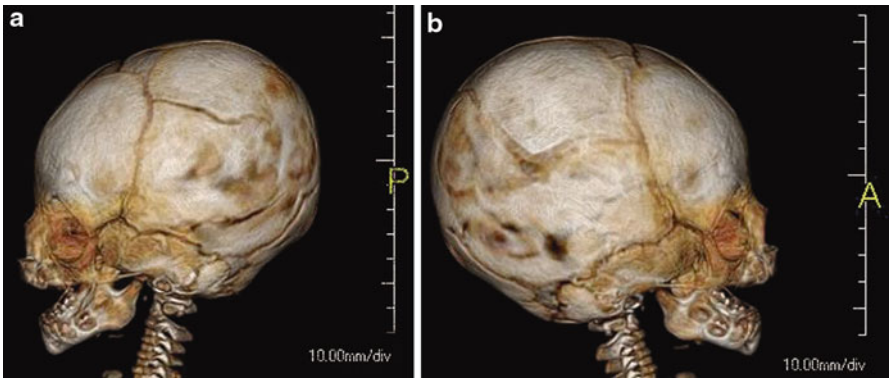


Fig. 36.21 Multiplanar reconstruction of left and right lateral views of the skull of a three-month-old child showing evidence of bilateral os parietale divisum (divided parietal bone) (Images courtesy of the VIFM)

In addition to interpretation of timing of a traumatic event, understanding the mechanism that results in the traumatic lesion is important. The mechanisms of skeletal injury can be broken up into two categories:

(a) High-energy trauma, for example, motor-vehicle accidents (whether occupant, pedestrian, or cyclist) or high-velocity gunshot wounds, and
(b) Moderate- to low-energy trauma resulting from lesser kinetic forces, for example, accidental falls, intentional child abuse, and some sport/recreational injuries

Where possible, interpretation of the manner of trauma (e.g., accidental versus child abuse) is undertaken, ideally in conjunction with a medical expert (e.g., pathologist and/or radiologist).

It is also important to be aware of conditions such as congenital variations that may mimic trauma. For example, in the case of a sudden death of a three-month-old child, the possibility of skull fractures was raised following the examination of radiographs. The forensic pathologist found no evidence of intracranial injury or histological features to suggest these were fractures. A reexamination of the remains showed the "fracture lines" were actually an accessory parietal suture (os parietale divisum – divided parietal bone) (Fig. 36.21). Although such variations are extremely rare (Becker et al. 2005), the importance of the implications of misinterpreting anomalous sutures (i.e., the false accusation of child abuse) has been noted in the literature (Tharp and Jason 2009).

Conclusions about the meaning of skeletal trauma have some of the most serious implications in suspected child abuse. Therefore, it is of paramount importance to fully describe then interpret skeletal changes, provide a differential diagnosis, and take into account any available contextual information. For example, skeletal evidence of nutritional deficiencies alone may not have any meaningful significance. However, in the context of such evidence where individuals are recovered from a mass grave, the skeletal changes may show signs of long-term child abuse (Ortner 2008).

Table 36.3 Summary of skeletal and dental alterations associated with child abuse although not diagnostic (after Buckley and Whittle 2008)

Injury	Age of victim	Mechanism of injury	Skeletal manifestation	Perimortem appearance	Antemortem appearance	References
Cranial fracture	Any	Blunt force impact (compression)	• Multiple fractures and bilateral injuries that cross sutures • Asymmetric • Basilar fractures (complex, stellate, or depressed) • Growing fracture (i.e., wide linear instead of a simple linear fracture)	• Fracture lines (radiating or concentric) • Breaks have sharp, jagged, irregular edges • Hematoma staining may be apparent at the fracture site • Cranial bone displacement along suture lines	• Evidence of healing • Blunting of fracture edges • Breaks have rounded edges porosity indicating bone remodeling	Crist et al. (1997) Carty (1999) Reece and Sege (2000)
Rib fracture (first rib considered most severe)	Any, but predominantly <1 year	Anterior-posterior thoracic compression (during violent shaking) or via direct blunt force trauma	• Fracture at the costovertebral angle • Fracture at costochondral junction • Fractured angle of rib • Bilateral	• Jagged and irregular fracture margins	• Callus formation 1–2 weeks post-trauma	Betz and Liebhard (1994) Bullock et al. (2000) Walker (1997) Wilber and Thompson (1998) Ubelaker and Montaperto (2011)

Scapular fracture	Any	Blunt force trauma (compression)	• Compression fracture of scapular blade • Fracture of acromion or coracoid processes • Fracture of scapular spine	• Visible fracture lines with irregular and sharp margins • Potential displacement of fractured bone	• Blunt fracture margins • Callus formation • Remodeling and porosity. may have disfigurement if callous forms without realignment of fracture	Carty (1993)
Clavicular fracture (acromial end)	Any	Blunt force trauma, compression, torsion, bending forces	• Oblique, greenstick, or linear fracture		• Callus formation	Brogden (1998) Resnick and Goergen (2002)
Vertebral fracture	Any	Hyperflexion and extension of vertebrae due to violent shaking	• Usually thoracic-lumbar fractures • Fracture of neurocentral synchondrosis • Anterior or posterior subluxation of vertebrae	• Malalignment of vertebral bodies • Irregular and sharp fracture lines		Vialle et al. (2006)
Phalangeal fracture	Nonambulatory infants	• Twisting, pulling, or compression force • Crushing digits	• Linear, oblique, or spiral fracture	• Sharp fracture boundaries, jagged and irregular • Bone displacement		Brogden (1998) Thompson (2005)
Long-bone fracture (particularly	Any, commonly <3 years	• Twisting, pulling, bending, or shearing forces • Falling awkwardly	• Linear, spiral, or oblique fractures • Proximal or distal metaphyses:	• Sharp fracture boundaries, jagged and irregular • Bone displacement	• Evidence of healing • Blunting of fracture edges	Brogden (1998) Carty (1999) Kleinman et al. (1995)

(*continued*)

Table 36.3 (continued)

Injury	Age of victim	Mechanism of injury	Skeletal manifestation	Perimortem appearance	Antemortem appearance	References
femur, tibia, and humerus)		• Warding off blows • Child pulled forcefully • Shaking with limbs hanging	separation of metaphysis from epiphyses may not be apparent macroscopically but histological examination shows corner fractures through metaphysis • "Bucket-handle" lesions at corners of metaphyses (radiological feature) • Mid-diaphysis • Greenstick fractures	• Difficult to view, no callus is formed through the growth plate	• Callus formation • Breaks have rounded edges • Porosity indicating bone remodeling	Mann and Rajmaira (1990) Schwend et al. (2000) Thomas et al. (1991) Thompson (2005)
Subperiosteal lesions	Any	• Blunt force trauma causing subperiosteal bleeding • Acceleration/ deceleration forces • Repetitive trauma • Rough handling	• Rough areas of new bone deposition • Raised bone • Porous bone • Delineated margins • Symmetrical lesions	• Porous lesions, vascular in appearance • Defined margins	• Rounded margins integrating into cortex • Lessened porosity indicating bone remodeling	Walker (1997) Carty (1999)
Dental changes	Any		• Caries, abscess, calculus		• Poor oral health	Greene et al. (1994)

Traumatic changes to the skeleton which may be interpreted as evidence of child abuse have been described and summarized in the literature (Abel 2011; Maguire 2010; Walker 1997) (Table 36.3). However, caution should be taken in making an interpretation of child abuse "on the basis of a few broken bones" (Kerley 1978).

Forensic anthropology and odontology practitioners see relatively few cases of fully skeletonized juvenile remains with traumatic injury (Ubelaker 1987; Kerley 1978). This is probably due to the fact that homicides involving juveniles account for only 8–14 % of all homicide cases (Yarwood 2004). For example, data collected between 1989 and 1993 on homicides in Australia illustrated that around 8.5 % of all homicides in that time period involved juveniles (Strang 1996). Other research shows similar figures for Australia: "In the 15 years between 1987 and 2001, 437 Australian children aged less than 15 years were victims of homicide, accounting for 1.5 % of all child deaths and 9 % of all homicides" (Nielssen et al. 2009). However, these percentages are higher than those from countries such as the USA where juvenile homicides comprise less than 1 % of all murders, due partly to the much higher numbers of adult homicides (Morton and Lord 2002).

The exception to this is investigation of cases of political, religious, and/or ethnic violence where juveniles have been specifically targeted (Lewis 2007). For example, a total of 143 individuals were recovered from El Salvador following the El Mozote massacre (1981), of which 136 (i.e., 95 %) were children whose mean age at death was 6 years (Annan 2008). In death investigations following periods of political violence in Guatemala, 20 % of all "arbitrary executions" were children (Lewis and Flavel 2006).

Conclusion

Variables such as the state of preservation of remains, the amount of material recovered, and the relative age of the deceased individual influence the detail of information that the forensic anthropologist and/or odontologist can deduce from the examination and analysis of remains. While specifics about the juvenile individual's ancestry, sex, and stature remain limited, information about the individual's age and health status may be ascertained. Such data can be useful in the establishment of the identification of a deceased juvenile, in separating juvenile from adult, or infant from child commingled remains, and in providing information about the possible manner of death. In addition, forensic odontologists and anthropologists may play a role in the estimation of age and interpretation of bite marks in clinical cases involving living juveniles.

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Ancillary Studies and Dissection Techniques in the Pediatric Autopsy

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Richard M. Conran and J. Thomas Stocker

Contents

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Abstract

This chapter discusses various techniques such as photography, radiology, postmortem chemistry, and genetic testing that are helpful in documenting disease and elucidating the cause and manner of death. As with any premortem laboratory test, correlation with clinical history, development of reference ranges, and factors interfering with the test that generate false positives and negatives are the responsibility of the pathologist performing the autopsy and the laboratory performing the test. Several anatomical dissections that serve as an adjunct to the standard autopsy critical in elucidating the cause of death are also illustrated.

Introduction

As an adjunct to the standard autopsy discussed in ▶ Chap. 3, "The Pediatric Autopsy," a number of techniques are helpful in documenting disease and elucidating the cause and manner of death.

Photography

Documentation of pathological findings and injuries is an inherent part of any forensic autopsy. Case and/or autopsy number (case identification) and a standard ruler should be included in photographs along with a color scale. Areas of suspected trauma along with nontraumatic areas should be photographed for comparison. In addition to general overviews, photographs that focus on specific lesions should be taken. Drapes can be used to eliminate distractions, such as chest tubes or intravenous lines, from the lesion(s) at the time of photography. Draping is effective in focusing photography on the site of injury and excluding extraneous features a jury may find offensive, therefore minimizing their exclusion as evidence in a legal proceeding. Critical in cases with developmental anomalies are images of the anomaly that can be shared with clinical consultants to reach the correct diagnosis. Quality images are also important in cases of possible malpractice alleging disfigurement of the body. Documentation that the incisions made were within the standard of care and that there was no body disfigurement that precluded viewing of the decedent may avoid a lawsuit ("Lashbrook v. Barnes," 1969). Selection of cameras, lenses, and different photographic techniques as well as specimen preparation has been detailed by Finkbeiner, Ursell, and Davis (2009a). Digital photography facilitates good-quality images (Belanger et al. 2000).

Radiology

Postmortem radiology as discussed in ▶ Chaps. 15, "Evaluation of Pediatric Fractures at Autopsy," and ▶ 20, "Neuroimaging of Pediatric Inflicted Injury" is important in documenting skeletal, visceral, and central nervous system (CNS) injuries. It also plays a role in documenting skeletal anomalies in chromosomal and nonchromosomal syndromes, such as pathological and/or traumatic fractures in osteogenesis imperfecta due to defects in type 1 collagen (Cole and Dalgleish 1995; Lamptey et al. 2009; Solopova et al. 2008). Whole-body skeletal surveys are easily performed and are preferable to a "babygram". The computed tomography (CT) scan and magnetic resonance imaging (MRI) have also been utilized (Patriquin et al. 2001).

Postmortem Chemistry

Carbohydrates, nitrogenous compounds, electrolytes, lipids, proteins, bile pigments, enzymes, vitamins, and hormones can be analyzed with variable degrees of accuracy postmortem (Coe 1993; Palmiere and Mangin 2012a, b; Uemura et al. 2008). Toxicological analysis of postmortem specimens for therapeutic drugs and drugs of abuse and poisonings is discussed in ▶ Chap. 29, "Pediatric Toxicology". Application of different test results as they pertain to specific disease states in children is discussed in ▶ Chap. 30, "Pediatric Natural Deaths" on natural deaths in children. Routine specimens obtained postmortem for chemical analysis include blood, serum, vitreous fluid, bile, cerebrospinal fluid, and urine. Interpretation of results needs to take into account several postmortem factors (postmortem interval, specimen source, method of collection, collection media, and instrumentation) which can influence the results. Furthermore, values reflected in the literature may vary due to differences in instrumentation (Coe and Apple 1985).

Vitreous Humor

Vitreous humor is an excellent specimen for the postmortem analysis of electrolytes, glucose, ketones, and some drugs. Vitreous humor fluid can also be analyzed after embalming. Embalming fluid contains formaldehyde, glutaraldehyde, perfume aldehydes, EDTA, germicides, and volatiles such as methanol and phenol. A separate sample of the embalming fluid should be sent with the vitreous fluid to the laboratory for correlation if needed. A sterile 15–18-gauge needle is inserted through the lateral canthus 4–6 mm posterior and lateral to the junction between the cornea and sclera. Fluid is gently aspirated to avoid ocular-tissue contamination and placed in a small sterile tube free of anticoagulant and preservative. Approximately 4–5 mL of fluid can be aspirated from each eye (Collins 2010). In infants

approximately 1 mL can be aspirated from each eye. Variation in electrolyte content does not differ significantly between eyes (Thierauf et al. 2009). Due to variation in methodology among laboratories, reference ranges for each analyte are calculated by the laboratory performing the tests (Thierauf et al. 2009; Coe and Apple 1985).

Electrolytes

Serum electrolytes undergo changes postmortem and do not reflect premortem values. Vitreous fluid, as mentioned above, is the best fluid to analyze electrolytes postmortem. Different electrolyte profiles have been outlined for specific conditions (Boulagnon et al. 2011; Coe 1969, 1977, 1993; Coe and Apple 1985; Thierauf et al. 2009):

Dehydration pattern: Characterized by increased vitreous sodium, chloride, and urea nitrogen

Uremic pattern: Characterized by marked increase in vitreous urea nitrogen and creatinine levels without substantial increases in sodium and chloride

Low-salt pattern: Characterized by low sodium, chloride, and potassium levels less than 15 mEq/L

Decomposition pattern: Characterized by low vitreous sodium and chloride levels with a high potassium level

In adults, postmortem vitreous potassium levels have also been reported as an adjunct in estimating the postmortem interval and therefore estimating the time of death (Boulagnon et al. 2011; Thierauf et al. 2009; Prasad et al. 2003; Munoz et al. 2006). Measurement of vitreous calcium, magnesium, phosphates, and sulfates is of limited value (Coe 1993).

Glucose

Postmortem analysis of glucose should be performed on the vitreous fluid since glycolysis continues postmortem affecting the serum glucose levels. CSF and urine are useful where vitreous fluid is not available (Coe 1993; Palmiere and Mangin 2012a).

Premortem, the diagnosis of diabetes mellitus is based on measurements of serum glucose, serum glycosylated hemoglobin (HbA1c), and urine glucose. Postmortem vitreous fluid glucose levels >200 mg/dL are consistent with diabetes mellitus. Ketoacidosis, a complication of type 1 diabetes mellitus, is a recognized cause of death. Vitreous-fluid analysis demonstrating an elevated glucose plus the presence of ketone bodies supports a diagnosis of ketoacidosis (Coe 1993).

The diagnosis of hypoglycemia is more difficult to make due to postmortem decrease in glucose levels. A normal vitreous-fluid glucose level argues against hypoglycemia.

Nitrogenous Compounds

Postmortem urea nitrogen can be measured in the vitreous fluid and reflects premortem levels (Palmiere and Mangin 2012a). Values >100 mg/dL are a good indication of renal disease or acute renal failure, such as secondary to shock (Uemura et al. 2008). The postmortem value of other nitrogenous compounds

(nonprotein nitrogen, ammonia, amino acids, creatine, glutamine and oxypurines) in serum in determining the cause of death is limited due to postmortem increases (Coe 1993). Creatinine levels can also be measured in the vitreous postmortem. However, the interpretation of creatinine levels is more problematic as an indicator of renal failure; several studies suggest that there are no changes postmortem (Coe 1993), while others suggest postmortem increases (Uemura et al. 2008).

Urine

Urine is easily obtained by aspirating the bladder with a syringe and placing the aspirated urine into a red-top tube or container free of anticoagulant. Alternatively, compressing the bladder at autopsy and collecting the expressed urine from the urethra is another method. Urine is used for alcohol and drug screens and dipstick-chemistry testing.

Cerebrospinal Fluid (CSF)

CSF is best obtained in young children by a cisternal puncture, placing the child in a prone position with the neck flexed and a block under the chest. A sterile 12-gauge needle is directed in an anterior–inferior direction in the midline beneath the occiput toward the nasal bridge, perforating the atlantooccipital membrane and the cisterna magnum. Aspirated fluid is placed into a sterile tube free of anticoagulant for chemical analysis and/or culture. Alternatively, CSF can be aspirated from the lateral ventricle after the calvarium has been removed, the dura reflected, and the hemispheres separated. A larger volume of CSF is obtained from the above two methods compared to an L3–L4 lumbar puncture.

Blood and Serum

For some analytes, variations have been reported depending on whether the blood specimen is obtained from the right or left cardiac ventricle or a peripheral vessel, such as the femoral or subclavian vein. Numerous data indicate that peripheral venous samples are preferable and better reflect premortem levels. A blind cardiac puncture is unacceptable, and a mixed pool of blood from several sources should be avoided (Coe 1993; Gilbert-Barness and Debich-Spicer 2005). The type of collection tube or container used depends on which analytes and specimens are being tested. For instance, sterile red-top tubes free of anticoagulant or a serum separator tube are used for the analysis of enzymes, proteins, viral antibodies, and lipids. A gray-top tube containing sodium fluoride preservative is preferred for toxicology. Whole blood in a tube with an anticoagulant such as EDTA is a good specimen for DNA analysis and hemoglobin electrophoresis.

Lipids

Serum cholesterol appears to be stable in the initial postmortem period, and measurements correlate with premortem levels, although some studies have reported variation in levels postmortem (Palmiere and Mangin 2012b). Cholesterol measurement has a role in evaluating possible cases of familial hypercholesterolemia (Coe 1993). Triglyceride and lipoprotein levels fluctuate during the postmortem period and are difficult to interpret. Many variables, including an underlying fasting state, affect the levels.

Proteins

Serum total protein and albumin levels reflect premortem levels in the early postmortem period. Electrophoresis of proteins has been shown of value in the diagnosis of plasma-cell dyscrasias, agammaglobulinemia, and hemoglobinopathies.

Specific serum-protein measurements that may be of value postmortem are HbA1c, C-reactive protein (CRP), troponin, and Interleukin-6. HbA1c is a marker for chronic glucose exposure and is extremely stable postmortem; it is helpful in the evaluation of postmortem ketosis and in the diagnosis of diabetes mellitus regardless of the cause of death (Palmiere and Mangin 2012a; Uemura et al. 2008). CRP, an acute-phase reactant, is a marker of inflammation and may play a role in distinguishing natural from accidental deaths (Palmiere and Mangin 2012b; Fujita et al. 2002; Uemura et al. 2008; Uhlin-Hansen 2001). Serum troponin, a marker of myocardial injury, is elevated in cases of myocardial ischemia/hypoxia (Palmiere and Mangin 2012b; Zhu et al. 2006a, b, 2007). Interleukin-6, a proinflammatory cytokine, has been reported as a marker for distinguishing between sepsis-related and non-sepsis-related deaths (Palmiere and Mangin 2012b; Tsokos et al. 2001a).

Bile Pigments

Bile pigments can be measured in postmortem serum, although these levels do rise after death. Total bilirubin levels show a mild but not significant increase from premortem levels (Uemura et al. 2008). Of note, urobilinogen is stable in the urine postmortem.

Enzymes

Many enzymes, including liver enzymes, are elevated in postmortem serum due to cell autolysis and therefore do not reflect premortem levels (Palmiere and Mangin 2012b). However, cholinesterase levels, useful in the evaluation of organophosphate poisoning, remain stable postmortem even when refrigerated. An elevated serum tryptase is useful in the investigation of anaphylaxis and death (Palmiere and Mangin 2012b).

Hormones

Hormones, such as prolactin, growth hormone, thyroid-stimulating hormone, luteinizing hormone, and cortisol, measured in the postmortem serum reflect premortem levels. Epinephrine, norepinephrine, thyroxine and triiodothyronine

may vary in the postmortem period, so caution is advised when interpreting these results. The postmortem level of parathyroid hormone is similar to or slightly increased from the premortem level. Elevated procalcitonin levels postmortem may indicate sepsis (Palmiere and Mangin 2012b; Tsokos et al. 2001b). A very high serum-insulin level suggests insulin overdose. An elevated postmortem serum insulin level with a drop in the C-peptide level is suggestive of exogenous insulin administration (Palmiere and Mangin 2012a).

Metabolic Disorders, DNA, and Cytogenetics

A large number of metabolic conditions are lethal. Postmortem chemistry and other ancillary studies are critical for the diagnosis. Metabolic disorders and cardiac channelopathies are discussed in ▶ Chaps. 31, "Cardiac Channelopathies and the Molecular Autopsy" and ▶ 34, "Pediatric Metabolic Diseases" and have been reviewed by others (Ackerman 2009; Ackerman et al. 2001; Edwards 2005; Michaud et al. 2009; Oliva et al. 2005; Pleger and Koch 2005; Tester and Ackerman 2006). Treated cards for metabolic panels are available for testing of blood. Blood spots of fresh whole blood on filter paper may also be analyzed. If possible, body fluids (blood, urine, bile, cerebrospinal fluid, vitreous fluid) and tissues (brain, heart, kidney, spleen, skeletal muscle, liver, spinal cord, peripheral nerve) need to be collected as soon as possible after death, ideally within 2 h. Tissue samples should be placed in plastic tubes/vials and snap-frozen with isopentane and stored at −70 °C. Tissue fragments, preferably fascia lata, should also be placed in sterile transport media, provided by most laboratories, for fibroblast culture. Fibroblasts can be used for chromosomal analysis, evaluation of enzyme deficiencies, and other studies (Meske et al. 1999, 2005; Yamamoto et al. 2012). Enzymatic activity in fibroblast cultures obtained up to 48 h postmortem reflects antemortem activity. Frozen tissue samples can also be used for molecular studies and enzyme histochemistry as needed. Samples of brain, heart, spleen, skeletal muscle, liver, and kidney can be processed for electron microscopy using standard protocols. Postmortem imaging should also be included as part of the metabolic autopsy and microbiological cultures obtained as needed (Gilbert-Barness and Debich-Spicer 2005).

Genetic Testing

In cases of suspected chromosomal abnormalities, metabolic syndromes, and cases with fetal malformations, chromosomal analysis/genetic testing should be performed.

Karyotyping

Traditionally, karyotyping has been utilized to demonstrate the overall pattern of chromosomes and chromosomal abnormalities. Standard techniques separate chromosomes based on number, centromere position, and banding pattern. Trisomies, sex

chromosomal disorders, gene rearrangements, and cases with prominent mosaicism are reliably detected with routine analysis of blood. Microdeletion syndromes, single-gene disorders, some chromosomal gains and losses, and subtle mosaicism are not detected by routine chromosomal analysis. High-resolution chromosomal analysis is more sensitive in detecting such subtle variations (Jarzembowski and Hill 2011).

Metaphase analysis of lymphocytes harvested from blood is the preferred method for cytogenetic analysis when uncontaminated and unclotted blood is obtained within 12 h postmortem. In newborns, placental cord blood is an acceptable alternative. Harvested cells are typically stained with phosphate-buffered Giemsa to produce G-banded chromosomes that are examined under a microscope and arranged in a standard format based on size, centromere location, and banding pattern. Other banding techniques (R-banding and C-banding) are available to detect subtle variations. The reference laboratory performing the chromosomal analysis should be contacted for submission requirements. Generally, approximately 3–5 mL of sterile unclotted blood is collected in a sodium heparinized (green-top tube) tube and transported at room temperature to the laboratory. EDTA (lavender-top tube) may also be used as an anticoagulant, but heparin is preferred. Frozen specimens are unacceptable.

In autopsy cases where blood is not available, tissue fibroblasts are a viable source. One-cm^3 tissue fragments should be placed in Hank's balanced salt solution or Ringer's solution, RPMI (Roswell Park Memorial Institute) media, or other sterile cell-culture media containing antibiotics, refrigerated, and transported to the laboratory. Cells are harvested by several methods, stained, and examined for abnormalities (Meske et al. 1999, 2005; Yamamoto et al. 2012; Buys et al. 1982; Wray and Stubblefield 1970). In cases with no cell growth, chromosomal microarray analysis can be performed (Jarzembowski and Hill 2011).

Fluorescence In Situ Hybridization (FISH)

FISH is a technique that employs a fluorescent-labeled oligonucleotide probe that is hybridized to a specific DNA or RNA sequence of interest. The technique is useful in detecting abnormalities in chromosome number, chromosomal translocations, amplifications, and gene deletions. Formalin-fixed paraffin-embedded tissue sections, 4–5 μ in thickness, are suitable for analysis. Tissue that has been fixed in formalin for less than 12 h is preferred as longer fixation times may diminish hybridization with gene-specific probes. Blood samples preserved with sodium heparin can be used. Alternatively 1-cm^3 tissue fragments placed in a sterile container containing Hank's balanced salt solution, Ringer's solution, or RPMI media and then refrigerated can be transported to the reference laboratory for analysis.

Polymerase Chain Reaction (PCR)

PCR is a technique that takes a sequence of DNA that is of interest and amplifies it through a series of steps of denaturation, annealing, and elongation to yield thousands to millions of copies of the specific sequence. PCR is an extremely sensitive

technique that allows identification of chromosomal abnormalities including gene fusions, deletions, polymorphisms, and point mutations in individual genes. PCR is also helpful in the identification of inborn errors of metabolism. DNA extracted from fresh autopsy tissue and preserved in RPMI media is preferred over formalin-fixed paraffin-embedded sections, although both are satisfactory specimens.

Over the past several years, there have been significant advances in molecular diagnostics. Their application to the autopsy has been limited primarily due to lack of reimbursement for autopsy ancillary testing. A detailed discussion of the newer advances is beyond the scope of this chapter, but these advances have been detailed by others (Jarzembowski and Hill 2011; Bluth and Zenilman 2007; Nolte and Hill 2007).

Postmortem Microbiology

Blood Cultures

Postmortem blood cultures, aerobic and anaerobic, may be problematic and usually generate mixed flora, although they have been of value in some cases (Ball et al. 1994; Klatt et al. 1986; Samuels and Rubio-Freidberg 1989; Srifeungfung et al. 2005; Suzuki et al. 2009; Tajiri et al. 2008; Wilson et al. 1993; Wood et al. 1965). Factors including the postmortem interval, decomposition, premortem use of antibiotics, body manipulation, and specimen collection technique affect the culture results. Traditional blood cultures obtained by searing the atrium with heat have been associated with postmortem bacterial contamination (Klastersky et al. 1972). The use of other collection techniques, e.g., iodine-subclavian or iodine–right atrium technique, correlates better with premortem blood cultures (Hove and Pencil 1998). Routine blood culture bottles used in standard hospital practice can be used. A culture of the spleen can be performed in lieu of a blood culture when necessary.

Correlation with the decedent's medical history when available is imperative. Measurement of postmortem C-reactive protein, interleukins (Il-6, Il-1β, Il-2 receptor), and procalcitonin has supported a diagnosis of sepsis in a case of sudden death when premortem cultures or clinical history were not available (Reichelt et al. 2005; Fraunberger et al. 2006; Ramsthaler et al. 2008; Tsokos et al. 2001a, b).

Tissue and Body Fluid Cultures

For tissue cultures, it is best to swab the site first with an iodine-containing disinfectant, make a sterile incision into the tissue, and obtain tissue for culture. A culturette can also be used to swab the incised site. Cultures of exudates or suspected bacterial-infected sites can be obtained with a culturette or sterile cotton swabs placed in culture media. For mycobacterial, fungal, viral, and parasitic cultures, tissues should be cut into small sections using an aseptic technique, placed in a sterile container or into the appropriate media, and promptly transported to the laboratory for processing. CSF and body fluids can be aspirated with a sterile syringe and placed into a sterile tube. For urine, the bladder can be seared and then aspirated.

Molecular Techniques

With advances in molecular biology, many infectious agents can be identified using molecular techniques. Molecular techniques that allow for accurate same-day diagnosis are helpful where conventional methods yield poor results or the sample size is limited. Technology based on isolating nucleic acids from microorganisms and mixing them with nucleic acid probes has supplanted many traditional cultures for bacterial, fungal, and viral agents (Table 37.1) (Cathomas 2009; Chiesa et al. 2003; Hashem and Menegus 2005; Jackwood 2004; Miller 2007; Muldrew 2009; Pfaller 2007; Sellon 2003; Taha and Alonso 2008; Yeh et al. 2009). Molecular techniques are also valuable when a rapid diagnosis is crucial for public health measures. With real-time PCR, the identification of pathogens can occur within an hour (Espy et al. 2006).

Special Autopsy Dissections

Special dissections that go beyond the standard autopsy procedure discussed in ▶ Chap. 3, "The Pediatric Autopsy" are needed at times to document injuries and to determine the cause of death. The College of American Pathologists and others have illustrated a series of special autopsy dissections that serve as an adjunct to the pediatric autopsy (Collins 2010; Adams 1991; Christiansen and Collins 2007; Finkbeiner et al. 2009b; Gilbert-Barness and Debich-Spicer 2005; Sheppard 2012; Sohn 1972; Wyatt-Ashmead 2001) (Table 37.2). Several selected dissections important in the evaluation of death in children are reproduced with permission below.

Cardiac Conduction System

Dissection of the conduction system (Figs. 37.1 and 37.2) is critical in cases of documented arrhythmias and cases of sudden death in a healthy individual or during bouts of physical activity (Miller 2010).

Indications for Procedure: Unexplained arrhythmia, sinus node dysfunction (sick sinus syndrome, tachy-brady syndrome, sinus bradycardia, sinus pause), atrioventricular block, repaired congenital defects of the atrioventricular septum, history of conduction ablation procedures, sudden death in an otherwise healthy individual, history of syncope, sudden death during physical activity, drowning in a swimmer, or falls.

Equipment: Scalpel, scissors, and forceps.

Procedures: Dissection of the cardiac conduction system involves examination of two different structures: the sinoatrial (SA) node and the atrioventricular (AV) node. Each structure is composed of specialized cardiomyocytes and is "insulated" from the surrounding myocardium by thin bands of collagen. Trichrome staining is recommended to help delineate the structures histologically.

Sinoatrial Node (SA): The SA node is an epicardial structure found along an imaginary line between the inferior and superior vena cavae, over the anterolateral aspect of the right atrium. It sits slightly above the midpoint of this

Table 37.1 Infectious agents identifiable with molecular diagnostics

Bacteria
Bacillus anthracis
Chlamydia trachomatis
Clostridium difficile
Coxiella burnetii
Escherichia coli
Enterococcus faecalis
Francisella tularensis
Gardnerella
Klebsiella pneumoniae
Mycobacterium tuberculosis
Neisseria gonorrhoeae
Pseudomonas aeruginosa
Staphylococcus aureus
Streptococci, group B
Streptococci, group A
Yersinia pestis
Fungi
Candida albicans
Leishmania
Trichomonas vaginalis
Viral
Adenovirus
Avian flu
Cytomegalovirus
Enterovirus
HBV
HBC
HIV
Herpes simplex virus 1 and 2
Human metapneumovirus
Human papilloma virus
Influenza virus A, A/H5, B, H1N1
Parainfluenza 1, 2, and 3
Respiratory syncytial virus A and B
Rhinovirus
West Nile virus

Modified from Pfaller, M. Molecular Pathology of Infectious Diseases (Pfaller 2007) and Holland, CA. FDA-Cleared/Approved Molecular Diagnostic Tests (Holland 2012)

line, nearer to the superior vena cava. Deep to the SA node can be found the crista terminalis of the right atrium.

When dissecting the heart, it is important to open the right atrium in a way that leaves the SA node intact; hence, incisions directed from the inferior to

Table 37.2 College of American Pathologists special autopsy dissections, step-by-step diagrams

1.	Cardiac conduction system
2.	Air embolism demonstration
3.	Esophageal varices demonstration
4.	Deep leg vein dissection
5.	Back (posterior trunk) and extremities cutdowns
6.	Disarticulations, removal of long bones and ribs
7.	En bloc pelvic dissection
8.	Peripheral nerve sampling
9.	Skeletal muscle sampling
10.	Facial dissection
11.	Upper and lower (maxilla and mandible) jaw resections
12.	Anterior neck strap muscle dissection
13.	Posterior neck dissection
14.	Vertebral artery dissections
15.	Spinal cord, anterior removal
16.	Spinal cord, posterior removal
17.	Spinal cord in continuity with brain, anterior removal
18.	Spinal cord in continuity with brain, posterior removal
19.	Eye enucleation, posterior approach
20.	Removal of the temporal bone, en bloc resection
21.	Fetal brain removal

From: Collins, KA. (Ed.). *Special Autopsy Dissections*. Northfield: College of American Pathologists. (Collins 2010)

superior vena cavae should be avoided (from inferior vena cava to right-atrial appendage is recommended).

Procedure, SA Node (Fig. 37.1)

1. Identify the location of the SA node on the epicardial surface along the imaginary line between the vena cavae, near the junction of the superior vena cava and right atrium (Step 1).
2. Using a scalpel, and working from the epicardial surface, incise an approximately 2 x 4 cm block of atrial tissue extending from the superior vena cava to the midpoint of the imaginary line mentioned above. This should include the portion of the crista terminalis that underlies this area (Step 2).
3. Using a scalpel, cut serial sections 2–3 mm thick perpendicular to the axis of the crista terminalis. Often, the sinus nodal artery can be seen as a pinpoint epicardial vessel in these sections (a reassuring finding) (Step 3).
4. The SA nodal tissue is not usually apparent grossly, but histologically can be seen as a discrete group of small cardiomyocytes with associated interstitial collagen surrounding the sinus nodal artery (Step 4). Nerve fibers and ganglia can often be seen nearby as well.

Atrioventricular Node (AV): The atrioventricular node, as the name implies, lies along the tricuspid annulus between the right atrium and ventricle. It is bounded

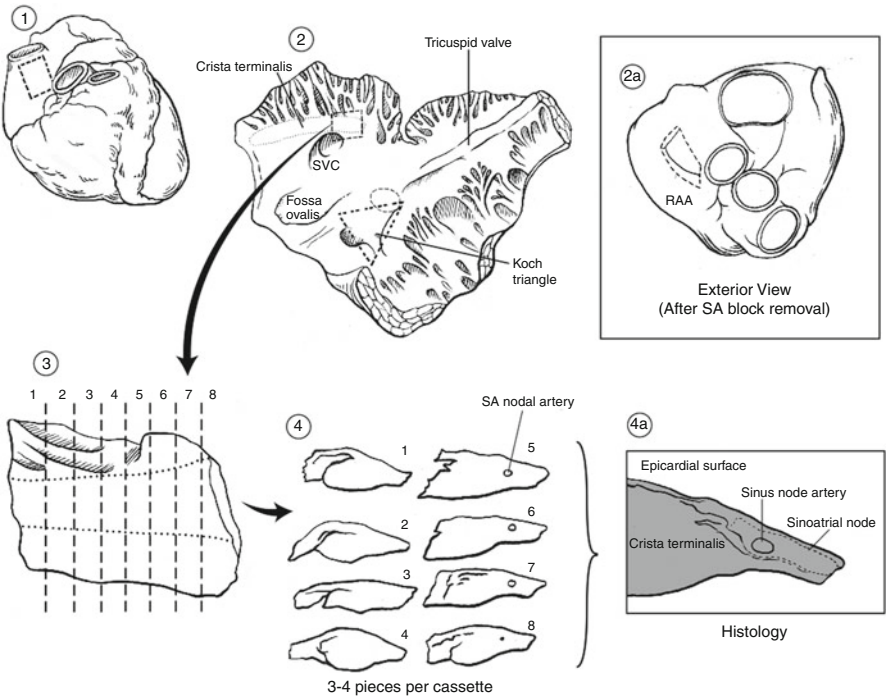

Fig. 37.1 Cardiac conduction system, sinoatrial node. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From: Collins, KA. (Ed.). *Special Autopsy Dissections*. Northfield: College of American Pathologists (Collins 2010). Reproduced with permission) (RAA- right atrial appendage)

by an imaginary triangle (of Koch) whose base is the tricuspid annulus, with the coronary sinus ostium comprising the left side and an imaginary line connecting the roof of the coronary sinus (the superior insertion point of the Thebesian valve of the coronary sinus) to the center of the atrioventricular septum (part of the membranous septum and central fibrous body) to the right.

Procedure, AV Node (Fig. 37.2)

1. Identify the location of the AV node by defining the *three* sides of Koch triangle. The atrioventricular septum can be best appreciated by (a) placing the thumb over the right atrial portion and then (b) pinching this part of the septum with the index finger from within in the left-ventricular outflow tract (Step 1).
2. Using a scalpel and working from the opened right-atrial side, incise an approximately 3 × 4 cm block of tissue that encompasses this triangle. The tricuspid annulus should be in the center of the block, and it should include about 1 cm of ventricular septum and right-atrial wall on either side of the annulus. The coronary sinus ostium marks the right border of the block, and the left border should be just beyond the atrioventricular septum (so it is entirely included).

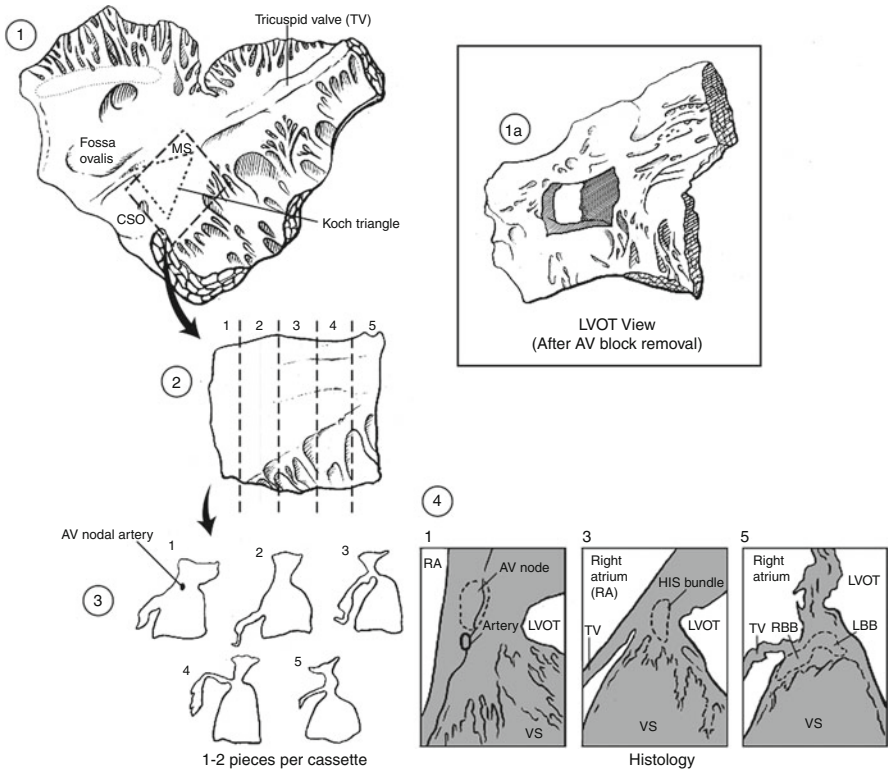

Fig. 37.2 Cardiac conduction system, atrioventricular node. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From: Collins, KA. (Ed.). *Special Autopsy Dissections*. Northfield: College of American Pathologists. (Collins 2010). Reproduced with permission)

The undersurface of the block will contain a portion of aortic and mitral valves, with the aortic–mitral fibrous continuity. Attachments to these valves can be trimmed with scissors once the block is excised (Step 2).

3. Using a scalpel, cut serial sections 2–3 mm thick perpendicular to the axis of the tricuspid annulus. And place them in order in 2–3 tissue cassettes (2 pieces per cassette) (Step 3).
4. The AV nodal tissue, again, is not usually apparent grossly but histologically can be seen as a discrete group of small cardiomyocytes with associated interstitial collagen surrounding the AV nodal artery. Dilated lymphatics can frequently be seen nearby as well. The AV node consists of a more compact portion toward the coronary sinus ostium, then the main body of the node, followed by a progressive narrowing to form the His bundle. The right bundle branch is a thin cord-like structure running in the direction of the tricuspid valve. It is much smaller than the left bundle branch and may require several levels of

section through the paraffin block to be seen. The left bundle branch is much broader and splays along almost the whole surface of the leftward ventricular septum (Step 4).

Removal of Spinal Cord in Continuity with Brain, Posterior Approach

In cases of cervical neck injury, CNS infections, demyelinating disorders, and neural tube defects, removal of the spinal cord attached to the brain is important (Miller and Collins 2010).

Indications for Procedure: Flexion or extension injury, vertebral trauma, craniocervical instability, ligament injury, posterior vertebral fractures, encephalocele, myelomeningocele, diseases affecting nerve-root ganglia, or surgical hardware removal.

Equipment: Body rest/head-neck block, scalpel, forceps, locking spreaders, oscillating saw, rongeurs, scissors, cork or Styrofoam, pins, and towels.

Procedure (Fig. 37.3): After evisceration of the thoracic, abdominal, and neck organs, the spinal cord may be dissected in preparation for removal along with the brain as a contiguous intact specimen.

1. With the decedent in the supine position, a scalp incision is made in the coronal plane beginning in the mastoid area behind one earlobe and extending over the palpable posterolateral ridges of the parietal bones to the opposite mastoid process. The anterior and posterior halves of the scalp are then reflected forward and backward, respectively, the anterior flap 1–2 cm above the supraorbital ridge and the posterior flap to just above the occipital protuberance.
2. The cranium is opened with an oscillating saw following the outline of the reflected scalp. The depth of the cut should extend just through the inner cranial table, and care should be taken to prevent entrance of the saw blade into the brain parenchyma. The calvarium is then removed and the dura incised along the same line. The anterior attachment of the flax is cut between the frontal lobes.
3. The frontal lobes are then gently elevated; the olfactory bulbs and tracts are peeled from the cribriform plates. The cranial nerves, pituitary stalk, and internal carotid arteries are cut as close as possible to their exit or entry point at the base of the skull.
4. Cut the tentorium cerebelli. Cut the remaining cervical nerves.
5. Turn the patient over into the prone position with clavicles/shoulders elevated to straighten (flex) the cervical spine. Place towels beneath to protect the face. A midline vertical incision is made from the posterior midline scalp to the coccyx (Steps 1 and 2).
6. Reflect the posterior scalp flaps and posterior-neck musculature to expose the occiput and the cervical spine (Step 3).
7. Continue reflecting the soft tissues, musculature, and ligaments from the vertebrae by sharp dissection. Locking surgical spreaders can be placed to maintain exposure to the transverse processes.

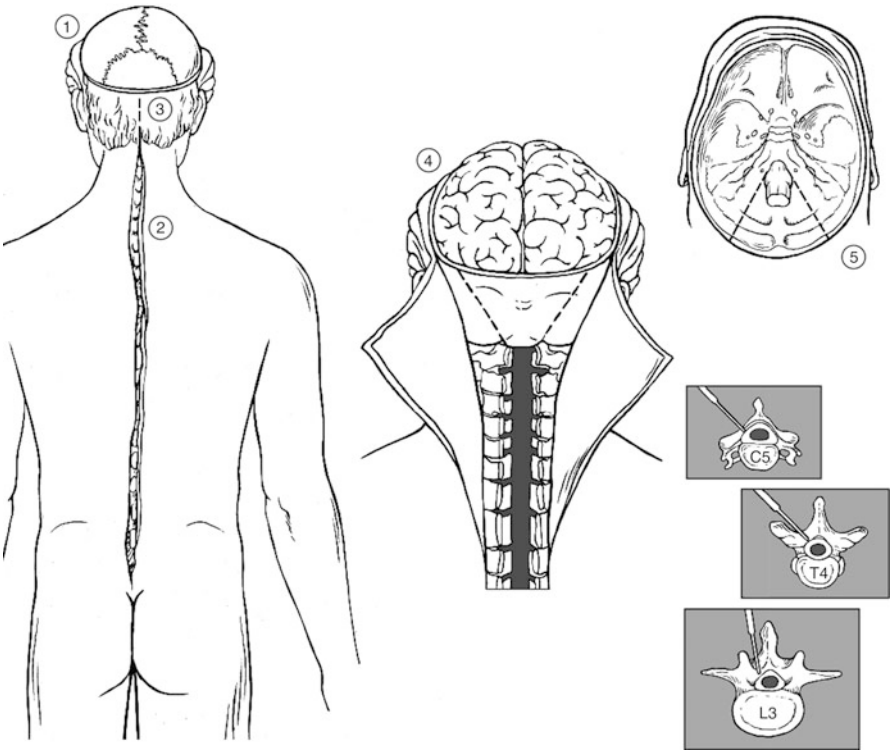

Fig. 37.3 Removal of spinal cord in continuity with brain, posterior approach. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From Collins KA, ed. Special Autopsy Dissections: Step-by-Step Diagrams. Northfield, IL: College of American Pathologists; 2010. Reproduced with permission)

8. Remove the spinous-process portions of the vertebrae by cutting (with an oscillating saw) through the laminae bilaterally from C1 to L5. The angle should be varied according to the segmental differences in vertebral anatomy (see insets). Remove the posterior portion of the vertebral column in a single contiguous piece (Step 4).
9. After exposing the cord, the intact dural sheath and cord with attached nerve roots and ganglia are removed by carefully excising with a scalpel blade or scissors and forceps. Excise the spinal nerves lateral to the posterior root ganglia. Do not squeeze the cord.
10. Remove any bony fragments covering the vertebral foramina with a rongeur instrument.
11. With an oscillating saw, make two oblique cuts through the lateral aspects of the squamous occipital bone toward the transverse processes of C2 (Steps 4 and 5).

12. Remaining occipital bone at the foramen magnum can be removed with rongeurs. The posterior aspect of the brain and brainstem are now exposed.
13. The brain with attached cord can now be removed.

Disarticulations: Removal of Ribs and Long Bones

Removal of long bones is important in children in cases of osteochondrodysplasia, osteomyelitis, nutritional disorders, osteopenia, and bone and soft tissue tumors and in cases of inflicted injury (Lantz and Collins 2010).

Indications for Procedure: Fractures, surgical long bone prosthesis, tumors, degenerative joint disease, (femur) bone marrow for DNA, assessment of hematologic tissue, septic arthritis, osteomyelitis, osteochondrodysplasia, nutritional deficiencies, malnutrition, osteopenia, soft tissue tumors, and inflicted injuries.

Equipment: Scalpel, forceps, scissors, oscillating saw, and retractors.

Procedures (Fig. 37.4):

Femur

1. Horizontally incise the skin at or below the patella (Step 1).
2. Extend the incision upward along the lateral aspect of the thigh (Steps 1 and 2).
3. Extend the depth of the incision deep through the subcutaneous soft tissue and musculature (Step 2). Extend the incision to the femur.
4. Reflect and retract the skin and underlying tissues.
5. Starting distally, separate the musculature from the femur. Cut the quadriceps tendon, joint capsule, and cruciate ligament. Note: If the case is a bone tumor, leave the musculature attached to the femur.
6. Continue upward to the hip joint. Incise the hip-joint capsule.
7. Rotate laterally and twist the femur and lift (Step 3).
8. Culture or radiograph as needed.

Other Long Bone Disarticulation

1. Incise the skin along the lateral aspect above and below the proximal and distal joints, respectively.
2. Separate the musculature from the bone.
3. Cut the ligaments and joint capsules.
4. Rotate and lift bone.

Spinal Column with Attached Ribcage

1. The chest plate and viscera have already been removed.
2. Remove the spinal cord by the posterior approach.
3. Dissect with scissors between the skin/subcutaneous soft tissue and the external surface of the ribs, around the back, and over the spine.
4. Cut between the vertebrae at the upper cervical and lower lumbar intervertebral discs (Step 4).
5. The entire rib cage with attached vertebral column can be removed as one unit (Step 5).

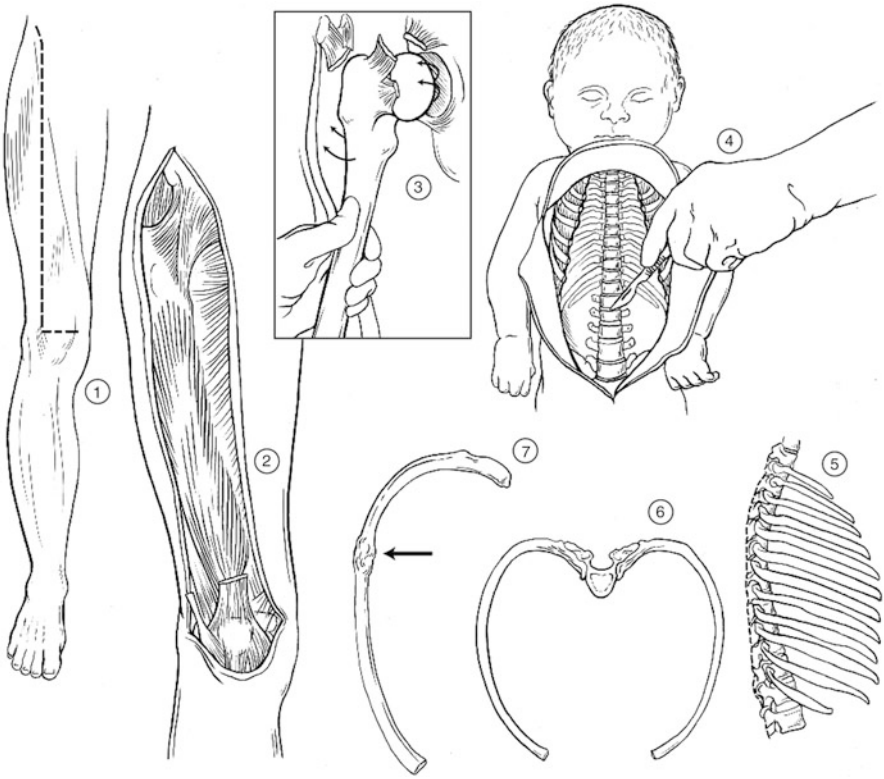

Fig. 37.4 Disarticulations, removal of ribs and long bones. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From Collins KA, ed. Special Autopsy Dissections: Step-by-Step Diagrams. Northfield, IL: College of American Pathologists; 2010. Reproduced with permission)

6. Fix specimen.
7. Cut through the intercostal musculature and corresponding intervertebral disc on both sides.
8. Repeat at each vertebral level.
9. Label each vertebral body with its paired ribs as to the level and the side (right or left).
10. Radiograph including axial radiography.
11. Remove abnormal areas, submit for decalcification, and submit for histology.

Individual Rib Disarticulation

1. The chest plate and viscera have already been removed.
2. Examine the vertebral body-transverse process-attached rib unit.
3. Remove the spinal cord by the posterior approach.
4. Dissect the skin and overlying musculature from the ribs.

5. Incise the spinal column by incising the intervertebral disc above and below the vertebral body/rib to be removed.
6. Cut through the intercostal musculature
7. Remove individual rib with the attached vertebral body if the pathology involves the rib head or rib neck (Step 6).
8. Remove an individual rib by disarticulating the rib head from its vertebral body if the pathology is more lateral to the vertebral column (as depicted by the arrow in Step 7).

Back (Posterior Trunk) and Extremities Cutdown

Indications for Procedure: Examination of the posterior trunk/back and the extremities is usually performed only in special cases, most often those in which child abuse is suspected, cases of blunt-force trauma, pedestrian–motor vehicle collisions, or when the descendent dies in a situation that involved the police and allegation of brutality may be rendered (Ross 2010).

Equipment: Scalpel.

Procedure (Fig. 37.5):

1. An incision is made from the posterior aspect of the neck just below the occiput of the skull vertically down the midline of the back, extending down each buttock and down the thighs and calves to the Achilles (patellar) tendons (Step *1*).
2. A horizontal incision is then made intersecting the vertical at the level of the scapula from the edge of the back to the other, with the variable degrees of extension down the arms to the wrists (Step *2*).
3. The skin is then dissected away from the underlying muscle in the four flaps:
   Left superior (Step *3a*)
   Right superior (Step *3b*)
   Left inferior (Step *3c*)
   Right inferior (Step *3d*)
   This allows visualization of the musculature of the back and the extremities. The underlying musculature can then be sectioned to evaluate for smaller/more focal injuries.
4. The anterior aspects of the extremities can also be examined for injury. An incision is made from the anterior superior thigh vertically down the thigh, through the pretibial region to the ankle. The skin can then be dissected away from the underlying subcutaneous tissues and muscle, and these tissues are incised to assess for injuries (Step *4*).
5. For examination of the anterior aspect of the arm, an incision is made from the shoulder vertically down the arm, with incision into the underlying muscle. Alternatively, the skin may be mobilized from the underlying tissue through the posterior incision and the muscle incised without creating a separate incision in the front of the arm.

The advantage of these techniques over simply making multiple incisions though the skin and muscle together is that the skin can be reattached at the point

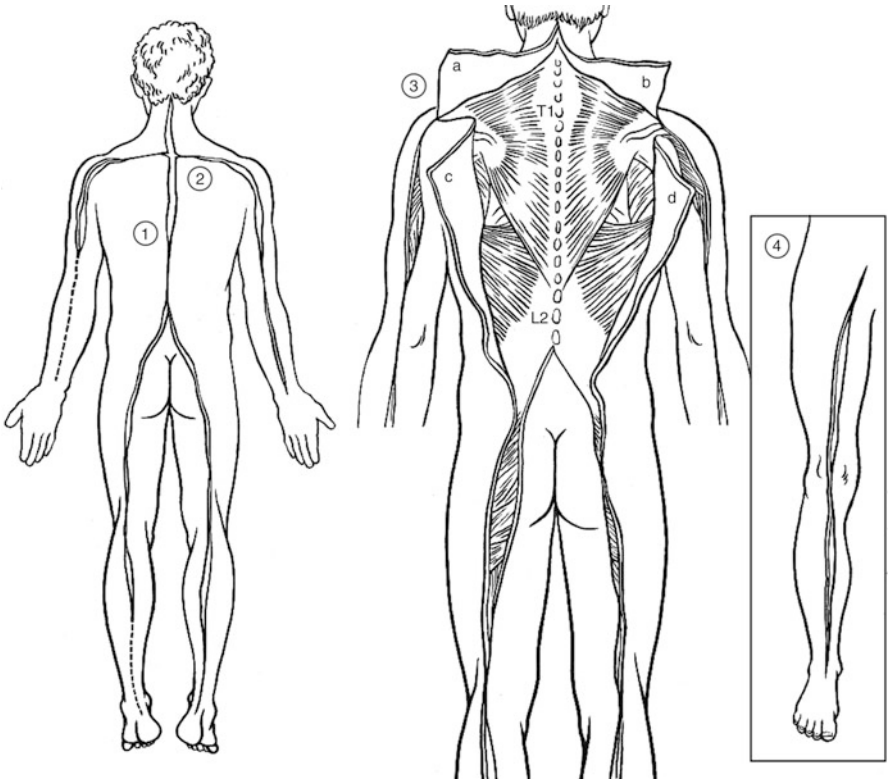

Fig. 37.5 Back (Posterior trunk) and extremities cutdown. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From Collins KA, ed. Special Autopsy Dissections: Step-by-Step Diagrams. Northfield, IL: College of American Pathologists; 2010. Reproduced with permission)

where the flaps meet and along the lines of dissection (either by suturing or gluing). This will minimize leakage of embalming fluid as opposed to the other technique, whereby more incisions are made through the skin.

Eye Enucleation, Posterior Approach

Indications for Procedure: In some institutions, removal and examination of the eyes are a routine part of every autopsy, which does not specifically exclude examination of the head. However, examination of the eyes would be particularly important in decedents with documented visual problems, tumors, metastatic melanoma of unknown primary, systemic disorders such as diabetes that affect the eyes, and head trauma with retinal hemorrhages. Removal of the eyes is particularly important in cases of ophthalmic neoplasms and in cases of head trauma and child

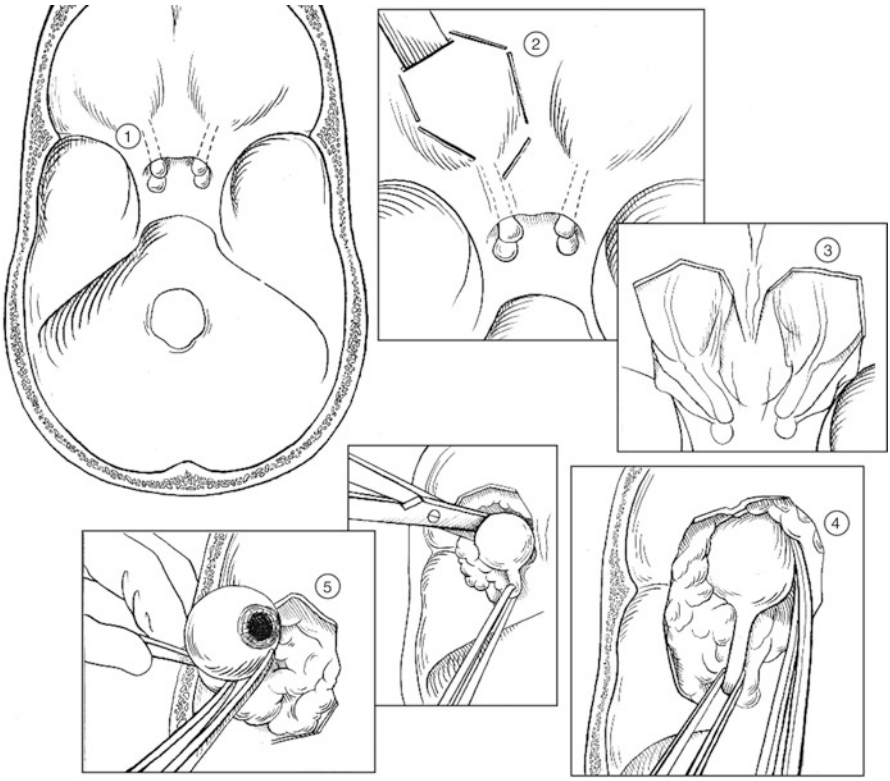

Fig. 37.6 Eye enucleation, posterior approach. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From Collins KA, ed. Special Autopsy Dissections: Step-by-Step Diagrams. Northfield, IL: College of American Pathologists; 2010. Reproduced with permission)

abuse. In cases of suspected abuse, the posterior approach is the correct method (Sinard and Belanger 2010).

Equipment Needed: Bone chisel, mallet, forceps, and curved dissecting scissors.

Procedure (Fig. 37.6): Permission for a complete autopsy may not allow for the removal of the eyes. Special care needs to be taken during any procedure that involves the eye or the face. Embalmers and funeral directors are usually trained to restore a body when a full autopsy has been done and a courtesy call to them may be advisable. Informing them of the enucleation may strengthen the relationship between your facility and funeral home staff. The enucleation of the eye from the posterior aspect can provide a safe method to reduce the risk of damage to the eyelid.

1. The calvarium is removed following anterior reflection of the scalp, and the brain is removed following established procedures.

2. Depending on the technique used to remove the brain, the optic chiasm or the distal cut ends of each of the optic nerves are to be located. The bone over the optic canal is very thin, and there should be a slight visualization of the nerve (Step 1).
3. With a flat sharp chisel, score the bone on each side of the optic nerve. Find the "bulge" inside the anterior cranial fossa. Score the circumference of the globe (Step 2). The superior orbital bones are also very thin.
4. Using the flat chisel and a mallet, cut through the bone following the score lines. If it is difficult to cut through the bone, reevaluate the positions of your scored region. Typically the bone is very thin and cuts easily. Alternatively a striker saw may be used.
5. Remove the bony material, unroofing the orbits to reveal the underlying soft tissue (Step 3). Using blunt and sharp dissection with a pair of scissors, delineate the optic nerve. (A 12-inch toothed forceps will be useful at this point.)
6. Carefully dissect along the optic nerve until the globe is identified (Step 4).
7. The globe is held in place by six extraocular muscles, five of which attach to the sclera just behind the anterior-posterior equator and the sixth near the optic nerve. Anteriorly, the conjunctiva attaches to the globe circumferentially at the corneal limbus. This is important, because the "other end" of the conjunctiva attaches to the upper and lower eyelids. Care must be taken during removal to not cut the eyelids, since this will impact the appearance of the face at a funeral.
8. First, dissect the soft tissues away from the globe, cutting the attachments of the extraocular muscles, leaving the anterior of the globe alone for the time being. (In the case of an orbital tumor, you may want to remove the orbital soft tissues with the globe. If so, dissect instead along the medial, lateral, and inferior orbital bones.)
9. Locate the external surface of the eyelid and lightly push against the globe with the finger of one hand while grasping the distal end of the optic nerve and pulling the eye out of the orbit into the cranial cavity. The globe of the eye should leave the socket with the eyelid attached at the corneal limbus. Cut the conjunctiva as close as possible to the globe to not cut the eyelid. Cut any remaining soft-tissue attachments to remove the globe (Step 5).
10. Carefully inspect the eyelid and fill the space beneath the lid with cotton or similar material. The embalmer will place "eye caps" and other restorative devices to provide a natural look.
11. Globes may be fixed in formalin for 24 h before dissection.

Removal of the Temporal Bone, En Bloc Resection

In cases of meningitis and otitis media, the middle ear must be examined (Conran 2010b).

Indications for Procedure: Meningitis, otitis media, deafness, and vestibular disorders.

Equipment: Oscillating saw, hammer, chisel, bone scissors, and scalpel.

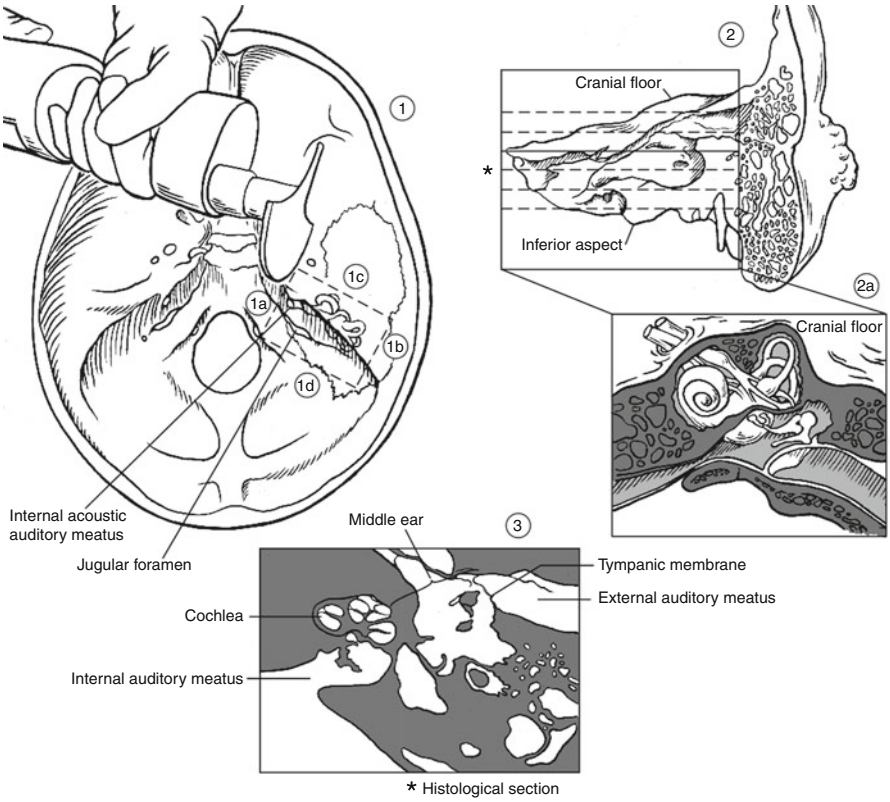

Fig. 37.7 Removal of the temporal bone, en bloc resection. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From Collins KA, ed. Special Autopsy Dissections: Step-by-Step Diagrams. Northfield, IL: College of American Pathologists; 2010. Reproduced with permission)

Procedure (Fig. 37.7)

1. After removing the brain, the dura is stripped off the petrous portion of the temporal bone.
2. Four cuts are made with an oscillating saw to remove the temporal bone en bloc (Step *1*).
3. The first cut is made in the vertical direction (cranial to caudal direction), approximately 2.5 cm in depth, through the superior aspect of the petrous portion of the temporal bone (ridge that separates middle from posterior fossa). The cut should be anterior and medial to the internal acoustic meatus (foramen for facial and vestibulocochlear nerve) and is perpendicular to the petrous ridge. The cut is then extended slightly anterior and lateral through the squamous part of the temporal bone in the middle of the cranial fossa (Step *1a*).

4. The second cut is made vertically through the petrous portion, parallel to the first cut a distance of 3 cm from the internal acoustic meatus. The cut is also 2.5 cm in depth and also extends into the middle cranial fossa (Step *1b*).
5. The third cut is also made in a vertical direction, 2.5 cm in depth, and extends between the first and second cuts in the middle cranial fossa. The third cut is parallel to the petrous ridge (Step *1c*).
6. Finally, the saw is placed in the posterior fossa, and a horizontal cut (fourth cut) is made at the level of the jugular foramen, connecting with the previous cuts, undercutting the petrous portion of the temporal bone (Step *1d*).
7. The cut temporal-bone specimen can be loosened and removed by gently rocking. Occasionally, a hammer and chisel may be needed to free the specimen. Care should be taken not to damage the middle- and inner-ear contents. (*Step 2a insert is for the purpose of orientation so that the prosector is aware of internal structures*.)
8. The resected bone sample is fixed in buffered formalin and then decalcified.
9. The decalcified bone specimen is cut horizontally (Step *2*).
10. Sections for light microscopy are prepared (Step *3*).

Examination of the Middle Ear

Procedure:

1. The middle ear can be examined by removing the roof of the petrous bone with a hammer and chisel. With the chisel (sterile chisel if bacterial cultures are indicated), open the bone midway between the internal acoustic meatus and the external auditory canal.
2. Place a thumb or index finger at the acoustic meatus and the other in the external auditory canal and pick the point midway between the two fingers.
3. Opening the roof of the petrous bone at that point will expose the middle ear.

Examination of the Fetal Middle Ear

Procedure:

1. In a fetus, the middle ear can be examined by removing the petrous portion of the temporal bone by making two cuts with bone scissors:
   - The first cut is made along the lateral junction of the petrous bone and extended in an anteromedial direction.
   - The second cut is made along the medial border of the petrous bone adjacent to the sella and extended in an anterolateral direction to join the first cut.

Fetal Brain Removal

Indications for Procedure: Examination of the brain and the cranial cavity in the fetus or neonate while the sutures are open and the cranial bones are soft. Also, medullary/brainstem defects, cervical-cord defects, Arnold-Chiari malformation, and Dandy-Walker malformation (Conran 2010a).

Equipment: Scalpel, scissors, forceps, bone scissors, hairnet/bonnet, and scale.

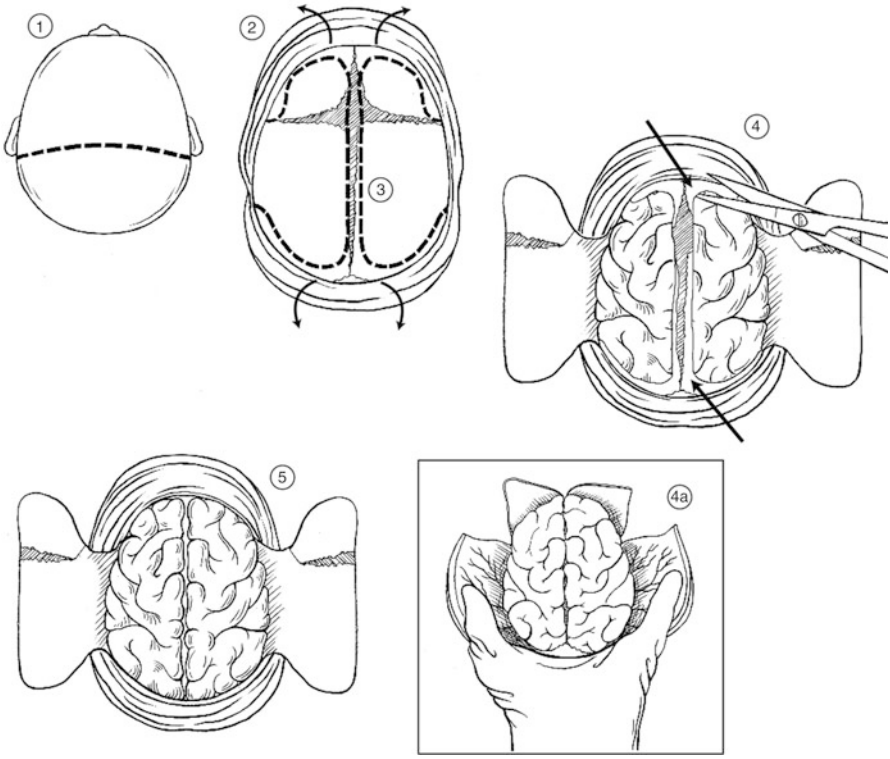

Fig. 37.8 Fetal brain removal. Diagram of step-by-step dissection (see text for details) (Artwork © Tania Litwak 2009. From Collins KA, ed. Special Autopsy Dissections: Step-by-Step Diagrams. Northfield, IL: College of American Pathologists; 2010. Reproduced with permission)

Procedure (Fig. 37.8)

1. With a scalpel make an intermastoidal incision in the scalp (Step *1*).
2. Using your fingers or scalpel, reflect the scalp from the cranium anteriorly to eyebrow level and posteriorly to the occiput (Step *2*).
3. The anterior fontanelle is then examined (depressed versus bulging), measured, and the mobility of the sutures documented.
4. The skull is opened by initially making a dural incision into the lateral extensions of the anterior fontanelle (adjacent coronal suture) on both sides using a scissors or scalpel blade.
5. A scissors with a rounded end is then inserted into the incision. An oval bone flap is created by cutting the frontal bone in an anterior direction, initially. The scissors should be a distance of 5–8 mm from and parallel to the sagittal suture. The incision is then extended laterally at a point above the eyebrow and then downward and posteriorly to a point anterior and superior to the ear (pinna). The scissors are then returned to the original incision, turned posteriorly, and an incision is made parallel to the sagittal suture through the parietal bone toward the occiput. The scissors are curved downward and

laterally to a point behind the ear (Step *3, dotted lines*). The procedure is repeated on the opposite side. Now the brain is exposed with a midline bone flap remaining (Step *4*).

6. Alternatively, the coronal sutures lateral to the sagittal suture and the frontal metopic suture can be cut, creating two frontal and two parietal bone flaps (Step *4a*).
7. The bone flaps are reflected, exposing the brain and leptomeninges. The brain is best viewed in situ by moving it forward and backward to inspect the falx and tentorium for any defects or signs of hemorrhage.
8. The midline bone flap containing the sagittal sinus is moved by cutting the bone flap at its anterior and posterior ends (Step *4, arrows*). The falx cerebri and sagittal sinus are examined. The sinus is sectioned looking for thrombosis.
9. Examine the brain in situ (Step *5*).
10. Holding the head in one hand, tilt the head backward, and retract the brain with a finger from the opposite hand. Cut the cranial nerves in an anterior to posterior direction with a scalpel or scissors followed by incising the tentorium cerebelli on each side. As the nerves are transected and entire tentorium cerebella cut, the brain should fall from the calvarium into the palm of your hand.
11. The cervical cord is transected with a scalpel to free the brain. The brain is then weighed and the external surface inspected. The brain can be fixed by suspending it in a hairnet in a bucket of formalin.
12. In markedly macerated fetuses, the brain may be removed using the above procedure under water. (In older infants, an oscillating bone saw may be needed. The circumference of the skull is cut with notched areas on the anterior and posterior ends, analogous to removal of the adult brain.)
13. Once the brain is removed, the base of the skull and the foramen magnum are examined. The dural, transverse, and sigmoid sinuses are opened with a scalpel blade. The pituitary gland is removed by severing the anterior and lateral tentorial attachments to the sella, followed by severing the posterior clinoid process with a scalpel and picking up the tentorium attached to the pituitary with a forceps. The middle ear can be examined by removing the petrous portion of the temporal bone by making two cuts with bone scissors. The first cut is made along the lateral junction of the petrous bone and extended in an anteromedial direction. The second cut is made along the medial border of the petrous bone adjacent to the sella and extended in an anterolateral direction to join the first cut. The petrous bone is then removed, exposing the middle ear cavity, ossicles, and eardrum. The dura is stripped from the skullcap. The skull bones are examined for fractures. In situations where a defect is expected in the medulla or cervical cord, e.g., Arnold-Chiari malformation, the brain and the spinal cord should be removed together as a unit using a posterior approach as discussed above.

Conclusion

The goal of death investigation is to identify the decedent and determine the cause and manner of death. Photography and imaging to document injuries, postmortem

chemistry and toxicology to identify metabolic disorders and drug-related deaths, microbiology to identify infectious diseases, and genetic testing to identify specific disorders and syndromes serve as an adjunct to the standard autopsy. Specimen collection, type of specimen, and other analytical variables play a role in test interpretation and the generation of false positives and negatives. Special dissections such as eye enucleation in cases of "shaken baby syndrome" are also critical as part of the investigation of death in a child or adolescent.

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Pediatric Organ and Tissue Donation

38

Charles V. Wetli and Jean Aiken Davis

Contents

Abstract

The shortage of organs and tissues for life-saving and life-enhancing transplantation continues as the list for potential recipients grows in both the adult and the pediatric populations. Difficulties unique to the pediatric population center about the fact that many of the organs and tissues needed for transplantation must be matched for size. In addition, there is often reluctance on the part of medical examiners and coroners to grant permission for organ and tissue removal in pediatric cases out of fear that a cause of death may not be

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determined or that there will be interference with a criminal prosecution. Over the past several years, these issues have been addressed at both the local and national levels so that the goals of the organ and tissue procurement organizations and the medical examiner/coroner can be achieved. The key to attaining the goal of "zero denials" is the establishment of good communication and cooperation between the procurement organization and the medical examiner/coroner. This includes the opportunity for the medical examiner/coroner to examine the potential donor prior to and during the removal of organs and tissues, the sharing of testing results, and providing a copy of the autopsy report in a timely fashion. Often times these goals can be achieved with noninvasive procedures such as computed tomorgraphy (CT) scans and X-rays, digital photography and videography. Concerns of organ and tissue donation in pediatric cases interfering with criminal and civil proceedings, or precluding the diagnosis of a cardiac abnormality as a cause of sudden death, have been virtually eliminated by studies and protocols developed over recent years. Today, there should be no denials for organ and tissue donation in pediatric cases under medical examiner/coroner jurisdiction, even in cases of suspected child abuse or sudden infant death syndrome/sudden unexpected death in infancy (SIDS/SUDI).

Introduction: A Critical Shortage of Donors

The shortage of organs and tissues for life-saving and life-enhancing transplantation continues as the candidate waiting list grows. However, the need is even more critical in the pediatric population where size-matched organs and tissues are required. Transplant and other medical professionals recognize the benefit of transplantation in this patient population particularly the considerable medical and quality-of-life benefits. The support of and collaboration with the Medical Examiner/Coroner is vital in addressing this critical shortage in the pediatric transplant population.

According to the United Network for Organ Sharing (UNOS) 2010 Annual Report (Association of Organ Procurement Organizations (AOPO) n.d.), the current national wait list for a solid-organ transplant stands at over 112,000 candidates, with those under the age of 18 years representing 1,775 candidates. Since 1988, more than 500,000 solid-organ transplants have been performed in the United States (USA), and 39,723 of these transplants have been performed in patients under the age of 18 years. The Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) Annual Data Report notes that for 2010, 28,662 organ transplants were performed; 1826 were performed in patients under the age of 18 years. The number of patients awaiting a life-saving transplant continues to significantly outpace the number of organs available. This is particularly critical in the pediatric population as the death rate in

children under age 5 years is higher than any other age group (Cherikh et al. 2008). According to Dr. David Campbell, Chair UNOS Pediatric Committee/Chief Pediatric Cardiac Transplantation, The Children's Hospital, Aurora, CO, children under the age of 1 year awaiting cardiac transplantation listed in the most critical status (1A) have a 25–30 % waiting-list mortality which is threefold greater than older children awaiting transplant and tenfold greater when compared to adults awaiting transplant (personal communication, 2011). The goal of the donation process is to honor the wishes of the decedent and donor family and recover every suitable organ every time. Given the critical nature of the organ shortage, not doing so will result in lives being lost. This critical organ-donor shortage remains the most significant challenge faced by the donation/transplantation community.

In 2003, to address the national organ shortage, Health and Human Services joined with key leaders in the nation's transplant system and health care to launch the Organ Donation Breakthrough Collaborative aimed at increasing organ donation through system redesign (Chessare et al. 2006). Overarching principles and best practices were identified to enhance the donation systems within organ-procurement operations and hospitals. One of the key strategies identified was the collaboration and cooperation of the Medical Examiner/Coroner (ME/C). Through collaboration with the National Association of Medical Examiners (NAME), a mutual goal of "zero denials" for organ and tissue donation was identified. A clear expectation was established that the ME/C would allow the recovery of organs and tissues to proceed as this was the practice in much of the USA. NAME became one of the key leadership organizations involved in increasing organ donation and transplantation on a national level.

As much as 70 % of potential organ and tissue donors fall under the jurisdiction of the Medical Examiner or Coroner (ME/C) in the USA (Goldstein et al. 1997). Although approval for organ and tissue donation is given in the vast majority of cases, a significant proportion are denied by the ME/C. Most frequently the reasons cited for donor denial are fear of being unable to determine the cause of death and potentially interfering with civil or criminal proceedings. Also, pressure for donor denial is sometimes exerted by law enforcement personnel, including prosecuting attorneys. "Problematically for pediatric patients awaiting transplantation, nearly half of all ME/C denials occurred in pediatric patients. Eighteen percent of potential organ donors aged five or less and 44.2 % of child abuse potential organ donors were denied recovery by the ME/C" according to one study (Shafer et al. 2003). For every denial there are at least three individuals who will not receive a life-saving transplant (Goldstein et al. 1997).

Studies have shown that organ donation does not interfere with criminal investigation and prosecution (Strama et al. 1994), and denial of organ donation, with its attendant loss of life of the potential recipient, is clearly not justified (Shafer et al. 1994). The issues of ME/C denials were examined in depth by an ad hoc committee on organ and tissue procurement of the National Association of Medical Examiners. A position paper (Pinckard et al. 2007)

was published as a result which states that "It is the position of the National Association of Medical Examiners (NAME) that the procurement of organs and/or tissues for transplantation can be accomplished in virtually all cases, without detriment to evidence collection, postmortem examination, determination of cause and manner of death, or the conducting of criminal or civil legal proceedings." Essentially, the position of NAME is that there is rarely a reason for blanket denial, even in homicide cases (including child abuse). However, there may be "approvals with restrictions" (Pinckard et al. 2007) depending on the circumstances of any particular case.

The responsibilities and agendas of organ/tissue-procurement organizations (O/TPO) and the ME/C are vastly different but they are not mutually exclusive, and the goals of each can and should be achieved for the benefit of all concerned: the family of the decedent, the organ and tissue recipients, and the medical examiner/coroner. To achieve these goals requires, first and foremost, adequate communication and cooperation of both the O/TPO and the ME/C (Wetli et al. 2009; Shafer et al. 1999; Wetli 2003). This applies to adult as well as pediatric cases. However, pediatric cases often present different and more complex challenges, which also give rise to the hesitancy of the ME/C to release organs and tissues for transplantation (Wetli et al. 2009). In the past, ME/C denials for organ/tissue procurement have frequently involved cases of known or suspected child abuse or sudden infant death syndrome (SIDS)/sudden unexpected death in infancy (SUDI), representing a substantial portion of pediatric donors. Denials in these types of cases have a critical impact on the availability of pediatric organs for transplantation. NAME encourages the approval of organ and/or tissue procurement in virtually all cases, including child abuse and SIDS cases (Pinckard et al. 2007).

Many ME/C offices have limited budgets and resources. It is therefore critical to establish collaborative practices that will facilitate the donation process without creating an undue burden on the ME/C office. Numerous best-practice guidelines and protocols have been developed to streamline the process which may include procurement of blood, urine, and other specimens as requested; diagnostic imaging studies; documentation of internal and external injuries; still and video photography of both injuries and the operative organ-recovery procedure (United Network for Organ Sharing (UNOS) 2000). Written follow-up is routinely provided regarding the outcome of the transplantation procedures as well as the continued progress of the recipients.

A delicate balance exists between protecting and preserving the medicolegal evidence and supporting donor families and recipients awaiting transplantation of life-saving organs and can be best accomplished through collaboration and partnership. Numerous models exist throughout the country where this partnership has resulted in "zero denials" for organ/tissue donation (Table 38.1).

With potential pediatric organ and tissue donors, it is paramount for the ME/C to be cognizant of the fact that denial or restriction may well mean that a potential recipient will be denied a life-saving transplant and, in pediatric cases, organ size is crucial. Hence denial or procurement restrictions require realistic justification.

Table 38.1 Proven framework for successful medical examiner/organ/tissue procurement organization collaboration

Establish relationships between key stakeholders
Develop written protocols/contracts combined with education and training of all staff involved in the process
Provide accurate/complete physical assessment and recovery documentation
Provide additional studies/laboratory tests as needed to include CT scan, MRI, ECG, cardiac catheterization
Provide digital photography or videography as requested
Ensure ME/C attends surgical recovery procedure as required
Provide immediate communication of pertinent autopsy findings
Reinforce willingness of transplant surgeon to testify at trial regarding surgical findings at recovery

Definitions and Terms

Dictionary definitions for "organ" and for "tissue" are vague and unsatisfactory inasmuch as a clear distinction between the two is lacking. To define an organ as "a somewhat independent part of the body that performs a special function or functions" does not clearly delineate it from the definition of tissue as "an aggregation of similarly specialized cells united in the performance of a particular function" (Dorland 1968). For the purposes of organ and tissue procurement, one may define an organ as a functional unit that requires continuous oxygenation and perfusion of nutrients (i.e., continuous blood flow and respiration) up to the time of recovery. Tissue would then be defined as an entity that can withstand a substantial period of time without blood flow and oxygenation prior to procurement. Thus, organs such as heart, lungs, and kidneys would properly be regarded as "organs." Skin, which medically is considered an organ, would be regarded as a "tissue" since procurement may take place hours after the cessation of respiration and circulation. The distinction is more than academic: procurement of organs must occur immediately upon cessation of vital functions whereas tissue procurement may take place hours after the cessation of vital functions and even after an autopsy is performed. Unlike organ procurement, brain death is not an issue with tissue donation.

It should be noted that the transplantation of organs is regarded as life saving, whereas the transplantation of tissues is considered as life enhancing. This, however, does not diminish the value of tissue donation since these tissues bring a significant reduction in morbidity (e.g., skin, heart valve, and corneal donations) and today is often a necessary component for a variety of surgical and dental procedures (e.g., bone grafting).

Table 38.2 Pediatric organs and tissues recovered/donor age limits

Organs	**Donor Age Limits**[a]
Heart	Ages 0–17 years
Kidneys	
Lungs	
Pancreas	
Liver	
Intestines	
Tissues	**Donor Age Limits**[b]
Skin	Ages 15–75 years
Bone	
Tendons	
Heart valves	Ages newborn to 55 years
Pericardium	Ages 15–50 years
Veins	Ages 15–55 years
Corneas/eyes	Ages 1 + year

[a]Defined as donation made prior to 18th birthday per United Network for Organ Sharing policies
[b]Criteria vary by local recovery agency, determined by transplant/research requirements
Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR). Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; available at http://optn.transplant.hrsa.gov/latestData/viewDataReports.asp

Obtaining organs and tissues was once referred to as "harvesting," a term which was felt to be offensive to many donor families. Today, the obtaining of organs and tissues for purposes of transplantation (or, in some cases, research) is regarded as "procurement" or "recovery," terms which are used interchangeably.

Organ-procurement organizations may provide tissue-recovery services as well as freestanding tissue and eye banks depending on the service area covered. Medical criteria for tissue donation are generally established by the local tissue recovery agency (Table 38.2).

The Organ Recovery Process

The organ recovery process involves a complex series of events coordinated by medical professionals in organ procurement organizations (OPOs) and hospitals often working in collaboration with local ME/Cs. The National Organ Transplant Act of 1984 (NOTA) was enacted to help ensure that the process is carried out in a fair and efficient manner resulting in the equitable distribution of donated organs. The act established the national Organ Procurement and Transplant Network (OPTN) for matching donor organs to waiting recipients. The United Network for Organ Sharing (UNOS) currently holds the federal contract for the OPTN and works with the 58 federally designated OPOs across the country to allocate organs locally, regionally, and nationally.

When death is imminent, a referral is made by the hospital to the local OPO which sets in motion a series of events culminating in the donation of organs/tissue for transplantation. Medicare Conditions of Participation mandate that every hospital notify the local OPO when death is imminent or about to be declared. The patient's medical condition is reviewed by the OPO coordinator to determine if the patient is a medically suitable candidate for organ/tissue donation. The donor registry is accessed in the state where the donor resided to determine if their donation preferences have been recorded. If the patient has indicated their wish to be a donor, the next of kin or health-care proxy is informed of their decision, and a medical/social history is obtained in order to facilitate the donation. If the decedent's wishes are unknown, the coordinator will then discuss the possible donation options. In the case of pediatric donation, appropriate authorization is obtained from the patient's next of kin who is usually the mother and/or father. The family is given sufficient time and support to understand the value of organ/tissue donation and to answer any questions or concerns they may have. The ME/C is notified according to local protocols to discuss the circumstances of the case in order to obtain clearance and provide any additional information or testing as requested.

After securing appropriate authorization, the organ/tissue donation process is set in motion and the OPO assumes responsibility for the management of the donor after the declaration of brain death. (Donation after cardiac death, or DCD, is another avenue for donation after the decision to discontinue treatment has been made by the family.) Donor management requires a high level of clinical expertise to ensure that all suitable organs remain viable for transplantation. The donor's hemodynamic stability is of utmost importance to the organ recovery process and is maintained through mechanical ventilation. The goal of donor management is to maximize the function of each organ prior to surgical recovery. Physical assessment and laboratory and diagnostic testing are performed to determine appropriate interventions to maximize the organs suitable for transplant. Blood and tissue samples are sent for tissue typing and infectious disease testing. The donor information is then entered into the UNOS computer to determine the appropriate allocation of the donated organs. The OPO coordinator accesses the list of potential recipients and begins the process of contacting the corresponding transplant centers for organ placement. The surgical recovery process often requires the logistic support and cooperation of multiple surgical teams from different transplant centers. ME/Cs are encouraged to attend the organ recovery procedure to address any concerns regarding the preservation/collection of forensic evidence. The organs are recovered, flushed, and preserved in protective solutions ready for transport to the recipient transplant center. OPOs provide support and follow-up regarding the outcome of the donation process to the donor family, hospital, and ME/C staff. Donor family follow-up begins immediately after the donation and continues for a period of time up to a year after the donation through telephone contact, grief programs, and annual services of remembrance. Donor families have expressed that the act of organ/tissue donation was the only comfort gained in an otherwise tragic situation.

The Tissue Recovery Process

Donation of musculoskeletal tissue such as bone, skin, and tendons, as well as heart valves and corneas, can dramatically improve the quality of life for recipients and can in fact save lives. Each year more than 30,000 tissue donors provide life-enhancing tissue for transplantation. In addition, more than 45,000 cornea transplants are performed in the USA annually. Cornea or whole-eye recovery generally occurs prior to the recovery of musculoskeletal tissue and may be accomplished through the recovery of the cornea with a rim of sclera or the enucleation of the whole eye. The tissue recovery process begins after the organs have been removed. Transplantable tissue does not require a blood supply and so the recovery can occur after the cessation of cardiorespiratory function. Time limits for tissue recovery vary depending on the type of tissue and the proceeds of the TPO. Recovery may be accomplished in the same operating room or the body may be transported to another facility. The tissues are recovered and packaged in a sterile fashion for transport to the tissue-processing facility. The body is treated with respect at all times, reconstructed as necessary, and transported to either the ME/C or funeral home. The recovery procedure should have no impact on the family's funeral plans. It should also be noted that tissue recovery may take place in the Medical Examiner facility and may occur after completion of the autopsy. Since tissue recovery often occurs without prior organ procurement, copies of the consent for recovery should be provided to the ME/C as well as a description of any unusual findings encountered during the recovery process (e.g., injuries, venous thrombosis).

External Examination

The ME/C must initially evaluate the circumstance of injury or death and the external appearance of the potential donor before permitting organ or tissue procurement. The initial contact with the ME/C may well come from the hospital treating physician, O/TPO coordinator, and subsequently police investigators as well. Following this initial assessment the ME/C should have the opportunity to perform an external examination of the potential donor and diagram and photograph anything of potential evidentiary value. In pediatric trauma cases this is especially important since there are often pattern injuries and injury patterns that may be of crucial evidence in subsequent criminal and civil legal proceedings and which may be altered, obscured, or destroyed by the procurement process. If the potential donor is already deceased, this external examination is generally not a problem unless there are timing and logistic issues. If the potential donor is undergoing the protocol for pronouncement of brain death, then the examination would necessarily take place in the hospital.

With today's technology, it should also be possible in many cases, particularly for potential organ donors in the hospital, to document the injuries with a digital camera and video recorder and electronically transmit these to the ME/C. This would be particularly helpful in those trauma cases, including child abuse, where external injuries are absent or minimal. Naturally, close and honest communication between the ME/C and the O/TPO coordinator is crucial. For example, it may well be important for the ME/C to instruct the O/TPO to arrange for a careful examination and digital photographs of the eyes to document the presence or absence of petechiae. Such electronic transmission of external findings, including pertinent negatives, coupled with good communication, should also be helpful when there are time and distance constraints for potential tissue donors as well.

Noninvasive Internal Examination

Proposed solutions to decrease ME/C denials in potential organ donors on brain-death protocols include taking advantage of radiological imaging techniques to further evaluate the donor and to reasonably detect or exclude additional injuries (Shafer et al. 1999). Such evaluations are most helpful in trauma cases, particularly when child abuse is an issue. Radiological skeletal surveys, computed tomography, and magnetic resonance imaging will all be helpful in the decision-making process of the ME/C. Also, particularly in suspected child abuse, an ophthalmological examination for retinal hemorrhages would be important with both diagrammatic and photographic documentation.

The ME/C and the Organ Recovery Procedure

Organ procurement begins with the pronouncement of brain death and the cessation of vital functions. It has generally been accepted that the ME/C may attend the procedure to assure there are no unexpected injuries or other surprises. In some jurisdictions the ME/C has the authority to halt the procurement process under such a circumstance. This would be a rare occurrence indeed. Again, with good communication and the digital technology available today, there is little reason for the ME/C to be actually present in the operating room at the time of organ procurement. However, it is incumbent upon the procurement team to document any findings in both the record and photograph (e.g., a hemoperitoneum due to a small hepatic laceration not previously detected). Some medical examiners may request a biopsy of all removed organs, but this is not a universal practice. Although it is a remote possibility, the procurement team must be aware that they may subsequently be required to testify as to their observations at the time of the organ (or tissue) procurement, particularly if the ME/C did not directly observe the injury at that time.

Donation of Pediatric Heart Valves

The issue of pediatric heart valve donation has been most extensively studied by Gunther (2005) who applied the technique of modified cardiectomy (Wetli et al. 2002) to pediatric heart valve donor subjects and helped establish the Virginia protocol for heart valve donation (see Figs. 38.1–38.7). To summarize her work, it is important to realize that size considerations are an important factor for potential recipients of heart valves needed to correct anomalies such as tetralogy of Fallot, congenital pulmonary stenosis, truncus arteriosus, congenital aortic stenosis, and other pediatric cardiac anomalies (see Figs. 38.8 and 38.9). Therefore adult cadaveric heart valves, porcine valves, and artificial mechanical valves (requiring anticoagulation) cannot be used. The only hope for these children is the transplant of a pediatric cadaveric heart valve. Again, ME/C resistance to allowing procurement of the heart valves (particularly in cases of suspected SIDS/SUDI, overlying, or apparent sudden natural death) is rooted in the fact that heart valve donation is a destructive process that would preclude the ME/C from determining a cardiac cause of death. This is especially worrisome considering that some anomalies may be familial and therefore have direct implications for siblings or other family members (e.g., idiopathic hypertrophic cardiomyopathy). The concern has been greatly diminished in studies by Pinckard and Graham (2003, 2004) which showed that the donation of pediatric heart valves does not preclude the diagnosis of clinically significant cardiac abnormalities. In addition, the Virginia protocol allows for the heart from the pediatric donor to be examined under sterile conditions so that coronary artery anomalies and other abnormalities are excluded by the examining forensic pathologist. The dissection technique, which takes about 20 min (and is conducted in the Medical Examiner Office) must be performed within 24 h of cardiectomy, and the technique allows for inspection of the heart valves without interfering with the procurement procedure. Additional observations by the procurement team (see Figs. 38.5–38.7, courtesy of Cryolife, Inc.), which generally includes a qualified pathologist (often a cardiac pathologist) as well as the procurement technicians, are reported to the ME/C, and the slide recuts as well as the heart remnants are provided if requested. During an 8 month period, 22 heart valves were procured in this fashion for transplant in the state of Virginia.

Sharing Data and Test Results

O/TPOs do extensive testing for the presence of natural diseases (such as HIV) and other medical conditions. It is imperative that the ME/C be given copies of these results for their evaluation of the case and also if there is a need to notify the next of kin of any abnormalities. Likewise, it is the responsibility of the ME/C to notify the O/TPO of any unexpected abnormalities seen at autopsy or upon microscopic examination of the tissues. In the case of organ or corneal donation, this must be

Fig. 38.1 Opportunity for sterile examination of the resected heart by the pathologist (Courtesy LifeNet Health, with permission)

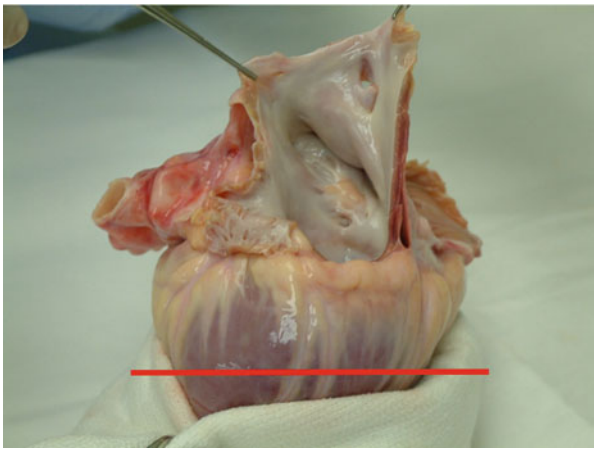

Fig. 38.2 Transverse section through mid-septum: The red line denotes highest level to transversely incise the heart. Coronary arteries should not be serially sliced above this line (Courtesy LifeNet Health, with permission)

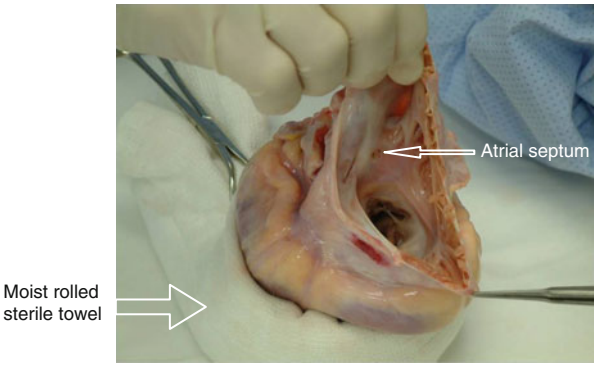

Fig. 38.3 Open the right atrium between the superior and inferior vena cava. View the atrial chamber and the tricuspid valve (Courtesy LifeNet Health, with permission)

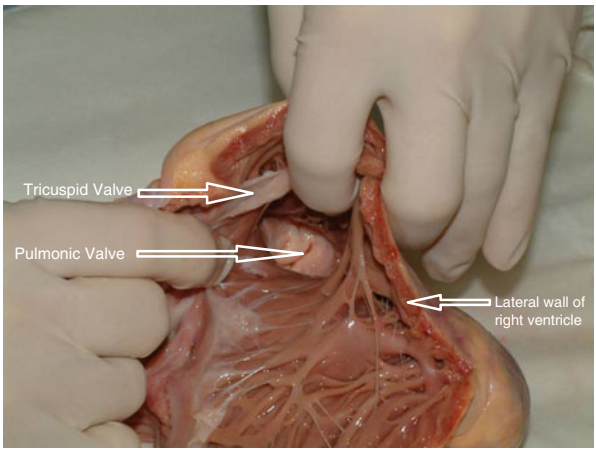

Fig. 38.4 The right ventricle is opened by incising the lateral wall and cutting through the tricuspid valve. The intact pulmonic valve can be viewed from the right ventricle (Courtesy LifeNet Health, with permission)

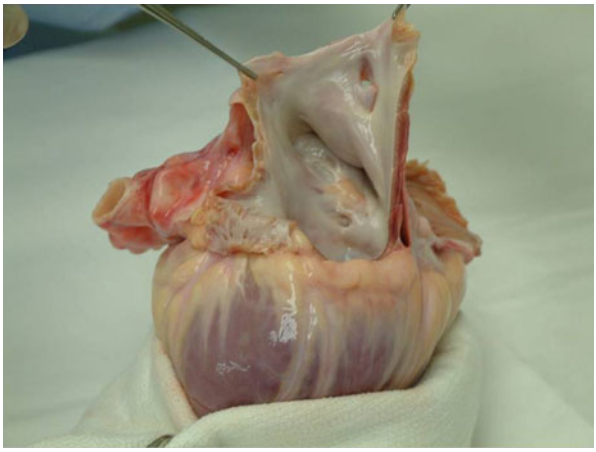

Fig. 38.5 The left atrium is opened by incising near the pulmonary veins (Courtesy LifeNet Health, with permission)

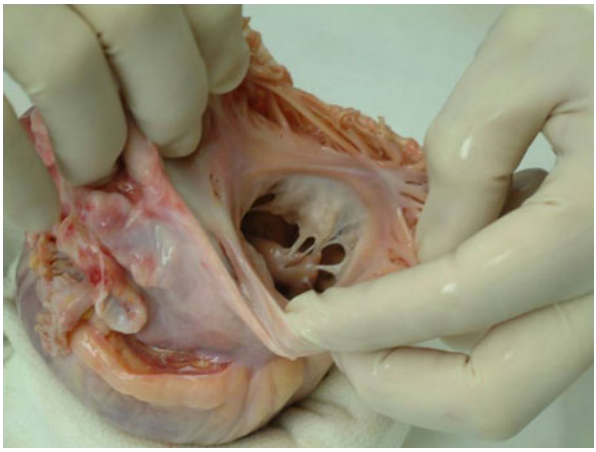

Fig. 38.6 The mitral valve is visualized and assessed from above via the left atrium (Courtesy LifeNet Health, with permission)

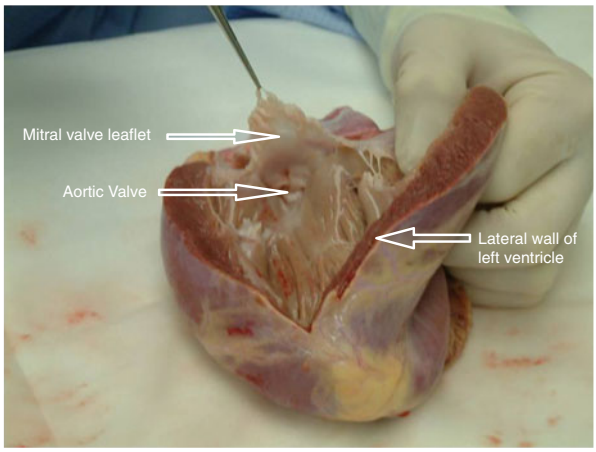

Fig. 38.7 The lateral wall of the left ventricle is incised. The intact aortic valve can be examined from the left ventricle below. The procurement organization can provide a written pathology report describing the aortic valve and coronary ostia at the time of processing (Courtesy LifeNet Health, with permission)

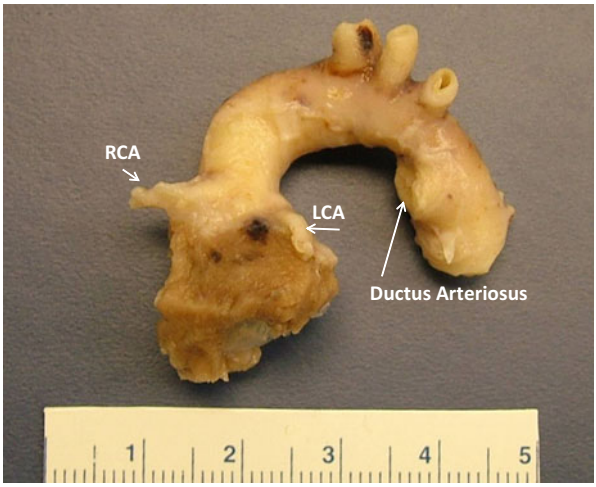

Fig. 38.8 Procured neonatal aortic valve allograft (Courtesy Cryolife, Inc., with permission)

done as soon as possible after completion of the autopsy since transplantation occurs within a matter of hours. In contrast, tissues (other than cornea) are often preserved for prolonged periods of time. Nonetheless, it is the responsibility of the ME/C to expeditiously provide a copy of the final autopsy report to the O/TPO which is necessary before the tissues can be released for transplantation. Since the toxicology report is usually considered a part of the autopsy report, it may be necessary to request expedited toxicological testing to allow completion of the autopsy report and thereby the timely release of tissues for transplantation.

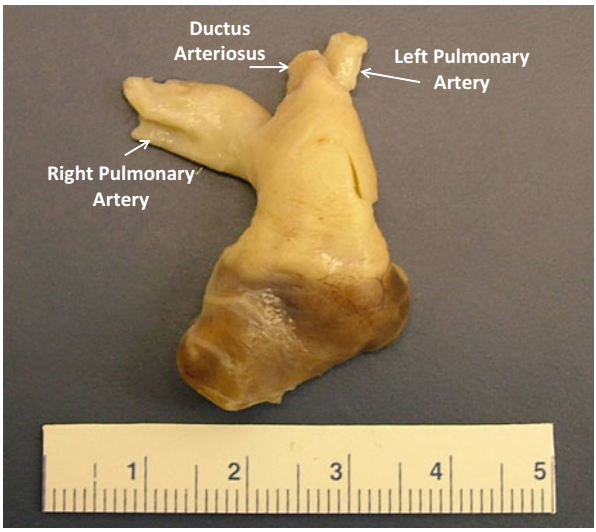

Fig. 38.9 Procured neonatal pulmonic valve allograft (Courtesy Cryolife, Inc., with permission)

Conclusions

Concerns of organ and tissue donation in pediatric cases interfering with criminal and civil proceedings or precluding the diagnosis of a cardiac abnormality have been virtually eliminated by studies and protocols developed over recent years. Of paramount importance is the establishment of good communication and cooperation between the ME/C and the O/TPO to achieve each other's goals. Today, there should be no denials for organ and tissue donation in pediatric cases under ME/C jurisdiction, even in cases of suspected child abuse or SIDS/SUDI. Authorized donations with restrictions should be conservative, reasonable, and justifiable. The ME/C is therefore in a unique position to save and enhance the lives of numerous transplant recipients and yet respond adequately to the stakeholders who depend on the work of the ME/C.

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Resources

American Association of Tissue Banks, 1320 Old Chain Bridge Road, Suite 450, McLean, Virginia 22101; Tel: 703-827-9582; www.aatb.org
American Society of Transplant Surgeons, 2461 South Clark St., Suite 640, Arlington, VA 22202; Tel: 703-414-7870; www.asts.org
Association of Organ Procurement Organizations, 8500 Leesburg Pike, Suite 300, Vienna, VA 22182; Tel: 703-556-4242 ; www.aopo.org
Donate Life America, 701 East Byrd Street, 16tl1 Floor, Richmond, VA 23219; Tel: 804-377-3580; www.donatelife.net
Eye Bank Association of America, 1015 Eighteenth Street NW, Suite 1010, Washington, DC 20036; Tel: 202-775-4999; www.restoresight.org
United Network for Organ Sharing, 700 North 4th Street, Richmond, VA 23219; Tel: 804-782-4800; www.unos.org

Death Certification

39

Randy Hanzlick

Contents

Abstract

Pediatric deaths – whether these involve a newborn, infant, toddler, preadolescent, or adolescent – fall into one of four categories. (1) Cause of death is known (clinically and/or after autopsy) and is basically incontrovertible. (2) Cause of death is known with reasonable probability. (3) There are competing causes of death, and decisions about the cause of death require careful consideration and judgment. (4) Cause of death is unknown and is unable to be determined with reasonable probability. While similar concepts and guidelines can be used to certify deaths in all of the pediatric age groups, the differential diagnosis and likely causes of death vary somewhat among these groups. This chapter is based

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DOI 10.1007/978-1-61779-403-2_40,

largely on principles outlined in definitions and guidelines that have been published specifically for death certification.

Introduction

Whether a pediatric death involves a newborn, infant, toddler, preadolescent, or adolescent, deaths fall into one of the following categories:

- The cause of death is known (clinically and/or after autopsy) and is basically incontrovertible.
- The cause of death is known with reasonable probability.
- There are competing causes of death, and decisions about the cause of death require careful consideration and judgment.
- The cause of death is unknown and is unable to be determined with reasonable probability.

Similar concepts and guidelines can be used to certify deaths in all of the pediatric age groups, although the differential diagnosis and likely causes of death vary somewhat among the age groups.

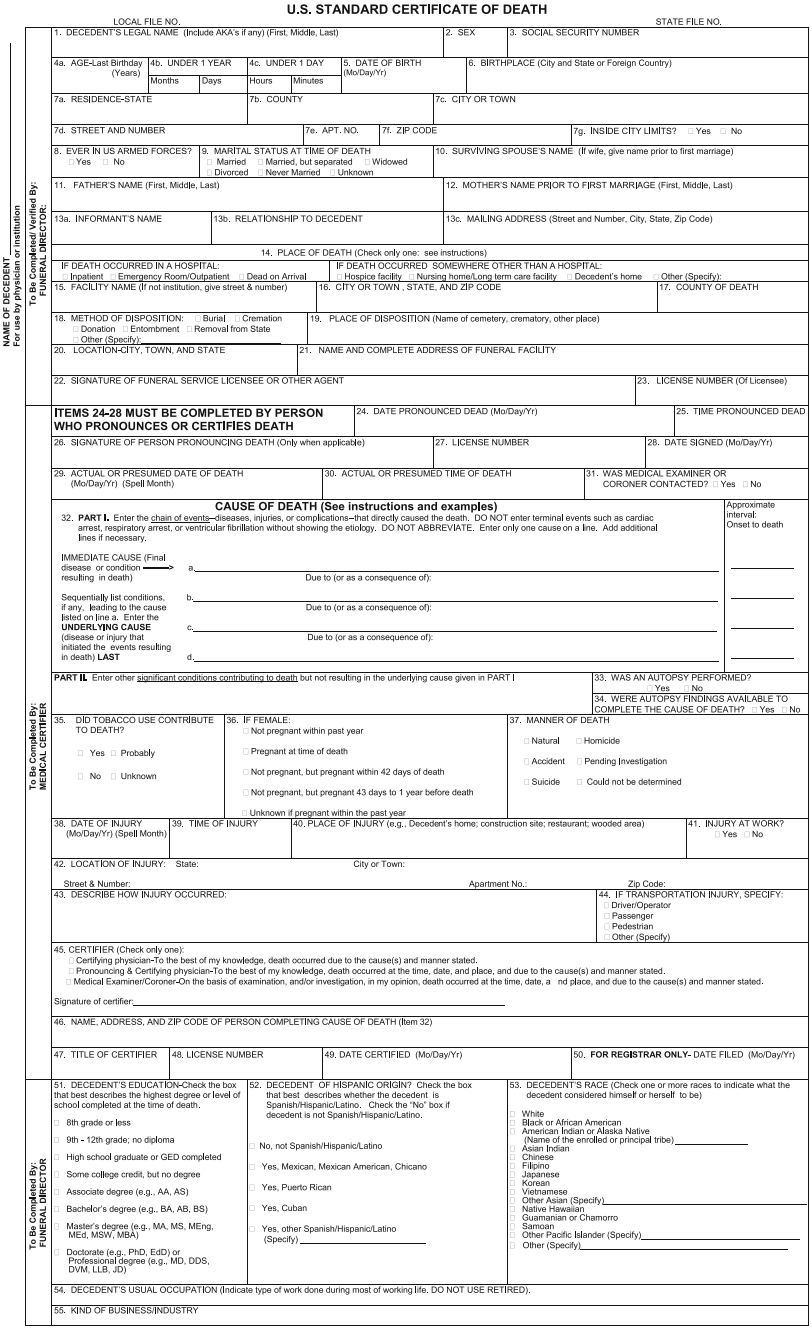
Definitions and guidelines have been published specifically for death certification (NCHS 2003a, b; Hanzlick 2006). This chapter is based largely on principles outlined in those publications.

The Death Certificate

Each state in the United States (USA) has an official death certificate form which must be completed when there has been indication of live birth and then death ensues, whether quickly or after a prolonged normal life span. The death certificate in each state is based on a US Standard Certificate of Death, the most recent version of which was prepared in 2003 (Fig. 39.1). Although official state death certificates may vary from the US standard in some respects, most have a similar appearance and content. Relevant to this chapter, which deals mainly with the medical certification portion of the death certificate (the section containing the cause and circumstances of death), the medical certification section is very similar in all states and is shown in Fig. 39.2. The US Standard Certificate of Death is based on recommendations of the World Health Organization (WHO), so the death certificate in many countries is of similar design and content when compared to the US standard. There are 193 member states (countries) which belong to the WHO and follow its guidelines.

The most critical information about the cause of death is contained in box 32 as shown in Fig. 39.2, and this box must be completed in all deaths. Boxes 35–37 and 45–49 are also completed in all deaths, while those items in boxes 38 through 44 are completed only if the manner of death indicated on box 37 is other than Natural (or is other than "Pending Investigation").

The numbers assigned to the boxes on the death certificate where you work may be different from the numbers on the US Standard Certificate of Death. In general,



U.S. STANDARD CERTIFICATE OF DEATH

LOCAL FILE NO. STATE FILE NO.

NAME OF DECEDENT — For use by physician or institution — To Be Completed/ Verified By: FUNERAL DIRECTOR

1. DECEDENT'S LEGAL NAME (Include AKA's if any) (First, Middle, Last) | 2. SEX | 3. SOCIAL SECURITY NUMBER

4a. AGE-Last Birthday (Years) | 4b. UNDER 1 YEAR Months Days | 4c. UNDER 1 DAY Hours Minutes | 5. DATE OF BIRTH (Mo/Day/Yr) | 6. BIRTHPLACE (City and State or Foreign Country)

7a. RESIDENCE-STATE | 7b. COUNTY | 7c. CITY OR TOWN

7d. STREET AND NUMBER | 7e. APT. NO. | 7f. ZIP CODE | 7g. INSIDE CITY LIMITS? ☐ Yes ☐ No

8. EVER IN US ARMED FORCES? ☐ Yes ☐ No | 9. MARITAL STATUS AT TIME OF DEATH ☐ Married ☐ Married, but separated ☐ Widowed ☐ Divorced ☐ Never Married ☐ Unknown | 10. SURVIVING SPOUSE'S NAME (If wife, give name prior to first marriage)

11. FATHER'S NAME (First, Middle, Last) | 12. MOTHER'S NAME PRIOR TO FIRST MARRIAGE (First, Middle, Last)

13a. INFORMANT'S NAME | 13b. RELATIONSHIP TO DECEDENT | 13c. MAILING ADDRESS (Street and Number, City, State, Zip Code)

14. PLACE OF DEATH (Check only one: see instructions)

IF DEATH OCCURRED IN A HOSPITAL: ☐ Inpatient ☐ Emergency Room/Outpatient ☐ Dead on Arrival
IF DEATH OCCURRED SOMEWHERE OTHER THAN A HOSPITAL: ☐ Hospice facility ☐ Nursing home/Long term care facility ☐ Decedent's home ☐ Other (Specify):

15. FACILITY NAME (If not institution, give street & number) | 16. CITY OR TOWN , STATE, AND ZIP CODE | 17. COUNTY OF DEATH

18. METHOD OF DISPOSITION: ☐ Burial ☐ Cremation ☐ Donation ☐ Entombment ☐ Removal from State ☐ Other (Specify):_____ | 19. PLACE OF DISPOSITION (Name of cemetery, crematory, other place)

20. LOCATION-CITY, TOWN, AND STATE | 21. NAME AND COMPLETE ADDRESS OF FUNERAL FACILITY

22. SIGNATURE OF FUNERAL SERVICE LICENSEE OR OTHER AGENT | 23. LICENSE NUMBER (Of Licensee)

To Be Completed By: MEDICAL CERTIFIER

ITEMS 24-28 MUST BE COMPLETED BY PERSON WHO PRONOUNCES OR CERTIFIES DEATH

24. DATE PRONOUNCED DEAD (Mo/Day/Yr) | 25. TIME PRONOUNCED DEAD

26. SIGNATURE OF PERSON PRONOUNCING DEATH (Only when applicable) | 27. LICENSE NUMBER | 28. DATE SIGNED (Mo/Day/Yr)

29. ACTUAL OR PRESUMED DATE OF DEATH (Mo/Day/Yr) (Spell Month) | 30. ACTUAL OR PRESUMED TIME OF DEATH | 31. WAS MEDICAL EXAMINER OR CORONER CONTACTED? ☐ Yes ☐ No

CAUSE OF DEATH (See instructions and examples)

Approximate Interval: Onset to death

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

IMMEDIATE CAUSE (Final disease or condition resulting in death) → a._____ Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b._____ Due to (or as a consequence of):
c._____ Due to (or as a consequence of):
d._____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH? ☐ Yes ☐ Probably ☐ No ☐ Unknown

36. IF FEMALE: ☐ Not pregnant within past year ☐ Pregnant at time of death ☐ Not pregnant, but pregnant within 42 days of death ☐ Not pregnant, but pregnant 43 days to 1 year before death ☐ Unknown if pregnant within the past year

37. MANNER OF DEATH ☐ Natural ☐ Homicide ☐ Accident ☐ Pending Investigation ☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month) | 39. TIME OF INJURY | 40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area) | 41. INJURY AT WORK? ☐ Yes ☐ No

42. LOCATION OF INJURY: State: City or Town: Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED: | 44. IF TRANSPORTATION INJURY, SPECIFY: ☐ Driver/Operator ☐ Passenger ☐ Pedestrian ☐ Other (Specify)

45. CERTIFIER (Check only one):
☐ Certifying physician-To the best of my knowledge, death occurred due to the cause(s) and manner stated.
☐ Pronouncing & Certifying physician-To the best of my knowledge, death occurred at the time, date, and place, and due to the cause(s) and manner stated.
☐ Medical Examiner/Coroner-On the basis of examination, and/or investigation, in my opinion, death occurred at the time, date, a nd place, and due to the cause(s) and manner stated.

Signature of certifier:_____

46. NAME, ADDRESS, AND ZIP CODE OF PERSON COMPLETING CAUSE OF DEATH (Item 32)

47. TITLE OF CERTIFIER | 48. LICENSE NUMBER | 49. DATE CERTIFIED (Mo/Day/Yr) | 50. **FOR REGISTRAR ONLY-** DATE FILED (Mo/Day/Yr)

To Be Completed By: FUNERAL DIRECTOR

51. DECEDENT'S EDUCATION-Check the box that best describes the highest degree or level of school completed at the time of death.
☐ 8th grade or less
☐ 9th - 12th grade; no diploma
☐ High school graduate or GED completed
☐ Some college credit, but no degree
☐ Associate degree (e.g., AA, AS)
☐ Bachelor's degree (e.g., BA, AB, BS)
☐ Master's degree (e.g., MA, MS, MEng, MEd, MSW, MBA)
☐ Doctorate (e.g., PhD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD)

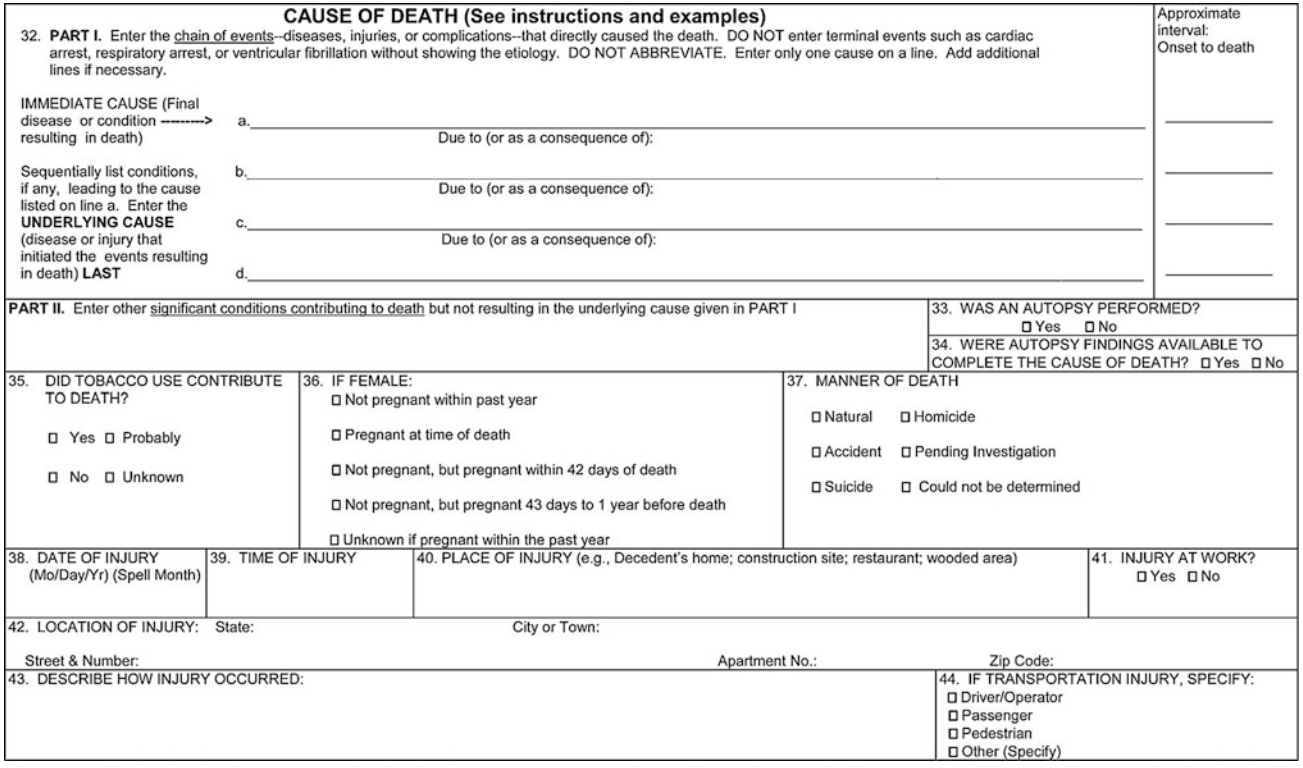
52. DECEDENT OF HISPANIC ORIGIN? Check the box that best describes whether the decedent is Spanish/Hispanic/Latino. Check the "No" box if decedent is not Spanish/Hispanic/Latino.
☐ No, not Spanish/Hispanic/Latino
☐ Yes, Mexican, Mexican American, Chicano
☐ Yes, Puerto Rican
☐ Yes, Cuban
☐ Yes, other Spanish/Hispanic/Latino (Specify) _____

53. DECEDENT'S RACE (Check one or more races to indicate what the decedent considered himself or herself to be)
☐ White
☐ Black or African American
☐ American Indian or Alaska Native (Name of the enrolled or principal tribe) _____
☐ Asian Indian
☐ Chinese
☐ Filipino
☐ Japanese
☐ Korean
☐ Vietnamese
☐ Other Asian (Specify)_____
☐ Native Hawaiian
☐ Guamanian or Chamorro
☐ Samoan
☐ Other Pacific Islander (Specify)_____
☐ Other (Specify)_____

54. DECEDENT'S USUAL OCCUPATION (Indicate type of work done during most of working life. DO NOT USE RETIRED).

55. KIND OF BUSINESS/INDUSTRY

Fig. 39.1 US Standard Certificate of Death



CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition --------> resulting in death) a. _____ Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. _____ Due to (or as a consequence of):
c. _____ Due to (or as a consequence of):
d. _____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☐ No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month)

39. TIME OF INJURY

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area)

41. INJURY AT WORK? ☐ Yes ☐ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.2 The medical certification section of the US Standard Certificate of Death. The corresponding section on various state death certificates is substantially the same

however, the various boxes, regardless of the box number, are in similar places on the death certificate and are intended to contain the same information as the US Standard Certificate of Death.

For case-example purposes, box 32 on the US Standard Certificate of Death can be shown more schematically as follows:

Part I	A.	Approximate interval between onset and death
	Due to, or as a consequence of: B.	
	Due to, or as a consequence of: C.	
	Due to, or as a consequence of: D.	
Part II	OTHER SIGNIFICANT CONDITIONS: conditions contributing to death but not resulting in the underlying cause of death in Part I	

This schematic will be used in the first part of this chapter to illustrate some of the principles and guidelines for certification of fatalities in the pediatric age group. The words placed into Part I and Part II are referred to as the *cause-of-death statement*. The person who prepares the cause-of-death statement and signs the cause-of-death section of the death certificate is the *certifier of death*.

Basic Principles

A case example can be used to facilitate discussion of most of the critical elements in writing a cause-of-death statement.

Part I	A. **Streptococcal septic emboli with systemic sepsis**	Approximate interval between onset and death Days
	Due to, or as a consequence of: B. **Infection of aortic bypass graft**	Weeks
	Due to, or as a consequence of: C. **Previous aortic dissection**	2 years
	Due to, or as a consequence of: D. **Marfan Syndrome**	15 years
Part II	OTHER SIGNIFICANT CONDITIONS: conditions contributing to death but not resulting in the underlying cause of death in Part I Type I diabetes mellitus	

In this example, Marfan Syndrome is the *underlying cause of death*. It is the disease or condition which started the downhill course of fatal events. Streptococcal septic emboli and sepsis are the *immediate cause of death*, which is the disease or condition which occurred closest to the time of death and is immediately

responsible for causing the death. Infection of aortic bypass graft and previous aortic dissection are *intermediary causes of death* because these conditions temporally occurred between the underlying and immediate causes of death. Type I diabetes is an*other significant condition* because it is a preexisting or coexisting condition which contributed to death but did not result in the underlying cause of death (Marfan Syndrome). In the example shown, the certifier believed that the patient's preexisting diabetes predisposed the patient to the development of infection.

In most cases, the certifier of death should try to enter only one condition per line in Part I of the cause-of-death statement. More than one condition may be listed as other significant conditions.

It is not always necessary nor required to use all of the available lines in Part I. For example, the following cause-of-death-statement is completely adequate in which only an immediate and underlying cause of death is reported:

Part I	A. **Cerebral anoxia**	Approximate interval between onset and death Days
	Due to, or as a consequence of: B. **Tetralogy of Fallot**	2 months
	Due to, or as a consequence of: C.	
	Due to, or as a consequence of: D.	
Part II	OTHER SIGNIFICANT CONDITIONS: conditions contributing to death but not resulting in the underlying cause of death in Part I	

In some instances, a *Single Line Part I Format* is acceptable, when an immediate cause of death is not known, but the underlying cause of death is apparent, as might occur when an autopsy is not performed following a prolonged and well-documented illness:

Part I	A. **Metastatic adrenal neuroblastoma**	Approximate interval between onset and death 6 years
	Due to, or as a consequence of: B.	
	Due to, or as a consequence of: C.	
	Due to, or as a consequence of: D.	
Part II	OTHER SIGNIFICANT CONDITIONS: conditions contributing to death but not resulting in the underlying cause of death in Part I	

Cause-of-death statements for deaths due to injury or poisoning can often be certified using concepts similar to immediate, intermediary, and underlying cause

of death using a general approach which includes the fatal derangement, the bodily trauma, and the injury event such as

Part I	A. **Hemorrhage into left hemithorax**	Approximate interval between onset and death Minutes
	Due to, or as a consequence of: B. **Puncture of aorta**	Minutes
	Due to, or as a consequence of: C. **Stab wound of left anterior chest**	Minutes
	Due to, or as a consequence of: D.	
Part II	OTHER SIGNIFICANT CONDITIONS: conditions contributing to death but not resulting in the underlying cause of death in Part I	

In the above case, the fatal derangement is the hemorrhage, the bodily trauma is the perforated aorta, and the injury event is the stab wound.

For poisoning deaths, a similar approach can sometimes be used such as

Part I	A. **Chlorine gas poisoning**	Approximate interval between onset and death Minutes
	Due to, or as a consequence of: B. **Inhalation of toxic gases**	Minutes
	Due to, or as a consequence of: C. **Inadvertent mixture of commercial cleaning products**	Minutes
	Due to, or as a consequence of: D.	
Part II	OTHER SIGNIFICANT CONDITIONS: conditions contributing to death but not resulting in the underlying cause of death in Part I	

In a good number, if not most deaths involving injury or poisoning, the fatal derangement and/or bodily trauma may be obscure, complex, or multiple to an extent which precludes the ability to state them concisely or completely in the cause-of-death statement. In such cases, a Single Line Part I Format may be required such as "ethylene glycol poisoning" or "generalized blunt force injuries."

Basic Definitions

Cause of death. The disease(s), condition(s), and/or external factors such as injury or poisoning which resulted in death. The cause of death is reported on the death certificate using Part I and Part II (if needed) in the cause-of-death section of the death certificate. This information is referred to as the *cause-of-death statement*.

Manner of death. A classification of how the cause of death occurred. The options are natural, accident, homicide, suicide, and undetermined. In some areas, there are additional options. In Oregon, "Other" is an option to classify deaths such as physician-assisted suicide. New York City uses "Therapeutic Complication" to classify some deaths. Use of such classifications is not widespread, however. Manner of death was added to the US Standard Certificate of Death in 1910 to assist those who tabulate and code causes of death in better understanding the circumstances of death. Manner of death is discussed more fully below.

Mechanism of death. A physiological derangement or biochemical disturbance incompatible with life, which is initiated by the cause of death, or, stated another way, a physiological derangement or biochemical disturbance produced by a cause of death and is the means by which the cause exerts its lethal effect (Adelson 1974; Kircher 1992). Entities such as hemorrhage, acidosis, and cardiac tamponade are examples of mechanisms. As a matter of general practice, it is acceptable and often appropriate to include relevant mechanisms in the cause-of-death statement so long as important immediate and underlying causes of death are also reported. Some people use the words "mode of dying" in a way similar to mechanism of death, but the term, in general, is not in common use.

Terminal events. These include conditions such as cardiac arrest, respiratory arrest, cardiopulmonary arrest, asystole, electromechanical dissociation, ventricular fibrillation, and pulseless electrical activity. These are final common pathways to death and in general, should not, and need not be reported on the death certificate.

Other Items Needing Completion

From this point forward, example cause-of-death statements will be shown using the format which actually appears on the US Standard Certificate of Death.

Item 33. Was an autopsy performed? "Yes" should be checked even if the autopsy was "partial" or "limited." If desired, such words can be written in the box to indicate the same.

Item 34. Were autopsy findings available to complete the cause of death? "Yes" should be checked if autopsy findings were used to develop the cause-of-death statement written on the death certificate.

Item 35. Did tobacco use contribute to death? In most pediatric deaths, the answer to this question will be "No." However, "Yes" should be checked if tobacco use did play a role by causing adverse health effects contributing to death or through other mechanisms such as a burning cigarette resulting in a fatal house fire.

Item 36. If female. In most pediatric age group cases, "Not pregnant within past year" will be the correct choice. This item may be ignored when the deceased is male. Some states may have a "not applicable" item which can be used for males or females who are not yet of childbearing age.

Item 37. Manner of death. This item is discussed more thoroughly below.

Injury-Related Information

If the manner of death is other than "Natural" and is not listed as "Pending Investigation," additional items must be completed.

Items 38 and 39. Date of injury and time of injury. If the date of injury or time of injury is not known, "Unknown" is acceptable, but it is also acceptable and preferred to qualify the date and/or time as "found" or "approx" (approximate).

Item 40. Place of injury. A brief description of the type of place is entered in this box. These should be generic and not include formal business names. For example, in the case of someone who was shot at a restaurant with a well-known trade name, "Fast-Food Restaurant" should be entered rather than the formal name of the business. When possible, enough information should be provided to make the place of injury clear, such as "Inside another's home," "Enclosed parking deck," "Found in river," "In own apartment," and "House construction site."

Item 41. Injury at work. For most pediatric deaths, "No" will be the correct choice. To check this answer "Yes," the decedent should have been on a paying job in which the decedent was being paid by an employer. Death while mowing a neighbor's yard, done periodically for $10 per mowing, for example, would not be considered "injury at work."

Item 42. Location of injury. The street number, street name, city, state, and zip code where the injury occurred should be placed in this box. If the body was found, it is acceptable to indicate "Found at" followed by the address. If the injury address is truly unknown, "Unknown" may be entered. In most pediatric deaths, the injury address will be known.

Item 43. Describe how injury occurred. The space provided in this box varies somewhat by state; one should try to be complete (while being concise) when completing this item. Typical examples are as follows: "Driver of car that struck utility pole," "Hanged self with rope from door," "Shot by another person(s)," "Ingested multiple over-the-counter medications," and "Injected illicit substance (heroin)."

Item 44. If transportation injury, specify. This item is self-explanatory. "Other" can be used in cases in which a person may have been riding on top of a car or in the bed of a truck, for example.

Items 45 through 49 are self-explanatory. Note that the words "to the best of my knowledge" and "in my opinion" are used in the choices contained in box 45. You do not have to be absolutely certain about a cause of death. Your cause-of-death statement is merely your best opinion based on the information available to you at the time you certify the death. It can be changed (amended) at a later time if additional, relevant information becomes available.

Manner of Death

Other than "Pending Investigation" which is utilized to initially file a death certificate which will need to be updated with a supplemental report at a later time, there are five choices for manner of death: natural, homicide, suicide, accident, and undetermined.

Natural deaths are due solely to disease conditions and/or process of aging. Usually, if an injury or poisoning contributes to death also involving natural conditions, preference is given to a manner of death other than natural. For example, if a child with cerebral palsy falls and sustains a fatal subdural hemorrhage, the manner of death would be classified as accident even though the fall may have been brought about by the cerebral palsy which is usually considered to be a natural condition.

Homicide is the death of a person at the hands of another either with intent to harm or via a volitional act which may not have been intended to harm, but which was directed at the victim intentionally. An example of the latter is a child who points a gun at a sibling and pulls the trigger thinking the gun is not loaded, when, in fact, it was loaded and it discharged and killed the other child.

Suicide is death brought about by a self-inflicted act which is meant to end one's life or do self-harm. Operational criteria have been published to assist with the determination of suicide as the manner of death. In the older pediatric age group, the most likely controversial cases are hangings which may be suicide or the result of so-called choking games such as Space Monkey. Russian roulette is another example. Most people consider these as suicide because the game is played knowing the potential outcome, using a known potentially lethal outcome, and the injury is self-inflicted (see ▶ Chap. 25, "Pediatric Suicide").

Accident is the classification used for deaths that involve unintentional death involving injury and/or poisoning. In the pediatric age group, motor-vehicle accidents, household injuries, and recreational drug use in the older pediatric group will be the most common types of accidental death encountered. Deaths from choking games are also considered as accidents.

Undetermined (*or could not be determined*) is used to classify deaths in which another manner of death cannot be determined with reasonable probability. It has become common for sudden unexplained infant deaths to also be classified as undetermined because there is often an indication of an external, nonnatural cause (injury or poisoning) which cannot be proven or disproven.

A previous publication includes extensive discussion and case examples which address manner of death classification (Hanzlick et al. 2002).

Likely Causes of Death in the Pediatric Age Group

Table 39.1 below shows selected causes of death for persons in three age groups ranging from infancy through age 14 years in the USA. The data were obtained from the National Center for Health Statistics (NCHS) (NCHS 2011). NCHS groups deaths of persons ages 15 through 24 years into another group, which makes it difficult to separate out those who are 15 or 16 years old and truly in the pediatric age group, and the data becomes somewhat biased toward mortality patterns in young adults which includes more homicides, suicides, and motor-vehicle accidents than the younger age groups. For that reason, the data below only include persons up to 14 years of age.

Table 39.1 Selected causes of death for persons in three age groups ranging from infancy through age 14 years in the USA. The data were obtained from the National Center for Health Statistics (NCHS) (NCHS 2011). The **bolded** categories are types of cases which would typically come to the forensic pathologist's attention. Source: National Center for Health Statistics 2007

Cause	Under 1 year	1–4 years old	5–14 years	Total
Perinatal conditions	14,466	70	22	14,558
Congenital/genetic	5,785	546	374	6,706
SIDSOID/Ill-defined (R00-R99)	**3,617**	**237**	**110**	**3,964**
Accidents	**1,285**	**1,588**	**2,194**	**5,067**
Influenza/pneumonia/respiratory	754	340	344	1,438
Cardiac	571	383	557	940
Other infection	484	162	156	802
Homicide	**352**	**398**	**346**	**1,096**
Malignancy	92	477	1,204	1,773
Suicide	0	0	**184**	**184**
Total, above + others	29,138	4,703	6,147	39,988

Table 39.1 provides some useful information. Firstly, about 25 % of pediatric deaths will probably come to the forensic pathologist's attention. Secondly, across all ages between infancy and 14 years, unexplained deaths (such as many sudden infant deaths), accidents, homicides, and suicides in the older age group will be the primary types of cases undergoing forensic investigation. The practical fact within these statistics is that most forensic pediatric death cases can be certified with a good understanding of methods used to certify deaths due to unexplained and ill-defined causes, along with deaths due to chemical or physical injury. Stating the underlying cause of death as specifically as possible should be the goal, while also trying to include an immediate and any intermediary causes of death, when possible. Later parts of this chapter provide information to assist in this endeavor (Table 39.2).

In the infant group, most of the cases of undetermined manner were sudden unexplained infant deaths. In the older age group, a specific manner of death was able to be determined in nearly all cases.

For deaths in the infant age group, the following were listed as underlying causes of death:

- Acute bronchiolitis
- Acute bronchopneumonia
- Anomalous origin of right coronary artery
- Asphyxia due to suffocation
- Blunt force abdominal trauma
- Blunt force injuries
- Bronchopulmonary dysplasia
- Candida pneumonia
- Coarctation of aorta
- Complications of Dandy-Walker Syndrome
- Complications of DiGeorge Syndrome
- Complications of meningitis

Table 39.2 Data for 678 pediatric deaths reported to the author's office during the years 2003 through 2010 showed the following types of death

	Infants	1–16 years	Total
Declined jurisdiction[a]	143	78	221
Non-MVA accidents	22	42	64
MVA accidents	6	56	62
Homicide	16	58	74
Natural	64	45	109
Suicide	0	13	13
Undetermined	133	2	135
Total	384	294	678

[a]Reported to, but not requiring complete investigation or certification by the medical examiner
MVA- motor vehicle accidents

- Complications of neuroblastoma
- Complications of thermal injuries
- Congenital adrenal hypoplasia
- Congenital heart disease
- Congenital hypothyroidism with trisomy 21
- Consistent with sudden infant death syndrome
- Craniocerebral trauma
- Drowning
- Failure to thrive
- Gunshot wound of chest
- *Hemophilus influenzae* pneumonia
- Herpes simplex viral meningoencephalitis
- Hypertension associated with repaired congenital heart defects
- Interstitial and intra-alveolar pneumonitis
- Malnourishment
- Maternal placental abruption with prematurity
- Microvesicular hepatosteatosis of unknown etiology
- Mycoplasma pneumonia infection
- Myocarditis
- Nuchal umbilical cord
- Overlaying
- Patent foramen ovale
- Perinatal cerebral hypoxemia
- Prone sleeping on soft bedding
- Scalding injuries
- Seizure disorder
- Spina bifida and myelomeningocele
- Sudden unexplained infant death (or similar wording)
- Surgical complications during repair of patent ductus arteriosus
- Tetralogy of Fallot
- Toxic effects of fentanyl

- Traumatic head injuries
- Undetermined
- Unexpected and undetermined cause
- Von Hippel-Lindau disease
- Wedging

For deaths in the post-infancy period (age 1–16 years), the following were listed as underlying causes of death:

- Acetaminophen poisoning
- Acyl-CoA dehydrogenase deficiency
- Anomalous origin of left main coronary artery
- Aspiration of hair ornament
- Bacterial pneumonia
- Blunt force craniocerebral trauma
- Blunt force craniocerebral trauma with skull fracture
- Blunt force head trauma
- Blunt force injuries of head, neck, and extremities
- Blunt force injuries of head
- Bronchiolitis
- Choking on food
- Chop wounds of head
- Complications of cerebral palsy
- Complications of congenital hydrocephalus
- Complications of GM-1 gangliosidosis
- Complications of prematurity
- Complications of spinal muscular atrophy
- Compressional asphyxia
- Congenital and chromosomal disorders
- Contact gunshot wound of head
- Dilated cardiomyopathy
- Drowning
- Entrapment
- Generalized blunt force trauma
- Group A Streptococcus infection
- Gunshot wound of chest
- Gunshot wound of head
- Gunshot wound of torso
- Gunshot wounds of head and right arm entering chest
- Hanging
- Hypertrophic cardiomyopathy
- Influenza A infection
- Inhalation of chlorodifluoromethane
- Inhalation of products of combustion
- Intrauterine hypoxia and premature birth
- Ligature hanging
- Lightning strike

- Lymphocytic myocarditis
- Methadone toxicity
- Multiple congenital anomalies
- Necrotizing colitis
- *Neisseria meningitidis* meningitis
- Posterior dislocation of the sternoclavicular joint
- Prader-Willi Syndrome
- Precursor B-cell acute lymphoblastic leukemia
- Premature birth
- Previous abdominal surgery for hernia repair
- Probable remote myocarditis
- Remote traumatic brain injury
- Seizure disorder
- Sickle cell disease
- Sickle cell trait exacerbated by physical altercation
- Smoke and soot inhalation
- Stab wound of neck into right chest
- Strangulation with ligature
- *Streptococcus pyogenes* infection
- Tracheal papilloma
- Undetermined

Many of the causes shown in the above two lists were used just once or just a few times, while others were utilized quite frequently. The listed causes are provided to show the scope of causes encountered in forensic pediatric death cases.

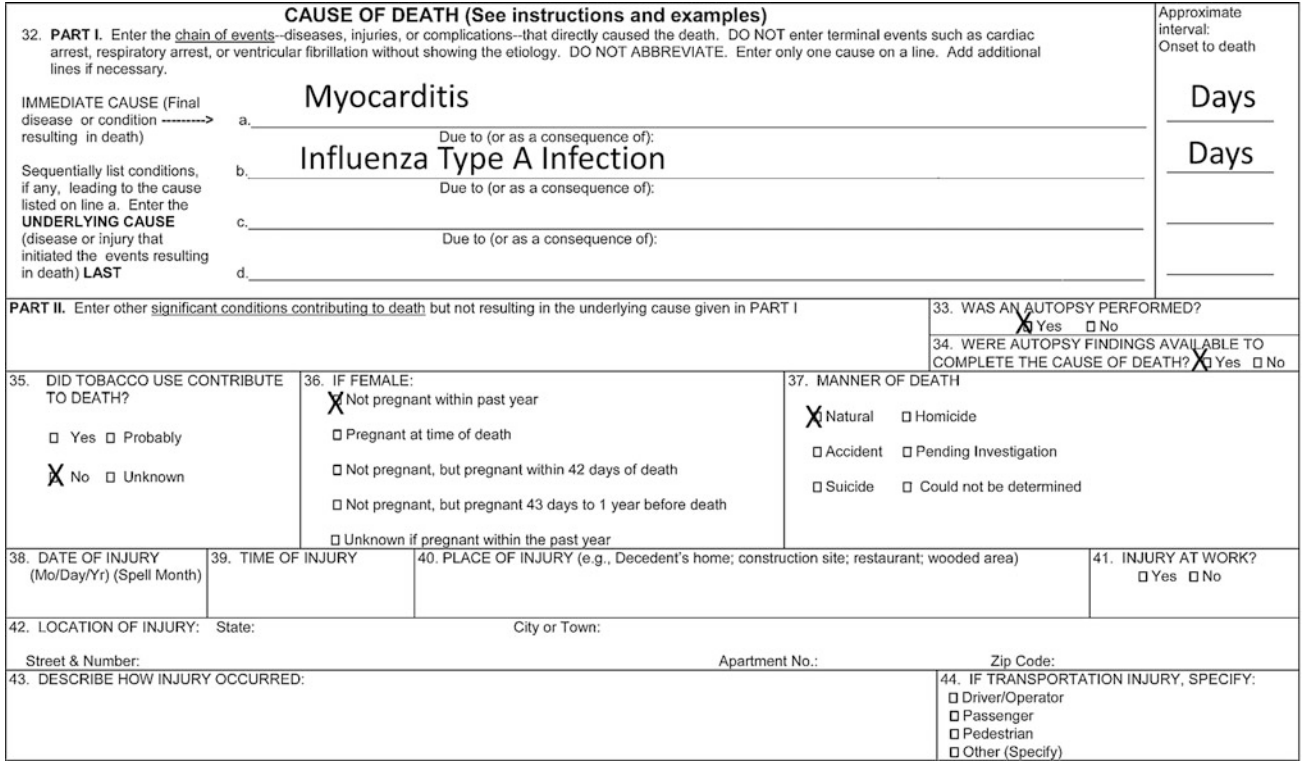
Although not always done in the above examples, in cases involving infections, one should always try to include the etiologic infectious agent in the cause-of-death statement, such as "*Neisseria meningitidis* meningitis." To do so may require cultures or other special immunohistochemical studies.

Infant Deaths

Two recent articles have examined sudden unexpected infant deaths such as those traditionally viewed as "sudden infant death syndrome" (Corey et al. 2007; Nashelsky and Pinckard 2011). Sudden unexpected infant deaths, after investigation and autopsy, will typically fall into one of two groups: those with clear causes of death and those that remain unexplained or incompletely explained. Based on recommendations in the cited references, examples of cause-of-death-statements are shown below (Figs. 39.3–39.6).

For deaths that fall into the "sudden infant death syndrome" scenario, the following two examples show methods that can be used to complete the cause-of-death statement (Figs. 39.7 and 39.8).

A recent paper recommends that the cause of death in cases such as the two previous examples simply be certified as "undetermined" cause and "undetermined" manner (Nashelsky and Pinckard 2011). The authors also suggest that the death



CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Myocarditis — Days

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Influenza Type A Infection — Days

Due to (or as a consequence of):
c. —

Due to (or as a consequence of):
d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? [X] Yes [ ] No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? [X] Yes [ ] No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
[ ] Yes [ ] Probably
[X] No [ ] Unknown

36. IF FEMALE:
[X] Not pregnant within past year
[ ] Pregnant at time of death
[ ] Not pregnant, but pregnant within 42 days of death
[ ] Not pregnant, but pregnant 43 days to 1 year before death
[ ] Unknown if pregnant within the past year

37. MANNER OF DEATH
[X] Natural [ ] Homicide
[ ] Accident [ ] Pending Investigation
[ ] Suicide [ ] Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month)

39. TIME OF INJURY

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area)

41. INJURY AT WORK? [ ] Yes [ ] No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY:
[ ] Driver/Operator
[ ] Passenger
[ ] Pedestrian
[ ] Other (Specify)

Fig. 39.3 Example certification of a natural death. Note that in natural deaths, Boxes 38 through 44 need not be completed. Although the examples shown in this chapter give approximate intervals between onset and death, those data items are requested primarily to assist the nosologists who provide ICD codes for mortality data as it helps them be sure of the order in which conditions occurred. Some vital statistics registrars do NOT require this item to be completed

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Coarctation of aorta — 3 months

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. ____
Due to (or as a consequence of):
c. ____
Due to (or as a consequence of):
d. ____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☒ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☒ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☒ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☒ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month)

39. TIME OF INJURY

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area)

41. INJURY AT WORK? ☐ Yes ☐ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.4 Example certification of a natural death using a Single Line Part I Format

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition --------> resulting in death)
a. Craniocerebral trauma — Minutes
Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Due to (or as a consequence of):
c. Due to (or as a consequence of):
d.

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? [X] Yes [ ] No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? [X] Yes [ ] No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
[ ] Yes [ ] Probably
[X] No [ ] Unknown

36. IF FEMALE:
[X] Not pregnant within past year
[ ] Pregnant at time of death
[ ] Not pregnant, but pregnant within 42 days of death
[ ] Not pregnant, but pregnant 43 days to 1 year before death
[ ] Unknown if pregnant within the past year

37. MANNER OF DEATH
[ ] Natural [X] Homicide
[ ] Accident [ ] Pending Investigation
[ ] Suicide [ ] Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): Jan 6, 2011

39. TIME OF INJURY: Found 0653

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Inside another's apartment

41. INJURY AT WORK? [ ] Yes [X] No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: B3 Zip Code: 44129

43. DESCRIBE HOW INJURY OCCURRED:
Child maltreatment. Injuries inflicted by other(s).

44. IF TRANSPORTATION INJURY, SPECIFY:
[ ] Driver/Operator
[ ] Passenger
[ ] Pedestrian
[ ] Other (Specify)

Fig. 39.5 Certification of a homicide case. Note that in non-natural deaths, boxes 38 through 43 must be completed. Also note that in homicide cases, the description of "how injury occurred' may be somewhat generic. Note that in Box 38, the month of injury is spelled out or abbreviated to avoid confusion with dates used on other countries which may report the day first and then the month. For example, in some countries, 1/4/2012 could be April 1

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Asphyxia — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Overlaying — Minutes

Due to (or as a consequence of):
c. —

Due to (or as a consequence of):
d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? [X] Yes [ ] No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? [X] Yes [ ] No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
[ ] Yes [ ] Probably
[X] No [ ] Unknown

36. IF FEMALE:
[ ] Not pregnant within past year
[ ] Pregnant at time of death
[ ] Not pregnant, but pregnant within 42 days of death
[ ] Not pregnant, but pregnant 43 days to 1 year before death
[ ] Unknown if pregnant within the past year

37. MANNER OF DEATH
[ ] Natural [ ] Homicide
[X] Accident [ ] Pending Investigation
[ ] Suicide [ ] Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): Jan 6, 2011

39. TIME OF INJURY: Found 1830

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Hotel Room

41. INJURY AT WORK? [ ] Yes [X] No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Room 211 Zip Code: 30513

43. DESCRIBE HOW INJURY OCCURRED:
Compressed between sleeping adult and bed mattress

44. IF TRANSPORTATION INJURY, SPECIFY:
[ ] Driver/Operator
[ ] Passenger
[ ] Pedestrian
[ ] Other (Specify)

Fig. 39.6 Certification of an accidental death of a male. Note the specific names of commercial places (such as the hotel name) are not included. For males, item 36 may be left blank

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Sudden unexplained infant death — Unknown

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Undetermined cause — Unknown

Due to (or as a consequence of):

c. —

Due to (or as a consequence of):

d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? X Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? X Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
X No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide X Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): Jan 6, 2011

39. TIME OF INJURY: Found 0805

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Inside own home

41. INJURY AT WORK? ☐ Yes X No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 30301

43. DESCRIBE HOW INJURY OCCURRED:
Face down on soft adult bedding. Bed sharing with 2 adults. Unknown if external causes were involved.

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.7 Sample certification of a case which presented as "sudden infant death syndrome" in which no cause of death could be identified after complete investigation, scene investigation, autopsy, and toxicology testing. In many offices, the manner of such deaths is classified as "undetermined" (or "could not be determined) and even though an injury was not proved, items 38-43 are completed

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Sudden unexplained infant death — Unknown

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Undetermined cause — Unknown

Due to (or as a consequence of):

c. —

Due to (or as a consequence of):

d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? [X] Yes [ ] No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? [X] Yes [ ] No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
[ ] Yes [ ] Probably
[X] No [ ] Unknown

36. IF FEMALE:
[X] Not pregnant within past year
[ ] Pregnant at time of death
[ ] Not pregnant, but pregnant within 42 days of death
[ ] Not pregnant, but pregnant 43 days to 1 year before death
[ ] Unknown if pregnant within the past year

37. MANNER OF DEATH
[ ] Natural [ ] Homicide
[ ] Accident [ ] Pending Investigation
[ ] Suicide [X] Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): Jan 6, 2011

39. TIME OF INJURY: Found 1405

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Day Care Center

41. INJURY AT WORK? [ ] Yes [X] No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 92501

43. DESCRIBE HOW INJURY OCCURRED:
Fund face down in crib. Dextromethorphan ingestion. Unknown if external causes were involved.

44. IF TRANSPORTATION INJURY, SPECIFY:
[ ] Driver/Operator
[ ] Passenger
[ ] Pedestrian
[ ] Other (Specify)

Fig. 39.8 Sample certification of death in which a drug was detected postmortem but the significance of the drug in causing death could not be established

certificate is not the place to include wording such as that shown in box 43 in the two examples above. Whether to follow the examples above or, instead, take the other recommended approach is at the discretion of the certifier. At this point, however, the author of this chapter prefers the hybrid method as shown above, as this method "tells it like it is" and does report factors which may have contributed to death.

There are a few other suggestions to keep in mind when certifying infant deaths. In general, when describing how an injury occurred in cases of homicide, avoid being too specific. For example, avoid terms such as "shaken baby" or "battered child syndrome" which connote specific mechanisms and may be an oversimplification or even inaccurate description of what actually happened. In such cases, it is probably better to use wording such as "injuries inflicted by another" or "child maltreatment." Discussion of specific mechanisms and possible scenarios is better left to consultations with attorneys, police, and legal proceedings. When the type of weapon is known, such as in a fatal gunshot wound, it is probably best to indicate "shot by other (s)" rather than including a specific type of weapon (such as handgun), especially if the weapon has not been recovered. In suicide cases when the type of weapon is known, it is perfectly fine to use words such as "shot self with handgun."

Finally, some vital records registrars do not require that the "approximate interval between onset and death" be completed. This item exists mainly to assist nosologists who code death certificate data to help them ensure that causes are reported in the correct sequence in Part 1. If you are not required to complete this item, complete it only if you wish to. Sometimes it is possible to report exact time frames such as "3 weeks," and in other instances one must be more generic such as "days," "months," "decades," or even "unknown," if applicable.

Cause of Death Versus Incident Information

In the case of a traffic fatality or other similar case, either of the following cause-of-death-statements is acceptable (Figs. 39.9 and 39.10).

People argue about the difference between the *cause* of death and the *fatal incident* and claim that the fatal incident (such as struck by moving vehicle) should not be reported in Part I. Doing so does no harm, the circumstances may even be more clear to a reader of the death certificate, and the ultimate choice as to certification method is at the discretion of the certifier.

Additional Examples

Below are some additional examples of cause-of-death statements for perhaps uncommon, but not unheard of, cases encountered in the forensic setting. The examples have been constructed to show a variety of certification methods. In these examples, the interval between onset and death has been omitted. Keep in mind that there is often more than one acceptable way to certify a death (Figs. 39.11–39.18).

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Blunt force head trauma — 3 days

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Impact by motor vehicle — 3 days

Due to (or as a consequence of):
c. —

Due to (or as a consequence of):
d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? [X] Yes [ ] No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? [X] Yes [ ] No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
[ ] Yes [ ] Probably
[X] No [ ] Unknown

36. IF FEMALE:
[ ] Not pregnant within past year
[ ] Pregnant at time of death
[ ] Not pregnant, but pregnant within 42 days of death
[ ] Not pregnant, but pregnant 43 days to 1 year before death
[ ] Unknown if pregnant within the past year

37. MANNER OF DEATH
[ ] Natural [ ] Homicide
[X] Accident [ ] Pending Investigation
[ ] Suicide [ ] Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): April 01, 2011

39. TIME OF INJURY: 0430

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Interstate Highway

41. INJURY AT WORK? [ ] Yes [X] No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 30333

43. DESCRIBE HOW INJURY OCCURRED:
Pedestrian struck by van while crossing interstate highway

44. IF TRANSPORTATION INJURY, SPECIFY:
[ ] Driver/Operator
[X] Passenger
[ ] Pedestrian
[ ] Other (Specify)

Fig. 39.9 Sample certification of an accidental traffic fatality. Note that Box 44 is completed. Some certifiers prefer not to include "impact by motor vehicle" in Part I since other information reported indicates that this was a traffic fatality. Whether to include such wording is a matter of style and preference rather than rightness or wrongness. Death occurred in the hospital 3 days after the accident

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Medium-chain acyl-coenzyme A dehydrogenase deficiency — 3 years
Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Due to (or as a consequence of):
c. Due to (or as a consequence of):
d.

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

Acute viral gastroenteritis

33. WAS AN AUTOPSY PERFORMED? [X] Yes [ ] No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? [X] Yes [ ] No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
[ ] Yes [ ] Probably
[X] No [ ] Unknown

36. IF FEMALE:
[ ] Not pregnant within past year
[ ] Pregnant at time of death
[ ] Not pregnant, but pregnant within 42 days of death
[ ] Not pregnant, but pregnant 43 days to 1 year before death
[ ] Unknown if pregnant within the past year

37. MANNER OF DEATH
[X] Natural [ ] Homicide
[ ] Accident [ ] Pending Investigation
[ ] Suicide [ ] Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month)

39. TIME OF INJURY

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area)

41. INJURY AT WORK? [ ] Yes [ ] No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY:
[ ] Driver/Operator
[ ] Passenger
[ ] Pedestrian
[ ] Other (Specify)

Fig. 39.10 This 3 year old died following an episode of acute gastroenteritis but was found to have the metabolic defect which had existed since birth. Gastroenteritis is reported in Part II because it was a co-existing condition which contributed to death but did not cause the metabolic defect. True, the gastroenteritis may have brought the metabolic defect into play, but it did not cause it

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Sudden cardiac death — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Long QT syndrome — 4 years

Due to (or as a consequence of):

c. _____

Due to (or as a consequence of):

d. _____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☒ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☒ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☒ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month)

39. TIME OF INJURY

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area)

41. INJURY AT WORK? ☐ Yes ☐ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.11 This 4 year old died quickly from an acute cardiac event. "Sudden cardiac death" is reported because it describes how this child died as opposed to some other mode such as delayed death in a hospital after resuscitation

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Anoxic encephalopathy — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Complications of premature birth — Hours

Due to (or as a consequence of):
c. Spontaneous maternal placental abruption — Hours

Due to (or as a consequence of):
d.

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☒ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☒ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☒ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month)

39. TIME OF INJURY

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area)

41. INJURY AT WORK? ☐ Yes ☐ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code:

43. DESCRIBE HOW INJURY OCCURRED:

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.12 This infant died shortly after live birth which is why a death certificate was completed. If stillbirth had occurred, states have a "stillbirth", "fetal death certificate", or "spontaneous termination of pregnancy" form to complete in such cases

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Environmental exposure with hypothermia — Hours

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. — Due to (or as a consequence of):
c. — Due to (or as a consequence of):
d.

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? X Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? X Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
X No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural X Homicide
☐ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): Found Apr 4, 2008

39. TIME OF INJURY: Found 1650

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Found in wooded area near city park

41. INJURY AT WORK? ☐ Yes X No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 40509

43. DESCRIBE HOW INJURY OCCURRED:
Live born infant abandoned in wooded area during cold weather

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.13 Certification of a death in which a live born infant was abandoned. Manner of death is homicide

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Probably cardiac dysrhythmia — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Inhalation of spray containing chlorinated hydrocarbons — Hours

Due to (or as a consequence of):

c. —

Due to (or as a consequence of):

d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☐ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☐ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☒ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
☒ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): April 4, 2008

39. TIME OF INJURY: Found 2200

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Bedroom of own home

41. INJURY AT WORK? ☐ Yes ☒ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 35203

43. DESCRIBE HOW INJURY OCCURRED:
"Huffing." Recreational inhalation of spray keyboard cleaner

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.14 Sample certification of a death involving "recreational" inhalation of a spray cleaner

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Acute heroin poisoning — Minutes
Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. _____ Due to (or as a consequence of):
c. _____ Due to (or as a consequence of):
d. _____

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☒ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☒ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
☒ Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): May 1, 2012

39. TIME OF INJURY: Found 2200

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Inside car in parking lot

41. INJURY AT WORK? ☐ Yes ☒ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 35203

43. DESCRIBE HOW INJURY OCCURRED:
Injected controlled substance (heroin)

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.15 Sample certification for heroin-caused death. In such cases, it is necessary to test for 6-MAM which is specific for heroin use. If 6-MAM cannot be detected, morphine and codeine suggest heroin use

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Asphyxia — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Hanging — Minutes

Due to (or as a consequence of):
c. —

Due to (or as a consequence of):
d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

History of depression and bipolar disorder

33. WAS AN AUTOPSY PERFORMED? ☒ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☒ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☒ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): June 2, 2011

39. TIME OF INJURY: Found 1830

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Bedroom closet of own home

41. INJURY AT WORK? ☐ Yes ☒ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 30513

43. DESCRIBE HOW INJURY OCCURRED:

Hanged self with rope from closet rod

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.16 Sample certification of a suicidal hanging death. Especially in children, thorough investigation is needed to be sure that death was not the result of a "choking game"

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Asphyxia — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. Hanging — Minutes

Due to (or as a consequence of):
c. —

Due to (or as a consequence of):
d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? X Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? X Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
X No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
X Accident ☐ Pending Investigation
☐ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): June 2, 2011

39. TIME OF INJURY: Found 1830

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Basement of own home

41. INJURY AT WORK? ☐ Yes X No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: Zip Code: 67202

43. DESCRIBE HOW INJURY OCCURRED:
Inadvertently hanged self with belt while playing a choking game

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.17 Sample certification of an accidental hanging death

CAUSE OF DEATH (See instructions and examples)

32. **PART I.** Enter the chain of events--diseases, injuries, or complications--that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. DO NOT ABBREVIATE. Enter only one cause on a line. Add additional lines if necessary.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition ---------> resulting in death)
a. Contact gunshot wound of the head — Minutes

Due to (or as a consequence of):

Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. —
Due to (or as a consequence of):
c. —
Due to (or as a consequence of):
d. —

PART II. Enter other significant conditions contributing to death but not resulting in the underlying cause given in PART I

33. WAS AN AUTOPSY PERFORMED? ☒ Yes ☐ No

34. WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH? ☒ Yes ☐ No

35. DID TOBACCO USE CONTRIBUTE TO DEATH?
☐ Yes ☐ Probably
☒ No ☐ Unknown

36. IF FEMALE:
☐ Not pregnant within past year
☐ Pregnant at time of death
☐ Not pregnant, but pregnant within 42 days of death
☐ Not pregnant, but pregnant 43 days to 1 year before death
☐ Unknown if pregnant within the past year

37. MANNER OF DEATH
☐ Natural ☐ Homicide
☐ Accident ☐ Pending Investigation
☒ Suicide ☐ Could not be determined

38. DATE OF INJURY (Mo/Day/Yr) (Spell Month): March 3, 2011

39. TIME OF INJURY: 2100

40. PLACE OF INJURY (e.g., Decedent's home; construction site; restaurant; wooded area): Another person's apartment

41. INJURY AT WORK? ☐ Yes ☒ No

42. LOCATION OF INJURY: State: City or Town:
Street & Number: Apartment No.: 123 Zip Code: 30096

43. DESCRIBE HOW INJURY OCCURRED:
Sustained an gunshot wound playing Russian Roulette

44. IF TRANSPORTATION INJURY, SPECIFY:
☐ Driver/Operator
☐ Passenger
☐ Pedestrian
☐ Other (Specify)

Fig. 39.18 Sample certification for a Russian roulette death. Although many people certify these as suicide, a significant minority of certifiers classify them as accident or undetermined. Although the risk of death is accepted playing the game, there are concerns about determining intent in such cases. Further discussion is beyond the scope of this chapter

Whether Russia Roulette deaths should be classified as suicide or accident is a matter of debate, but the most common approach is to classify them as suicide. Reasons are discussed in the Guide for Manner of Death Classification (Hanzlick et al. 2002).

Conclusion

There is usually more than one acceptable way to complete the cause-of-death statement. The certifier of death needs to ensure that the underlying cause of death is reported as specifically as possible and that the immediate cause, any intermediary causes, and other significant conditions are included as needed. One needs to avoid oversimplification, but sometimes the Single Line Part I Format is the best option. Efforts should be made to develop policies within a death investigation office so that cause and manner of death determinations are made consistently from case to case and among the various certifiers of death who work in a given jurisdiction. The cause and manner of death are the best opinion of the certifier and are based on the information available at the time the death is certified. Cases originally filed as "Pending Investigation" need to be updated later with a supplemental report, and if a cause-of-death statement needs to be changed, an amended certificate can be prepared following the procedures established by the vital records registrar who serves your jurisdiction. For additional examples of cause-of-death statements, see Hanzlick (2006).

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Expert Testimony in Pediatric Forensics

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Abstract

This chapter defines expert testimony in legal proceedings as it occurs in the United States and in other English-speaking countries. It explains the different classes of litigation that are likely to affect infants and children – especially infants and children who may have been victims of maltreatment. These classes include criminal proceedings affecting both adult and child defendants, dependency proceedings to protect affected infants and children, tort cases in which persons seek redress for the harms of child maltreatment, probate proceedings, and civil rights proceedings.

The chapter explains how expert testimony is controlled by law and by the policies adopted by professional societies. It defines responsible and irresponsible expert testimony and provides advice to potential expert witnesses on how to provide responsible work.

It points out the problems created by irresponsible testimony and provides some general advice on how testimony can be improved.

Introduction

It is the purpose of this chapter to assist health professionals in providing helpful expert testimony in court. We explain the role of expert testimony in a typical trial and the rules pertaining to qualification, preparation and confidentiality, and cross-examination. We outline the common litigation settings for such testimony and how confidentiality and varying standards of proof differentiate them. We list and describe the areas of common child abuse expert substantive coverage. Finally, we discuss the way in which expert testimony can be improved.

Each of the 50 US states has laws requiring persons who are professionally involved with children to report a "reasonable suspicion" of child abuse when encountered (Smith 2009). States vary on some details, including precisely who must report, but all require notice to state or local child protection authorities. Some buttress this requirement with a possible criminal sanction for its failure. In contrast, international mandates to report vary. For example, the United Kingdom lacks a reporting requirement, and Australia has a modified form of reporting with local variations. In Canada, if someone knows of or suspects that a child is being abused, that person has a legal obligation to report the known or suspected abuse. Failure to report can result in charges being laid as well as a fine of up to $10,000.

Not long after the passage of reporting laws, it was discovered that a report by someone with possible expertise and based on "reasonable suspicion" did not at all

exhaust the need for expert evaluation of possibly endangered children. Beyond factual testimony about what a possible expert may have observed in the field and reported, courts making placement and other decisions rely on expert testimony about what facts may mean. Testimony about human and child psychology, the identity of involved persons given the forensics at a scene, patterns of human behavior, and other matters, properly illuminated by those with specialized knowledge, became necessary. But the need for testimony beyond simple reporting by physicians with specialized knowledge that may be relied upon can be a perceived burden and entanglement that may discourage reporting by some family physicians and general pediatricians (Flaherty 2006).

Expert testimony may be required in several types of legal proceedings. An overview of the common types follows. These descriptions apply to the United States (USA), and similar, although differently named, proceedings generally occur in the other English-speaking countries that have adopted the principles of jurisprudence originating from England. Continental European, Asian, Middle Eastern, Latin American, and African countries may employ totally different proceedings.

What Is Expert Testimony in Court?

Judicial trials have two differentiated aspects: facts and law. Where a jury is present, those jurors serve as the "triers of fact." The judge also has a role in fact-weighing and, if there is no jury (often by stipulation of the parties), may itself serve as the exclusive "fact finder." The person or persons making these factual findings judge the credibility of witnesses and essentially decide "what happened." For example, was the child injured seriously from an intentional blow from the defendant?

In all trials, the court renders the conclusions of law. These conclusions determine how the facts will be applied to arrive at a final legal judgment. In a jury trial, this will take the form of "instructions" to the jury as to how they will apply their factual findings in arriving at a verdict. And it will also guide the court in making decisions about the admissibility of evidence on the front end – including any expert opinions. The line between what is a "fact" and what is the "law" in a given case is not always a bright one. Judgments about "relevance," "prejudice," and "reliability" will be made by a court to determine which facts or what parts of an expert opinion will reach the jury or what those facts will mean to the case outcome.

In terms of the substantive expertise that may be needed to make relevant and optimum factual findings, both juries and judges tend to be "generalists." They often lack the detailed, specialized knowledge that might assist them in determining what happened, and jurors may even be disqualified for extraordinary involvement in or knowledge of the subject of the trial. A typical example of how expertise can assist is in an evaluation of an arson case (a crime disproportionately committed by children). A specialist in how fires start may be able to review the evidence at the site of a fire; contribute his expertise about indications of an accelerant, its composition, and the manner of its distribution; and perhaps render an opinion that the fire was started by a volitional human act.

Such expert testimony may take many forms in a child-related case. A child may have been whipped by some person, with blood on a strap found in the closet of the defendant. In the assault trial that may follow, an expert in DNA may test (or review the testing of other experts) and render an opinion as to whether the blood is the child's. Such an opinion will not be the ultimate factual or legal issue in the case, since who used the strap, whether it accounted for the relevant wounds, and other factual questions may well remain for factual resolution. But such expertise is increasingly used to assist in identifying who is associated with evidence, i.e., "expertise on identity."

In addition to "who," expert testimony can assist in establishing "what," "how," and even "why." For example, a parent may repeatedly present a child for hospital treatment of an apparently acute illness, giving a plausible history and symptoms which are false or fabricated or artificially induced. Such a pattern, although rare, may be a "set of symptoms which tend to occur together." Hence, the literature may recognize such false presentation of illness as "Munchausen syndrome by proxy." Evidence about such habitual false presentation may be better understood in light of expert testimony about such a syndrome's causes and manifestations. Similarly, other mental health–related patterns that qualify as such syndromes under the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association 2000) may be implicated in child abuse cases. Discussed below, these syndromes include most commonly battered child, shaken baby, posttraumatic stress, reactive attachment disorder, parental alienation, and child sexual abuse accommodation. Expert testimony may help the trier of fact to understand the how and why of what happened factually.

Expert Testimony: Who and What Qualifies

Foundation: Personal Qualification as an Expert

Procedurally, the attorney who is offering the opinion of an expert witness will seek to qualify him or her as an expert by asking questions about relevant background, prior expert testimony, education, or experience. Counsel opposing the anticipated testimony of an expert may seek to "take the witness on voir dire." That is, he or she may seek to cross-examine the witness as to qualifications as an expert on the questions before the court. If the case is a jury trial, this examination is likely to be out of the hearing of the jury. In some cases, this issue may be decided by a defense "motion in limine" just before the trial starts. This is a motion to bar some anticipated evidence or witness the other side proposes to offer. Whether a pretrial motion or at trial, the attorney proffering the expert's testimony will present the relevant qualifications and move the court to "accept the witness as an expert" on the questions to be addressed. Opposing counsel may object and seek to disallow that testimony based on failure to have relevant expertise. Where a witness has a particularly impressive background, clever opposing counsel will usually attempt to short-circuit that foundation by offering to "stipulate to Dr. Smith as an expert witness in this matter." Wise counsel calling Dr. Smith will decline to accept such

a stipulation and ask the court, "Your Honor, I appreciate counsel's courtesy in offering to so stipulate, but this witness's qualifications are extraordinary and the jury should properly know of them in weighing his opinion; I promise to be brief."

Substantively, an expert must have sufficient knowledge, skill, experience, training, or education in the specific subject matter covered by the opinion. Wide latitude is given to the court to accept a witness as an expert. Certainly the acceptance by other courts of expert status and prior admitted testimony is highly persuasive for most courts. However, a person need not be the leading expert or even well known in the field to qualify for status as an expert. As noted above, an extraordinary resume may give the opinion rendered enhanced weight for the trier of fact (Federal Rules of Evidence). An expert who is not in the optimum subspecialty for a particular opinion is generally allowed nevertheless to testify, although being somewhat off point may subtract somewhat from the weight given the opinion (particularly if there is a contrary opinion by an expert with directly on-point expertise). For example, in *Deese v. State* 786 A.2d 751 (2001), the court allowed an expert who was an ER pediatric physician to testify on shaken baby syndrome over the objections of defense contentions that only a forensic pathologist was qualified to opine as an expert on the cause of the child's death. The Maryland Court of Appeal held that expert testimony need not be confined to the witness "having the most sharply focused" expertise on the question at hand, so long as the expertise could assist the jury (at 756).

Specific Qualification for Child Abuse Testimony

Pediatricians pioneered the twentieth-century recognition of child abuse. Pediatrics is also the first medical specialty to establish a subspecialty for child abuse and to formalize training and testing qualifications for it. However, note that these trainings and testings do not automatically qualify one as an expert for court-allowed child abuse testimony. The number of child abuse cases in a physician's experience, and on-point background, together with such specialized training, will all be relevant to qualification and will certainly be important to the trier of fact in giving appropriate weight to any opinion proffered.

While other medical specialists, especially pathologists and psychiatrists, may become involved in child abuse cases, they have not established specific child abuse criteria for their work. In these specialties there is a need for defining at least an area of concentration. Many pathologists spend most of their time running clinical laboratories. This may not constitute "recent or current experience" with child abuse. Because of some now rejected collateral theories of Sigmund Freud, many psychiatrists have been very late in recognizing the now commonly accepted realities of child abuse. Attorneys who plan to offer pathologists and psychiatrists as expert witnesses in child abuse cases should be very cautious in evaluating their "on-point" qualifications. As discussed above, the testimony of persons not conversant with the body of knowledge most applicable may be allowed into evidence, but its introduction opens the door to what may properly be devastating rebuttal by more specifically qualified expert testimony and may be a disservice to the purposes of expert contribution.

The Basis for an Expert Opinion

As an expert, it is your role to interpret scientific information to help the decision-makers. You are providing information to provide part of what may be a much larger picture. Although it is not a technical requirement that an expert state the basis of his or her opinion (Federal Rules of Evidence), as a practical matter opinions are properly preceded by their factual basis. In child-related cases, that predicate often involves an examination of the child. If relying on such direct examination, the degree, nature, and number of examinations will be relevant. If a patient has been examined multiple times and over a substantial period, it may be easier to testify regarding patterns – and what those patterns typically imply.

An opinion may also be based on a review of records reflecting examination or collection of evidence by others. In *State v. Moyer* 727 P.2d 31 (Az Ct. App. 1986), the court approved expert testimony on battered child syndrome without a direct examination of the child. An expert may rely on what would otherwise be inadmissible hearsay. For example, it may not be an official or business record or spontaneous statement or statement against interest or otherwise normally allowed into evidence. The expert may consider such evidence, notwithstanding its origin from a third person not subject to court cross-examination.

It is not uncommon for experts to rely upon police and social service reports and child medical histories provided by doctors or parents. The test for such reliance on information provided by others is that it warrants "reasonable reliance" by experts in the particular field in forming opinions or inferences upon the subject (Federal Rules of Evidence). However, note that the court may exclude from the jury such factual predicates to an admitted opinion from direct disclosure to the jury by the proponent of the opinion unless the court finds that their "probative value substantially outweighs their prejudicial effect" (Federal Rules of Evidence). Of course, that limitation does not preclude the use of such evidentiary reliance on cross-examination to undermine an opinion – although adverse counsel may risk the admission of other evidence favorable to the opinion (and unfavorable to his client's case) once he has "opened the door" to challenge an opinion's factual bases. Hence, cross-examining counsel walks a tightrope in challenging factual bases that are favorable to the opinion but that would not be directly eligible for jury consideration separate and apart from that opinion. If he inquires in too much detail about the factual predicates that he has successfully kept from the jury by preliminary motion, he may find them now allowed in to fully explain what has been challenged.

Foundation: Relevance and Reliability

The expert opinion must be preceded or accompanied by facts that inform the opinion and upon which it relies. Counsel offering the opinion will ask the witness if he "has formed an opinion." If the expert has such an opinion, counsel will ask "and what is that opinion?" It is generally not advisable for the expert to presume to render an opinion on the ultimate conclusion of law at issue in the case, "e.g., in my opinion the defendant intentionally struck the child without provocation or excuse and with the specific intent of inflicting serious injury." Such broad opinions often exceed the scope of expertise and, as a practical matter, are counterproductive to the

side proffering it. To preempt the triers of fact of their role implies an arrogance and lack of confidence in their ability to draw conclusions from underlying facts. An experienced attorney solicits modest opinions that support his or her legal theory and may lead inexorably to a conclusion that the jury or court will adopt but does not seek to preempt their function as the final decision-makers.

Opposing counsel may concede the qualifying expertise of the witness but object to the inclusion of the testimony on other grounds, e.g., that the opinion exceeds the scope of that expertise or that it is irrelevant to the germane issues before the court. As part of this process, the sponsoring attorney may make an "offer of proof" to the court of the expected opinion and its relevance. This is counsel's summary of the evidence to be presented behind the opinion, its connection to the legal issues, and the relevance of the opinion itself to assist the trier of fact.

Where scientific conclusions as to identification or causation are offered and laboratory or other tests are conducted, counsel must lay a "foundation." The first part of that foundation is to establish that the process has sufficient reliability to be admissible evidence. For example, lead composition of comparative bullets was at one time considered sufficiently precise and reliable to allow testimony comparing fired bullets to ammunition possessed by a defendant. But additional scientific evidence has since cast doubt on its reliability. Similarly, lie detector evidence is considered too unreliable to be admitted into evidence. Note that such reliability need not be the "one in fifty million" odds common in DNA testimony at all, but it needs to have substantial reliability to be admitted into evidence, especially where juries may give it substantially more weight than its scientific basis warrants.

The basic test for admissible reliability is stated in a leading case as whether the subject matter "had gained general acceptance in the particular field in which it belongs" (*Frye v. United States*, 54 App. D.C. 46, 293 F. 1013 (D.C. Cir. 1923)). Cases have further refined the *Frye* test, e.g., the expert testimony must be "sufficiently reliable and relevant to help the jury in reaching accurate results." Such reliability must meet three criteria: (a) the underlying scientific theory must be valid, (b) the technique applying the theory must be valid, and (c) the technique must have been properly applied on the occasion in question." For example, see the discussion in *Kelly v. State* 824 SW 2d 568 (Texas Crim. App. 1992) at 572–73.

Courts have elucidated additional nonexclusive tests for reliability and overall admissibility qualification, e.g., "1. the extent to which the underlying scientific theory and technique are accepted as valid by the relevant scientific community, if such a community can be ascertained; 2. the qualifications of the expert(s) testifying; 3. the existence of literature supporting or rejecting the underlying scientific theory and technique; 4. the potential rate of error of the technique; 5. the availability of other experts to test and evaluate the technique; 6. the clarity with which the underlying scientific theory and technique can be explained to the court; and 7. the experience and skill of the person(s) who applied the technique on the occasion in question." As explained in the *Kelly* case cited *supra*, these criteria are explicitly applied by courts as "gatekeepers" to prevent the consideration of "junk science" (see discussion below).

In the leading case of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), the US Supreme Court spelled out the criteria for this gatekeeper function: "1) whether the theory or technique can be and has been tested; 2) whether the theory or technique has been subjected to peer review and publication; 3) the known or potential rate of error; and 4) whether the methodology is generally accepted by the relevant scientific community" (at 592–594).

Factual Foundation on Point

Immediately before or following the rendering of an opinion (or sometimes several opinions), the expert will be expected to explain its "basis." Hence, the expert must describe what tests were performed, if any, or who was interviewed, or what facts were assumed to be true in rendering the opinion. Opposing counsel may object to the opinion because it relies on facts that are not admitted, not admissible, or not reasonable factual findings given the state of the evidence. For example, if counsel sponsoring an expert's opinion makes an "offer of proof" concerning its underlying facts but later in the proceedings some of those facts are not admitted into evidence or are undermined so that a trier of fact does not properly rely upon them, counsel may be expected to ask that the opinion based on that evidence "be stricken from the record."

The cross-examination of the expert will include challenges to qualification, implications of bias, and disputes over the foundational facts. It will often focus on alternative facts consistent with the other party's view of the evidence. Often, the expert will be asked "hypothetical questions" during such cross-examination (see discussion of cross-examination below). Where the expert relies upon the tests/observations of others, he may be asked who conducted the test, who interpreted it, and its relevance and sufficiency.

Where the opinion is the result of a scientific test of some kind, the attorney must separately (or through the expert) demonstrate that the sample tested was from the material taken from the relevant scene at the relevant time by persons trained in its removal or extraction and that there is a "chain of custody" of that material to the location of the examination by the expert. Note that some of this foundational material seems to address what appears to be obvious to those involved, including the expert witness. But samples can be misidentified and contaminated, and the tracking of how evidence was collected and who touched it is important to opinion admissibility. In many cases, professional counsel for the other side, aware that these foundational elements are not in dispute, will stipulate to them. But counsel for the expert must be able to provide every step from collection to examination and findings if called upon.

Confidentiality and Expert Testimony

It is common for attorneys who hire expert witnesses to retain them initially as "consultants," often by defense counsel in a criminal case and almost always by both sides in a civil case. Hence, such **c**onsultant**s** can provide the hiring attorney

with the facts believed to be relevant and learn their opinions relevant to the case in advance. If the prospective opinion is not helpful to the position advocated, counsel may never disclose the identity, status, or opinion of the consultant, and those communications may be privileged and properly kept confidential as attorney "work product" in preparation for the case. If the opinion is helpful to the case, counsel may then formally "designate" that consultant as an "expert witness" by giving notice to all parties that this person will so serve. That designation of a person as an expert usually includes a summary of his or her qualifications as such and a description of the subject matter that the opinion will cover.

In a civil case, there is usually a scheduling order that specifies deadline dates for such expert witness designation disclosures by all parties. This then gives the other side the chance to question or depose the witness – in advance of trial – to review any "expert report" they may have written, to examine the bases for the opinion, and to test it with cross-examination prior to trial (see discussion below of likely cross-examination coverage).

Upon formal designation as an expert, the witness is no longer merely a hired "consultant" helping to prepare counsel for a case but is a witness to be proffered to the trier of fact and is subject to full discovery. Importantly, the prior communications between counsel and that person – including communications and work performed under the prior "consultant" designation – are then subject to full disclosure and are not "work product" protected. It will likely be demanded by opposing counsel. Any letters, documents provided, notes of phone calls, and especially e-mails will be examined to indicate possible preconceived assumptions, bias in the facts given to the expert or in the opinion expected, or even disinterest in facts contrary to the position of the party retaining the expert. Not only communications but notes, documents relied upon, and prior drafts of expert reports and opinions will all be discoverable. Expert witnesses, whether retained as such or initially as "consultants," should consider every communication and draft in the formulation of their opinion, to be eventually viewed by the other side and possibly the court and jury.

Cross-Examination of Expert Witnesses

Undermining Qualifications

Because of the liberal allowance of expert qualification discussed above, there may be room for cross-examination challenge to lessen the "weight" of an opinion before the trier of fact. Hence, if opposing counsel has an expert witness with a graduate degree or experience more on point, cross-examination will highlight the disparities that disfavor the other party's witness. Even if there is no expert witness on the other side, counsel may seek to establish that elements of this case are unique and are not within the typical scope of the witness's expertise. Hence, in a sexual abuse case, an attorney may ask "isn't it true that in all of your previous six cases where you have appeared as an expert, the victim has been a little girl, not a little boy as in this case?"

"In fact, you have never before testified or been accepted as an expert by any court in any case involving sexual abuse of a male at all, have you?" Such questions may require redirect by the sponsoring attorney to undermine the doubts that are created, e.g., "what is there about this case that is gender specific, if anything?" An answer that may be implicitly solicited by that redirect question is "nothing about that gender difference is relevant to the particular science involved here, nor to my opinion." And the redirect might continue: "Would you please explain why it is not relevant?" Or it might include "Have you, in fact, examined both girl and boy victims of sexual abuse?" followed by "Would you please describe your training and experience involving abuse of males, such as the one at issue here?"

Implying Bias

Expert witnesses, as with all witnesses, are influenced by their empathy lines, friends, allegiances, and their own economic interests. Indeed, much of the human brain engages in filtering of facts based on those emotional preconditions. Triers of fact are well aware of that predilection, and the weight of an opinion may be reduced if such factors might color it. Hence, experts are commonly asked how they are being paid for their testimony, who is paying them, and how much. Expert fees are best set at levels consistent with the compensation of the witness in other, similar contexts. A disproportionate retainer or hourly rate raises issues of emolument bias. However, a typical hourly rate allows the witness to imply "anyone who wants me would pay this amount and my opinion is my opinion and will cost a given amount whatever it may be and whoever wishes to present it." Nevertheless, where a witness is used often by a particular party or interest, counsel will seek to imply that the prospect of yet further return engagements at personal profit (even if not an extraordinary profit) has some influence.

It is typical to ask where an expert witness is and has been employed. And often cross-examination will explore how often an expert has testified for a given side or interest in previous court appearances in order to imply that he or she has a "canned" bias that can be counted upon to favor plaintiff or defendant and that predisposition is what accounts for his or her retention. Similarly, prior publications taking one side or another on issues that are in dispute within the scientific community are likely to be the subject of questions. For example, cross-examination may include: "Then as a Jungian, you reject many of the psychological theories of Freud, do you not?" Followed by: "Are not psychologists of the Freudian school commonly licensed and considered competent practitioners?" Followed by: "And if we had a Freudian-aligned psychologist to opine on your theoretical basis, would he disagree with you on some aspects of it?" Followed – if the witness is so unfortunate – by: "In fact, in one prior publication, and I am now reading from page 387 of an article of yours already admitted into evidence, did you not describe such theories as 'nonsense masquerading as science?'" Followed by: "Would a Freudian not say the same thing about your analysis? In fact, haven't many such experts so described your work?"

Finding Contradictions

It is likely that a prepared attorney has actually read (or had a clerk or researcher read) prior public testimony and prior publications of a given expert to prepare for cross-examination. A favorite deflationary tactic is to find a quotation that appears to contradict any part of the relevant opinion or any part of its predicate description. Usually, counsel will hand the article to the witness and ask him to read the marked section, followed by "now are not those your words, you wrote that just 3 years ago did you not?" "Yes or no?" Followed by "Just what amazing revelation has occurred in recent months to change your mind, other than the deposit of the retention check in this case?" The witness should certainly be allowed to explain why the previous quote and the current opinion are, in fact, quite consistent. And counsel defending the witness's opinion should object to allow such an explanation. But two *caveats* are advisedly offered: First, counsel retaining the witness should do his or her own review of prior testimony and publications of his expert to anticipate and prepare for such contradiction confrontation. The witness may be able to immediately respond that the questions addressed in each are quite different and explain how. But be forewarned that a skilled cross-examiner may make such an explanation difficult. Second, where the cross-examination does score points and cast doubt upon an opinion, the redirect examination by retaining counsel will allow that explanation. Indeed, sometimes clever counsel supporting an expert's opinion will deliberately not object to slanted and unfair questions where he/she knows there is an explanation. Counsel will know that a redirect that rehabilitates the opinion by explaining the contradiction and persuasively pointing out that the questions addressed were different allows the expert to repeat and hence reinforce the opinion while at the same time casting doubt on the good faith of adverse counsel whose now apparently unfair cross-examination sought to dishonestly impeach a witness who had a good explanation and perfect, professional consistency.

Note that finding contradictions is easier where opinions are overly broad. Often, understating an opinion, and directing it narrowly at an undisputed and designated set of facts, creates a more defensible and often more persuasive end result. The witness should perhaps regard the final opinion as the roof of a house that must be well supported on all four sides and constitute the natural and expected covering given the four walls underneath it.

Use of Hypothetical Questions

It is permitted and common for cross-examination to include hypothetical questions. For example, "On direct examination, you testified that the child's wounds were not the result of a single blow to the head, but of repeated blows, and informed your opinion that this child was repeatedly struck by a powerful person. But what if the child fell down the stairs and bounced his head off of a railing, then the stairs tread at the edge, and then the landing – would that not also be consistent with the wounds you examined?" Such a tactic is well advised, because it may

allow the adverse party to make an expert witness into a beneficial source of factual material with enhanced credibility given his or her selection as an expert by the other side. Such hypothetical questions are fraught with danger, because they may leave out critical variables that are not in dispute and would not lead to the conclusion sought by counsel. Ideally, the attorney who retained and called the expert will listen carefully to such queries and will object to hypothetical questions with facts that are incomplete, misleading, or based on inadmissible or rejected evidence. To that end, expert witnesses are well advised not to immediately answer complex hypothetical questions on cross-examination without (a) providing a moment of time for the attorney sponsoring his testimony to object and (b) without carefully qualifying the answer by mentioning what hypothetical facts may be missing from the question and which may be critical. Contrary to common perception, such explanations are permitted, and witnesses are not properly brow beaten into "just answer yes or no to my hypothetical." And if hypothetical questions are asked and answered on cross-examination, that would possibly mislead the jury as to the relevant opinion applicable to the case; that is why a brief recess to confer with counsel is often advisable, to allow for redirect examination that will rehabilitate or clarify the opinion. It is important for the trier of fact to understand which facts underlie the opinion offered and which will, in contrast, contradict its conclusions.

The Varied Court Settings for Use of Expert Child-Related Testimony

The vast majority of expert child-related testimony occurs in state court and as such is subject to often varying statutory and common law settings. However, we outline the various proceedings that involve expert testimony relevant to children and discuss the burden of proof and confidentiality rules commonly applicable to each (Table 40.1).

Adult Criminal Proceedings

Misdemeanor criminal cases may proceed directly to trial in most states following the simple filing of a "criminal complaint." However, felony criminal cases are more complicated, and because of their high stakes, most jurisdictions require a preliminary proceeding before a trial is permitted. As described below, most jurisdictions reach such felony trials either through the filing of a criminal felony pleading called an "information" or alternatively because of a felony pleading called an "indictment." The former requires a "preliminary hearing" and a decision to allow a felony "information" (or similar term) filing for trial, and the latter involves a decision by a grand jury to file an "indictment" of a defendant. Either may involve expert testimony at that preliminary stage and/or at final trial.

Table 40.1 Types of legal proceedings stemming from child abuse

Type of case	Type of court	Trier of fact	Burden	Standard of proof
Pretrial criminal preliminary hearing	Criminal, municipal	Judge	State	Violation Probable cause and reasonable suspicion Defendant is offender
Pretrial criminal indictment	Grand jury	Grand jury	State	Violation Probable cause and reasonable suspicion Defendant is offender
Adult criminal prosecution	Criminal, superior or trial court	Jury; judge alone if parties stipulate	State	Beyond reasonable doubt
Adult criminal in military jurisdiction	Court-martial	Panel	Government	Beyond reasonable doubt
Child criminal	Juvenile delinquency court	Judge (juries in a few states)	State	Beyond reasonable doubt
Child protection	Juvenile dependency court	Judge or referee	State	Clear and convincing evidence for parental rights termination
Damage suit at law (individual or class action in tort)	Civil	Jury; judge alone if parties stipulate	Plaintiff or plaintiff class	Preponderance of evidence
Equitable class action or mandamus v. government	Civil	Judge	Petitioner class or petitioner	Preponderance of evidence that an "abuse of discretion"
Professional discipline	State administrative law judge and agency	Agency governing body with administrative law judge proposed opinion	State (agency)	Clear and convincing evidence

Preliminary Hearing Leading to an "Information" Felony Filing

Where a felony is involved and is to reach trial by way of an "information" or similar state trial court criminal pleading, a "preliminary hearing" is held to determine if there is sufficient evidence to conduct a trial. These hearings are heard by a judge without a jury. If the state can show reasonable or probable cause that a crime was committed and strong suspicion that the defendant committed it, the defendant will be "bound over" for trial, and a "criminal information" will be filed. These preliminary hearings are usually public. And the defendant is commonly in court and is represented by counsel. Any witness called by the state (or the "people") to provide adequate cause for such a felony trial is therefore subject to cross-examination by defense counsel. For this reason, prosecutors commonly present a skeletal case. They seek to avoid calling an expert, or any

witness who is not essential, in order to spare those persons from pretrial cross-examination under oath and with a transcript. However, in many child-related cases, expert testimony may be necessary at this initial stage. As such, the expert should be prepared for vigorous cross-examination by defense counsel. These preliminary hearings are an opportunity for defense discovery, and competent counsel take full advantage of it. And expert witnesses should be well aware that counsel will have the transcript of that preliminary hearing testimony available for use at the later trial. If there is a contradiction between that prior testimonial record and the testimony at trial, counsel will use that inconsistency on cross-examination, as discussed above. If retained as an expert for the defense, such pretrial examination is rare. It is very unusual for the defense to present any defense case at a preliminary hearing.

Grand Jury Proceedings

A felony criminal case may also reach trial through grand jury indictment. These proceedings are markedly different. First, although a judge may be commonly available for consultation, he or she is not normally part of the grand jury function. The jury is made up of citizens who are independent from the state, but the proceeding is controlled by the prosecution – the only legal expert involved and who determines what witnesses will be called, questions those witnesses, and decides what evidence is to be presented. Grand jurors may and often do ask questions of witnesses and request additional or clarifying evidence. The prosecutor usually makes opening and closing statements, answers questions, and proposes criminal charges suggested for the grand jury to include in a proposed indictment. The prospective defendant is not present nor is defense counsel. The proceeding is confidential. In fact, revealing any part of the proceedings of a grand jury (including disclosures by an expert witness about the subject matter, the target, or of what he was asked and said) may be a criminal offense.

Some states will require notice to a "target" and opportunity to appear and answer questions in an effort to preclude an indictment. And the grand jury proceeding involves a transcript that may be tested by a "motion to dismiss" prior to trial. The transcript must include admissible evidence that provides probable cause that a crime was committed and reasonable suspicion that the defendant committed it.

Importantly, child-related cases are a prime category for grand jury indictment over the preliminary-hearing route to felony trial. The reason involves sensitivity to the trauma that repeated cross-examinations may have on child witnesses/victims. Accordingly, experts relevant to such cases are likely to experience the grand jury alternative if their contribution is needed prior to trial. They may be presented to explain the meaning of evidence to the nonexpert citizens who make up the grand jury. And the jurors may have questions of the expert. But it is a mistake to become overly informal and familiar in what is often superficially a rather collegial setting. Although counterintuitive, the presence of defense counsel has some advantages for the prosecution. A failure by defense counsel to object in a preliminary hearing may waive that objection if the defense takes a writ or otherwise seeks review of its

adequacy. And the prosecution can often learn what the defense contentions may be at trial. In contrast, the transcript of the grand jury proceeding is not tested, there is no waiver, and informal comments or answers to juror queries may be used to win dismissal of the indictment upon its immediate appellate review for adequacy (which all states allow) or be used to impeach the expert at trial.

Adult Criminal Trials

Following preliminary hearing "bind over" for an information or grand jury indictment, a felony trial is scheduled in the major trial court jurisdiction of the state. This trial will be public, and the defendant has a constitutional right to a jury, which may be waived. Interestingly, child-related cases form a category that draws more jury waivers than do other criminal cases. The defense may be sensitive to the emotional impact of a child victim on the general population subject to jury call and seek to have a trier of fact who is less likely to be shocked or who may take a professional approach more appreciative of technical flaws in the prosecution case. On the other hand, defense counsel are well aware that a judge can serve as the 13th juror and dismiss a case without sending it to the jury, and any one of the 12 jurors may not be convinced at the required burden of "proof beyond a reasonable doubt" and persevere with a "not guilty" vote. A guilty verdict requires a unanimous vote. Its lack results in a "mistrial" and the prosecution must retry the case from scratch with a new jury. Counsel are aware of the exact vote count of a hung jury. And if more than a few jurors have voted "not guilty" or if a retrial yields a similar result, the prosecution may accept a plea to a much-reduced charge or dismiss the case.

Expert testimony can be important to a case either in providing connections convincing the court and jurors of guilt or of casting doubt on the veracity of the charges or the selection of the defendant as the perpetrator. While most child-related testimony in adult trials will pertain to victims, it may be relevant to the acts of juveniles allegedly complicit in or concealing the violation. And in an increasing number of "adult" trials, the defendants are juveniles being "tried as adults."

Juvenile Delinquency Trials

Where crimes are allegedly committed by persons under 18 years of age, the proceedings are generally in the delinquency division or part of juvenile court. As noted above, many states have enacted statutes allowing many juveniles, particularly those 16 years of age or older, to be "tried as adults" for specified crimes in adult criminal court. That decision rests with juvenile courts in some states, but a trend allows the prosecution to be the critical determiner of whether a youth will be tried as an adult (with greatly enhanced penalty exposure) or in juvenile court.

In most states, juvenile courts have regular trial judges who are increasingly assigned for specialized court proceedings. Hence, criminal, civil, probate, juvenile, and other trial departments are presided over by judges with some expertise in the subject matter, although some jurisdictions rotate judges regularly between trial subject matter departments. At one time, juvenile courts were informal and

paternalistic, with proceedings consisting largely of conferences with a judge, who received evidence substantially from social workers or law enforcement and without testimony under oath, confrontation and cross-examination, transcripts, or appeal rights. That changed in the seminal case of *In Re Gault* 387 U.S. 1 (1966). From that point on, juvenile criminal proceedings replicated the adult due process guarantees, including required notice of charges, appointment of counsel for the youth, testimony under oath, confrontation and cross-examination, a transcript, and right of appeal. And the same burden of "proof beyond a reasonable doubt" applies (*In Re Winship* 397 U.S. 358 (1970)). However, three features most distinguish juvenile delinquency proceedings from adult criminal trials. First, juries are not constitutionally required and most states do not use them (*McKeiver v. Pennsylvania* 403 U.S. 528 (1971)). Second, proceedings are generally confidential – trials are not public. Third, there remains a distinctive emphasis on rehabilitation, given the age, maturity, and the relative malleability of a youth as opposed to what is popularly conceived as a more "hardened criminal" adult.

In a juvenile delinquency proceeding, the testimony of experts has traditional importance when pertaining to scientific evidence indicating identity of a perpetrator and other issues where experts are commonly used to show guilt. But the expert mental-health professional has a perhaps enhanced role given the rehabilitative purpose of this court. Expert evaluation of the crime and of the defendant may weigh heavily in the court's decision about culpability and especially about appropriate punishment.

Juvenile Dependency Cases

The other branch of juvenile court does not deal with children accused of crimes, but rather with children who are endangered and require protection. This court is part of the "child welfare system" extant in all 50 states and many nations. That system includes Child Protective Service social workers who receive indications of possible child abuse, often from "mandated reporters" – doctors, nurses, teachers, and other professionals who are legally required to report child abuse or neglect. Indeed, failure to so report may invoke criminal liability. Psychologists are among those commonly required by state law to so report (see discussion of the conflict between due process and discovery rights and psychotherapy privilege discussed below).

The dependency side of juvenile court also generally lacks juries and, in most states, is presumptively confidential. But the proceedings are otherwise quite different. The court here is in civil mode; this is not a criminal court that will sentence any person to a fine or incarceration. It is a proceeding to protect children from abuse and neglect, which can include injurious beatings, molestation, severe neglect, and even abuse that is not physical but endangers a child's mental health. For example, in many states violent domestic disputes between parents in front of children may so qualify.

These proceedings include substantial protections for parents, recognizing the often less-than-ideal consequences of foster-care entry for involved children.

The process begins with a detention hearing in front of the juvenile court trial judge, with the burden on the state to show (a) child endangerment and (b) reasonable efforts not to remove the child (e.g., to provide in-home counseling or other remedies short of removal). At this initial step, the parents are provided with counsel in all states, and children are provided with an adult *"guardian ad litem"* (GAL), who are increasingly attorneys who specialize in this representation. Many jurisdictions also appoint a "Court Appointed Special Advocate" or "CASA," a trained adult volunteer who will consult with the child and others and advise the court as an independent set of eyes and ears. Then within weeks there is a critical hearing, the "jurisdictional hearing" where the court may take "jurisdiction" over the child, temporarily supplanting parental authority. This jurisdictional hearing is often accompanied by a "disposition hearing" to determine where the child will remain for the duration of the case and what services are needed to perhaps make the family whole again.

Since federal law requires "reasonable efforts to reunify" removed children with their parents, most of the next year will be devoted to possible counseling or other services necessary for the child's safe return. Most of these steps are subject to the "preponderance of the evidence" test. The logic here is that the state is not intervening for its own offices, but to protect a weak private party. However, if at the end of the process (usually taking from 1 to 2 years) the state contends that the child should not be returned but should be placed permanently elsewhere, there may be a "termination of parental rights" hearing. At this stage, the permanent and profound nature of the taking means that the state must show the parents to be "unfit" by a harsher evidentiary test of "clear and convincing evidence" (*Santosky v. Kramer* 455 U.S. 745 (1982)).

Juvenile court judges are not medical professionals, and the rules of evidence are somewhat relaxed. For example, hearsay that would not be admitted in a criminal case may be considered, including especially social worker and mental-health professional reports. The standard in many state juvenile court cases is evidence that is of the sort that persons "rely upon in the conduct of serious affairs." Accordingly, the role of mental-health experts is influential in this forum. Is this a battered child? Is the child's testimony influenced by child sexual abuse accommodation syndrome? Is the infant a victim or likely victim of shaken baby syndrome? Is the child suffering or likely to suffer "reactive attachment disorder?" These and many other questions are relevant to whether the child was endangered, remains endangered, and has the likelihood of future endangerment in alternative settings.

Civil Litigation

Child-related expertise may be relevant in many different types of civil litigation. However, three categories of civil cases most often employ experts on children: tort cases, civil rights challenges to foster-care systems, and probate proceedings. Each of these fora is quite different in their proceedings and expert witness use.

Tort Cases

Tort cases involve suits against private parties or government for injuries suffered due to actionable negligence. They can often involve children. A common issue in such cases is whether the defendant has created an "attractive nuisance" that will stimulate child interest and increase the likelihood of child injury. Expertise in child psychology may be important in establishing whether such an attraction will draw children and hence imposes an enhanced duty of care.

Beyond actionable negligence, torts may lie from assault or injuries resulting from purposeful acts to harm or from gross indifference. In the 1970s and 1980s, as knowledge of child abuse was disseminated, lawsuits against perpetrators of abuse began to be initiated by victims. This trend has continued, and suits of this type are no longer rare. In one controversial leading case, the Supreme Court rejected liability under federal civil rights law for the failure of a county or state to protect a child from abuse, even after multiple reports and the failure of the adult to comply with alleged conditions allowing the child's return. The Court bafflingly ruled that there is no "special relationship" between states and abused children (notwithstanding mandated reporting, etc.) that imposed a duty that could give rise to public liability for negligent performance; see *Deshaney v. Winnebago County* 489 U.S.189 (1989). However, note that liability may lie under state laws and standards, and, of course, liability may generally apply to private parties for child injuries resulting from intentional or negligent acts – ranging from a backyard swimming pool to corporate product liability.

When the person who is suspected of child abuse is connected to an institution such as a school or church, a day care center, or hospital, the institution may also be liable for damages. In these circumstances, the institutions sometimes avoid detection and protect perpetrators by transferring employees to new locations or assignments – rather than reporting abuse or cooperating in investigations.

The typical civil tort case seeks damages. Such actions imply the right to a jury, which may be waived if both parties consent. The burden of proof is preponderance of the evidence, and the trial is public except to the extent the court has granted a "protective order" to protect trade secrets or privacy upon petition of one of the parties.

Civil Rights Cases

Civil rights cases may be based on child protection issues. In particular, class actions or petitions for writs of mandamus against public officials, or declaratory relief actions, may seek to enforce constitutional requirements or statutes for child beneficiaries. For example, the Innocence Project has utilized civil rights grounds to launch petitions for writs of habeas corpus to free convicted felons, often involving expert DNA and other testimony. Broader, class actions and mandamus actions (suits against public officials for "abuse of discretion") are commonly brought against state foster-care systems, which are notoriously underfunded and sometimes deficiently serve the children who are literally and legally the "children of the state" (under the parental authority of courts). Two different organizations have filed over 15 cases in total challenging foster-child systems in multiple states: the

National Center for Youth Law Center in San Francisco and Children's Rights in New York. An example of expert testimony relevance is the case recently won by the Children's Advocacy Institute against the state of California for paying family foster-care providers 40 % below the enumerated out-of-pocket costs that federal law requires be covered (see *California Foster Parents Association v. Wagner* 624 F.3d 974 [9th Cir. 2010] at www.caichildlaw.org). In the *Wagner* case, relevant expert testimony ranged from an economist on the actual cost of raising a child to the effect of below-cost payment on family foster-care supply and to the resulting impact on adoption rates. Expert testimony there established that because group homes receive nine times the amount given to families for foster care, increasing family foster-care rates increases the supply of families providing foster care and directly saves public funds on an out-of-pocket basis (as children move from institutional settings into families at a fraction of the cost).

These civil rights cases are often filed in federal court and seek to leverage federal minimum requirements for the state receipt of federal matching funds. Federal monies are allocated to medical services for children (including Medicaid, EPSDT, and the State Children's Health Insurance Program that provides a 2–1 federal match), child welfare services (foster child care and protective services), and the child safety net (Temporary Assistance for Needy Families), among others. The cases are subject to the preponderance of the evidence test. They are tried in "equity" for injunctive and perhaps restitution or declaratory relief, rather than "at law" for damages. This means that they are tried without juries. The cases are public.

Probate Court Proceedings

A third setting for expert child-related testimony is probate court. Such courts often deal with trusts that involve judgments about maturity. Moreover, there is an increasing trend by parents who fear possible child-protective services intervention, to agree to probate-court guardianships (e.g., with their relatives who will not cut children off from future contact). Hence, counsel for many parents subject to juvenile-dependency court intervention or threat may advise the surrender of children to cooperative relatives in a guardianship arrangement. The probate court is then confronted with a mix of mental health–related questions: Is this parent incapacitated or otherwise appropriate for parental rights supersession from a guardian? Is the proposed guardian able to parent competently? What will be the impact on the child of a given guardianship arrangement? What should be the terms of the guardianship, and how often should it be reviewed, in order to assure protection of the child?

These probate cases generally use a "preponderance" test, do not involve juries, and are public proceedings. However, no party is provided with public counsel in these proceedings. This tends to bias their incidence toward middle or upper class litigants, unless legal aid addresses such cases. In the latter case, much of the expert testimony may have to be on a pro bono basis (without compensation). The disadvantages of the probate guardianship option include, in addition to lack of counsel, (a) the disqualification for compensation available to those caring for

a child in the child welfare system and, more critically, (b) the absence of a mechanism or advocate to represent directly the interests of involved children.

Although all three areas of civil litigation are public fora, it is possible to apply to the court for a "protective order" to "seal" portions of a proceeding from public scrutiny. This confidentiality is commonly used in commercial litigation, usually under the pretense that all evidence adduced will involve some sort of "trade secret." But note that a more defensible order of confidentiality may also be used for a child protection rationale. Such an order may be particularly appropriate for sensitive expert testimony pertaining to matters of child mental health.

Licensing and Administrative Law

Each state has its own system for licensing the trades and professions, ranging from contractors to lawyers and including teachers, physicians, psychologists, and counselors. Professionals who teach, treat, and counsel children are all subject to the licensing boards of 50 states, each determining entry (who may receive a license), standards of practice, and discipline. Expert child-related testimony may be highly relevant to all of these functions. Certainly, expertise on child impact is important in the setting of entry conditions and practice standards for any professional interacting with children.

More specifically, experts may be called upon in a court-like setting to provide testimony where individual disciplinary cases are brought. Quasi-judicial in nature, these cases are tried in a court-like setting. Where a licensing board deals with professions that interact with children, competence or practice methods may be subject to sanction. These proceedings are subject to the "administrative procedure acts" of the respective 50 states and different nations, which vary in their details. However, in most cases, the matter is investigated by the regulatory agency and prosecuted by counsel from the state office of the Attorney General or its equivalent. The pleadings may allege violation of rules intended to protect patients or clients, including children, or they may allege incompetence.

Licensure discipline does not normally occur based on any single act of negligence but rather is more usually imposed where there is a dangerous practice method or a pattern of negligence that implies incompetence. The rationale behind such discipline rests with the basis for regulation itself and the attempted assurance of a minimum level of competence, particularly where its absence portends irreparable harm to those relying on the professional skills of others. Children harmed by such incompetence have special priority because of their inability to independently choose alternative practitioners and their relatively helpless status. Accordingly, expert testimony may be arranged by the agency or the Attorney General or by the accused respondent. The legal proceedings here will require proof of incompetence or a violation of existing law or rules by "clear and convincing evidence" given the challenge to a "vested right" that state licensure provides once it is obtained. No attorney will be provided at state expense for the accused respondent. The proceeding will be tried normally before an administrative law judge (or ALJ). That person

acts as a trial judge would, although he or she is technically part of the executive branch. There is no jury, and the proceeding is public. The rules of evidence are somewhat relaxed, as with dependency court discussed above, hearsay is more liberally allowed, and evidence in most jurisdictions may be admitted if used by persons "in the conduct of serious matters."

The administrative process does not involve the kind of extensive advance discovery common in civil litigation. Hence, while expert witnesses will be cross-examined in advance of trial in criminal matters where there is a preliminary hearing and they are called and in civil trials where there are advance depositions (as discussed above), such depositions normally are not authorized in administrative proceedings unless needed to preserve the testimony of a witness unavailable for the ALJ hearing. At that hearing, the ALJ will hear the evidence, rule on admissibility, and then write a "proposed decision," including findings of fact, conclusions of law, and recommended discipline, if any. That discipline may vary from a private reproval to license revocation. The decision is usually submitted to the regulator, whether it be a single person heading a department or bureau or, as is more common, a board or commission. That regulator reviews the decision, and perhaps the written record, and makes the final decision, allowing further argument by all parties if considering an increase in the recommended punishment. Because the case has not yet been reviewed by the judicial branch and a vested right is theoretically at issue, the matter is then reviewed on an "independent judgment" basis by a state trial court. That is, the court looks at the record (and may allow additional evidence to be presented in court) and makes his or her decision as if hearing the evidence for the first time and without special deference to the findings of the ALJ or agency. Then there is a right of appeal to the state court appellate branch and usually a possible request for state supreme court review, which is discretionary and is not commonly granted.

Disciplinary cases involving physicians, counselors, psychologists, and others may turn on technical competence. A few states, including California, enhance the competence of involved disciplinary officials by creating specialized medical-quality units in the Office of the Attorney General providing the prosecutors and in the Office of Administrative Hearings providing the ALJs who judge the hearings. And many states use expert "consultants" among respected practitioners to advise the agency as to standards of care and possible dangerous practices. However, in most states, counsel and judges commonly themselves lack expertise, particularly on-point and relevant to a specific child impact. Accordingly, the testimony of expert witnesses can be a critical factor.

In the United Kingdom, the licensing agency for physicians known as the General Medical Council disciplined two prominent pediatricians for providing allegedly below-standard testimony in child abuse cases. This controversial action created apparent disruption and problems in the child protection system in that country. Licensing agencies in the USA and Australia have not concerned themselves with discipline based on expert testimony. That absence has partly been the result of a lack of capacity and partly because of the contentious nature of the court process itself, which has its own truth-seeking format.

Litigation, Legal Discovery, and the Psychological Privilege

Most physicians and mental-health professionals dealing with children assume that their own treatment is subject to traditional doctor–patient confidentiality. Such a privilege is common in state statutes and is often relied upon by expert witnesses who conduct examinations of children possibly subject to court proceedings. However, that privilege does not override state statutes that require mandated reporting of abuse. So where a psychologist, for example, interviews a child or a parent and has knowledge of child abuse, a report may be required notwithstanding a privilege that would otherwise apply. However, note that in at least one leading case, where an initial report has been made, the privilege may moot the requirement to make an additional report from a second source of the same abuse; see *People v. Stritzinger* 34 Cal.3d 505 (1983).

Another limitation on confidentiality may apply more directly to expert witnesses retained post–court filing. Where a criminal case is pending involving a crime against a child, defense counsel may request discovery of counseling and mental-health treatment by a professional, including examinations that may be prepared for the litigation or simply treatment of the child to ameliorate the trauma of the alleged abuse. Defense counsel will contend that the Fifth and Fourteenth Amendment rights of the accused overcome confidentiality, even where privacy had been promised to the child. The leading case reconciles this conflict by allowing the court to examine such confidential treatment records *in camera* (privately) and to disclose only those aspects that may indicate defendant exoneration; see *Pennsylvania v. Ritchie* 480 U.S. 39 (1987).

Syndromes and Expert Testimony in Child-Related Cases

Syndrome Testimony in General

Syndromes involve concurring symptoms that form a common pattern. Most such syndromes are listed in existing medical manuals (e.g., the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders). With many physical diseases, the relationship between symptoms and etiology is clear. The same is true for some mental syndromes. However, there is a spectrum of certitude and predictability value that may vary widely between them. Many of the syndromes that are the subject of litigation in child-related cases may not have high diagnostic value, that is, one may not necessarily work backward from the common patterns to a certain cause.

A good example of this obvious limitation is child sexual abuse accommodation syndrome, a dynamic where a child will not disclose abuse out of attachment to the abuser or other reasons that make sense to the child. The absence of a child's complaint is not reliable evidence of such a syndrome, because it presumes the abuse, and virtually all children who are not subject to abuse will similarly not report. Such syndromes may be characterized as "non-diagnostic" (Myers 2010).

Table 40.2 Frequently litigated medical syndromes

Name	Essential expert offering	Reference
Battered child syndrome	Injury(ies) inflicted by other than accidental means	Kempe et al. 1962
Shaken baby syndrome	Serious mechanical brain injury without evidence of external head impact	Guthkelch 1971
		Caffey 1972
Munchausen syndrome by proxy	Illness in a child fabricated or induced by parent	Meadow 1977
Child sexual abuse accommodation syndrome	Explanation of children's denial and recantation about sexual abuse	Summit 1983
Posttraumatic stress disorder	Anxiety, depression, rages, nightmares, flashbacks following documented trauma	Herman, J. Trauma and Recovery 1997
Reactive attachment disorder	Absent or distorted attachment to others	Lyon (APSAC) 2006
Parental alienation syndrome	Not formally recognized	Gardner

On the other hand, battered child syndrome includes elements which, taken together, are more likely to have suffered non accidental injury.

Commonly Relevant Syndromes

Battered Child Syndrome

The battered child syndrome was described as a syndrome category in 1962 (Table 40.2). It is most often applied to children under 3 years of age and typically includes convincing evidence of non accidental injuries, sometimes accompanied by neglect. It convincingly connects abusive actions by caretakers to medically diagnosable conditions of infants and children. Its study awakened professional consciousness of child abuse in the twentieth century (Kempe et al. 1962). Leading cases support expert testimony on this syndrome (see, e.g., *U.S. v. Boise* 816 F.2d 497, 503 (9th Cir. 1990)).

Shaken Baby Syndrome

Shaken baby syndrome/abusive head trauma (SBS/AHT) is a term used to describe the constellation of signs and symptoms resulting from violent shaking or shaking and impacting of the head of an infant or small child. The first description of the condition was made by Arthur Guthkelch in 1971 (Guthkelch 1971), and the syndrome was named by John Caffey 3 years later (Caffey 1974). The linking of shaking to serious brain injury has largely been accomplished from the recording of confessions by adults who have shaken babies, buttressed by some eyewitnessed cases.

In serious and fatal cases, the pathology includes subdural hematoma which may be of any thickness or volume, brain swelling, and, usually, retinal hemorrhages – which may be very extensive. Many cases also have associated skeletal injuries,

which may antedate or be of the same age as the brain injury. There may or may not be signs of external head impact – such as scalp bruising or skull fracture. Bruising on other parts of the body, such as the arms or the chest, may be present.

Shaking is a fairly common way to attempt to discipline infants and young children (Theodore et al. 2005). Less serious cases with spontaneous recovery occur but are not often reported. In the serious and fatal cases, confessions indicate that the child's change in state of consciousness and change in behavior follow promptly after the shaking occurs. The features of the shaken baby syndrome have been described and confirmed by the Committee on Child Abuse and Neglect of the American Academy of Pediatrics and by a consensus statement of the National Association of Medical Examiners (Case et al. 2001).

A small set of dissident experts continues to dispute the existence of this syndrome. Forensic medical testimony about the shaken baby syndrome has been generally accepted by US courts to date.

Munchausen Syndrome by Proxy

Munchausen syndrome by proxy (MSBP) is a form of abusive parental behavior and is manifested as repeated presentation of a child for medical treatment for an apparent illness, with a plausible and dramatic history which is false (Meadow 1977). Tragically, it is at times an apparent bid for attention and may also involve parental creation of dangerous symptoms. It is categorized in manuals from the child's perspective as "fabricated or induced illness by carers" and as "factitious disorder by proxy" from the perpetrator's perspective. It has also been named "pediatric condition falsification" and "medical child abuse," and these names also have merit (see Chap. 10, "Factitious Illness by Proxy in Children").

Munchausen syndrome by proxy is not common but is highly dangerous to affected children (9 of the first 100 reported cases were fatal) (Rosenberg 2003). It does not involve an easy predictive test. Proof may require such difficult measures as covert video surveillance in a hospital or a trial of separation of the victim from the suspected perpetrator. However, the patterns that attend its incidence qualify it as a diagnosis acceptable for expert testimony. Disqualification as a subject for expert testimony under the limitations of the *Frye* or *Daubert* cases does not apply. This expert testimony is accepted. See, e.g., *State v. Hanover* 7 P.3d 329 (Mont. 2000); see also *Reid v. State* 964 SW2d 723 (Texas App. 1998).

Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a psychiatric diagnosis related to extreme trauma response, including rape and sexual assault. It is a well-established diagnosis, defined as being generated by a traumatic event where (a) the person witnessed or was confronted with threatened death or serious injury to himself or others and (b) the response elicited intense fear, helplessness, or terror. In children, PTSD may be manifested through "disorganized or agitated" behavior. The existing psychiatric manual further defines PTSD as involving persistent reexperience or recurring nightmares (in children, often without recognizable content), hallucinations, dissociative flashbacks, intense distress, or physiological reaction with reminders or

cues. It is usually accompanied by persistent avoidance of associated stimuli or reminders, memory lapses, feelings of detachment or estrangement, alienation, and a sense of personal doom.

It also involves new symptoms following the trauma, including two or more: (a) insomnia, (b) angry outbursts, (c) difficulty concentrating, (d) hypervigilance, or (e) exaggerated startle response. The duration of the symptoms noted above exceeds more than a month and causes significant impairment to important work or social function.

For young children, the Manual of Mental Disorders (DSM IV) explains some variation from adult PTSD, noting that distressing dreams of the event may, within several weeks, change into generalized nightmares of monsters, of rescuing others, or of threats to self or others. Rather than reliving the event, young children tend to be reflected in repetitive play or exhibit various physical symptoms, such as stomach aches and headaches (American Psychiatric Association Manual 2000).

PTSD symptoms may be caused by a number of different factors. As a syndrome, it takes on probative value when independent evidence establishes the date of onset of the symptoms relevant to a traumatic event and when they are a marked departure from well-established past behavior. They may not independently prove an alleged traumatic event (e.g., a sexual assault), but they may provide useful and probative evidence to add to other facts that support such a conclusion.

Child Sexual Abuse Accommodation Syndrome

The child sexual abuse accommodation syndrome (CSAAS) was described by Roland Summit in a publication in 1983 (Summit 1983). At the time he published this work, a belief prevailed to the effect that children's complaints about sexual abuse were often based upon fantasies as theorized by Sigmund Freud. Dr. Summit used real-world experience from his own contacts with adults who had been abused in childhood to explain the sometimes mysterious behaviors of children after abuse. The resulting article does not describe a syndrome in the usual sense of that word. Rather, it provides a logical and often accurate explanation of why children may recant their reports of abuse and avoid the statements and actions that tend to harm the people upon whom they depend for nurture and whom they do not wish to harm.

Most of the sexual abuse of children is committed by persons who are close to the victims and who have friendly and often loving relationships with them. This fact does not reduce the harm that the abuse causes, but it puts the child in a very difficult position. Revelation or testimony about the abuse can destroy an important relationship and can result in the imprisonment of a father or another person on whom the child depends for support. Summit illuminated this dilemma and the associated behaviors. A number of critics, particularly criminal defense attorneys with clients who were suspected of child sexual abuse, have been highly critical of the Summit analysis. However, the accuracy of his observations has generally prevailed among neutral experts, and the validity of his work retains forensic utility.

Parental Alienation Syndrome

Parental alienation syndrome is a term coined by a psychiatrist, Dr. Richard Gardner, to describe a situation in which one parent attempts to contribute to alienation between a child and parent so that false allegations of everything bad, including sexual abuse, are common. The term describes a dynamic that relates to substantial litigation in family courts in the USA. The accusation of child abuse (including sexual molestation or beatings) by one parent in a contentious divorce action – where the court believes that child confirmation is induced by one parent – may lead to a "parental alienation" determination by a court. Such a finding is more likely against the parent with custody and possibly greater influence over the child and where there is evidence of bitterness, a lack of direct evidence of such abuse, and the belief of a court that it did not occur. A "parental alienation" finding may have substantial consequences on custody and visitation. Those consequences may, in turn, lead to drastic action by one of the parents either to retaliate or – particularly where the accusing parent strongly believes the accusation to be accurate – to protect a child by abduction or otherwise. However, such alienation of children by inducing them to make false accusations against one parent is not easily determinable from established and predictable patterns, and this condition has not been accepted by any professional body as a forensically useful syndrome.

Reactive Attachment Disorder

Reactive attachment disorder (RAD) is a mental-health condition of infants and young children that results from abuse or neglect and manifests itself by impaired capacity to form attachments to other persons. It is recognized in the International Classification of Diseases (ICD) and the Diagnostic and Statistical Manual (DSM). Its diagnosis and treatment is the work of mental health professionals who are familiar with child maltreatment. It is a dynamic of particular concern to the foster-care system, where children are removed from adjudicated "unfit parents" and then may suffer from what is termed "foster care drift" – moving between multiple placements without the steady anchor provided by a secure and long-standing parental bond.

Boundaries of Responsible Expert Testimony

Formal Guidelines and Limiting Advice

Professional societies have produced guidelines to assist and improve the expert testimony of their members. Generally, these guidelines lack the force of law – but are nevertheless influential in guiding professional standards relevant to expert opinions.

The American Medical Association (AMA)

The American Medical Association Council on Ethics and Judicial Affairs has published an extensive document about the rules for physicians who provide expert

testimony (American Medical Association and Council on Ethical and Judicial Affairs 1997). Possibly the most important principle in this document is the statement that providing expert testimony is a duty for physicians to society and that it is a part of the practice of medicine, subject to peer review and as such within the purview of standards of professionalism and of possible state discipline for their egregious breach.

The AMA also requires that physicians have recent and significant experience in the medical area for which they are to testify and that they testify objectively – pointing out contrary views where relevant. The AMA has taken public note of a case in which a specialty society disciplined a member for providing irresponsible expert testimony in a malpractice case. In particular, the American Association of Neurological Surgeons was supported in its decision by a trial court and in its appellate review (Posner 2001). Such cases are rare because the process of peer review of expert testimony is time consuming and expensive and because private medical societies may risk antitrust or other liability in sanctioning their horizontally competing colleagues.

The American Academy of Pediatrics

The American Academy of Pediatrics (AAP) has published guidelines for expert testimony that echo the AMA standards. The AAP standard specifically discusses testimony in child abuse cases and emphasizes the need for special qualifications in this subspecialty (Pediatrics 2008). In addition, the AAP Committee on Child Abuse and Neglect has published guidelines on a number of specific forms of child maltreatment including abusive head trauma.

The National Association of Medical Examiners (NAME)

In the USA, medical examiners (pathologists) routinely testify in litigated cases connected to fatalities in which they have performed the autopsies and determine the causes of death. Their national organization (NAME) publishes position statements on a variety of topics, but they have not included expert testimony as such.

NAME has published a position statement on abusive head injury that incorporates the medical consensus view on that subject as of 2001.

The American Academy of Child and Adolescent Psychiatry (AACAP)

AACAP has published guidelines on the forensic evaluation of abused children (American Academy of Child & Adolescent Psychiatry 1997).

The American Professional Society on the Abuse of Children (APSAC)

APSAC has published guidelines for the forensic evaluation of abused children (Myers 2001).

The American Society of Pediatric Neurosurgeons

The American Society of Pediatric Neurosurgeons published a position statement on abusive head injury in 1993 (Luerssen et al. 1993). It has not yet been updated.

State Regulators and Courts

The respected peer groups listed above, and others, have work products on specific syndromes and other topics of expert testimony. As indicated above, their work on more direct expert-witness standards has been more limited. One variable possibly influencing their involvement is the legal advice they receive from business and antitrust counsel. Note that the concerted action of any private group of competitors/colleagues has some exposure that may discourage involvement. See, e.g., the antitrust implications in physician peer review in *Patrick v. Burget* 486 U.S. 94 (1988), holding hospital peer-review committees to be vulnerable to antitrust liability as engaging in per se unlawful "group boycott" offenses. This case, while on appeal, triggered the Congressional enactment of limited antitrust immunity in the Health Care Quality Improvement Act of 1986, 42 U.S.C. § 11101 et seq. The statute now allows peer-review action where "in the reasonable belief that [it] was in the furtherance of quality health care." Where private, peer-group standards do not act to exclude competition or where they meet the "reasonable belief" standard, they will not expose their participants to the possibly harsh liability of antitrust-law public and private enforcement. Peer attempts to raise standards for expert qualification and testimony or to certify expert qualification – based on objective, scientific bases – should so qualify.

Meanwhile, state regulators are often limited in expertise but may have a more advantageous position from which to draw minimum lines for acceptable expert testimony. However, they do so even more rarely than do the private bodies discussed above. They have substantially avoided such criteria and enforcement for three reasons: (a) Such standards require specific expertise that is beyond the scope of most state medical regulation (which tends to license in broad categories such as "physician" and has essentially delegated specialized certification to private peer bodies), (b) public bodies lack the resources to become involved in the assurance of specialized competence and have generally not occupied that subject area, and (c) state bodies tend to avoid the contention of litigation and leave the weighing of credibility to the court process.

For their part, courts may indeed find testimony to fall below applicable standards, but do not impose sanctions nor recommend professional discipline by applicable state agencies. They may disallow certain testimony but, as discussed above, do not often impose dispositive admissibility standards where there is legitimate controversy. A skilled attorney may well present an untenable scientific position in a manner to allow its consideration by the trier of fact. The attorney here need only persuade a generalist court that enough uncertainty exists and sufficient expertise is proffered by the sponsoring expert to allow its consideration. In addition, trial courts are not reversed on appeal as easily because a dubious opinion was heard as they are when they block consideration of evidence. Accordingly, the mindset of courts is to err on the side of admissibility. Such license adds to the obligation of professionals not to succumb to adversarial zealotry and expert-fee emolument in advising generalists – particularly where the health and safety of children are implicated.

Irresponsible Expert Testimony

There is an extensive medical literature dealing with irresponsible expert medical testimony (Brent 1978, 1982, 1988; Weintraub 1995; Chadwick and Krous 1997; Kaufman 2001; Myers and Stern 2002; Halsey 2004; Horton et al. 2007; Jackson 2007; Kesselheim and Studdert 2007). Most of it centers on problems in malpractice cases, but child abuse cases are also discussed. Irresponsible testimony can take a variety of forms. The most common ones are as follows.

Inadequate Qualifications

This may be the most common form of irresponsible expert testimony. Judges tend to give the benefit of the doubt to proposed medical experts. Often, the expert is qualified for some of the testimony but then is led by questioning to areas where his/her qualifications no longer apply. For example, a pathologist might be asked to provide an opinion about a treatment of a patient – although he has never treated similar patients or studied the treatment under discussion.

Unique or Eccentric Causal Theory

Unique causal theory is also common. An example is the theory that there is a disease or condition of "transient brittle bones" that causes fractures resembling those associated with inflicted injuries in infants. The theory that the violent shaking of an infant cannot cause fatal head injury is also far outside the mainstream of medical opinion.

Distortion or Omission of Knowledge Pertinent to Opinion

Litigated medical cases often involve voluminous medical records that must be reviewed by the experts who are providing opinions in the case. The sheer volume of detail involved in these cases makes it possible for an irresponsible witness to alter the "facts." For example, in a California case, a pathologist stated that the patient had "spontaneous bleeding" from the nose and mouth when the medical record actually documented the fact that the bleeding was caused by a physical injury. These alterations are regrettably common and are perhaps partially driven by the English/American common-law litigation format of extreme adversarial confrontation – where some consider it fair game to simply omit evidence or science that does not support the position sought by the party retaining them. Such omissions are often justified by an atmosphere of "it is not my job to state the exceptions or contrary facts that is for the other side to provide. If the other party does not do so, the misleading conclusion resulting is his failure, not mine."

Misquoting of Medical Journals or Texts

Medical experts often depend upon and cite authorities in the form of published medical research. As in the case of patients' medical records, the amount of material may be bewilderingly large, and the expert may alter it without easy detection.

False Statements

Although penalties for perjury exist, blatant false statements by medical experts are far from rare and may be difficult to document and to prove. To be actionable, perjury must be both "knowingly false" and "material" to the proceeding in which it occurs. Prosecutors bring such criminal charges very, very rarely – and usually where the deceit pertains to known factual events and where the consequence is the criminal conviction of the wrong person. Even false statements that lead to the acquittal of guilty persons are rarely pursued.

Pushing the Boundaries: Examples of Litigation-Generated Science and Publication

Given the importance of many of the issues, it should come as no surprise that the subjects that are often argued in court would give rise to research and publication. Articles of this sort are not suspect just on that basis. However, it has been observed that the financial considerations that are present in many litigated cases put major pressure on expert witnesses and that litigation-generated research deserves special attention and careful review before publication (Anderson et al. 2001).

The creation of "reasonable doubt" in the mind of a juror can sometimes be accomplished by the expert witness who testifies that there is no scientific consensus and that his novel theory must be taken seriously.

Abusive Head Injury and Shaken Baby Syndrome

The shaken baby syndrome was first described in the 1970s (Guthkelch 1971; Caffey 1972). The descriptions were based upon the occurrence of infants with severe or fatal brain injuries and minimal or absent external head injury and caretaker confessions of shaking the baby, often accompanied by typical abusive extremity fractures. In the intervening decades, hundreds of additional similar cases have been described, many accompanied by similar confessions (Starling et al. 2004). However, a law professor has recently challenged the concept that fatal head injury can be caused by shaking (Turkheimer 2009). She cites authors that support her thesis (Ommaya et al. 2002) but omits a contrary view endorsed by the American Academy of Pediatrics (Christian and Block 2009).

The Short-Fall Debate

The short-fall debate is also connected to the issue of serious and fatal inflicted head injuries in infants and toddlers. A defense expert analyzed playground injuries recorded by the Consumer Product Safety Commission and concluded that short falls might cause fatal head injury (Plunkett 2001). Chadwick analyzed that study and the literature on the subject and calculated the population-based risk of short fall–related fatal injuries in the first 5 years of life. He showed that less than one per million young children die from short falls each year. Recognized homicide is 40 times more frequent as a cause of death for young children than recognized possible

short falls (Chadwick et al. 2008). Fatal cases of head injury in which child abuse is suspected may require that this issue be discussed by experts for the benefit of juries.

The Rebleeding Theory

The rebleeding theory is another way of attempting to explain the brain death or injury of an infant or young child – by attributing it to a birth event causing a subdural hematoma which escapes notice and later rebleeds with sudden and catastrophic neurological consequences. Competent and responsible neurosurgeons do not endorse this theory (Dias 2010).

The Retinal-Hemorrhage Debate

Retinal hemorrhages occur in inflicted head injuries in a very specific pattern (and in accidental injuries as well but to a lesser extent). Levin has recently reviewed this issue and is the recognized international authority on the subject (Levin 2010). Still, the specificity of given patterns of retinal hemorrhage for abusive head injury remains under debate by experts.

Immunizations and Brain Problems

Possibly, the most egregious examples of litigation-generated science writing are in the area of immunization side effects. For example, a paper attempting to link immunization for measles, mumps, and rubella to the developmental problem called autism (Wakefield et al. 1998) in *The Lancet* was later retracted following widespread criticism of its methodology and conclusions. Subsequently, in hearings before the General Medical Council of the United Kingdom, substantial evidence was adduced that data had been falsified (Kmietowicz 2010). Data in a publication about immunization possibly causing brain damage (Innis 2006) have not been substantiated.

Improving Expert Testimony: Preserving Physician/Expert Credibility

The spectacle of apparently competent senior medical doctors appearing on opposite sides of a litigated case and making diametrically opposite statements on specific issues of the case tends to diminish the general credibility of the medical profession and of expert witnesses in particular. It would be wise to consider ways and means of restoring confidence and improving the quality of expert witness testimony.

No simple method is at hand which can quickly improve testimony. It may be that the "natural selection" exerted by the adversarial process coupled with communications technology that allows the easy review of any witness's prior work will result in improvements over time. Peer review and the influence of standards established by professional societies will also be very important.

Conclusion

Expert testimony in child-related cases requires a high level of education, experience, competence, and ethical principles. Irresponsible expert testimony is a low-risk activity that is difficult to recognize and to control. The best hope of reducing it is through the use of peer review and a process known as continuous quality improvement. It is also necessary for professional journals to develop methods for the recognition and rejection of irresponsible litigation-generated research and publication.

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Appendix I: Infant Organ Weights (in Grams)

K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2,

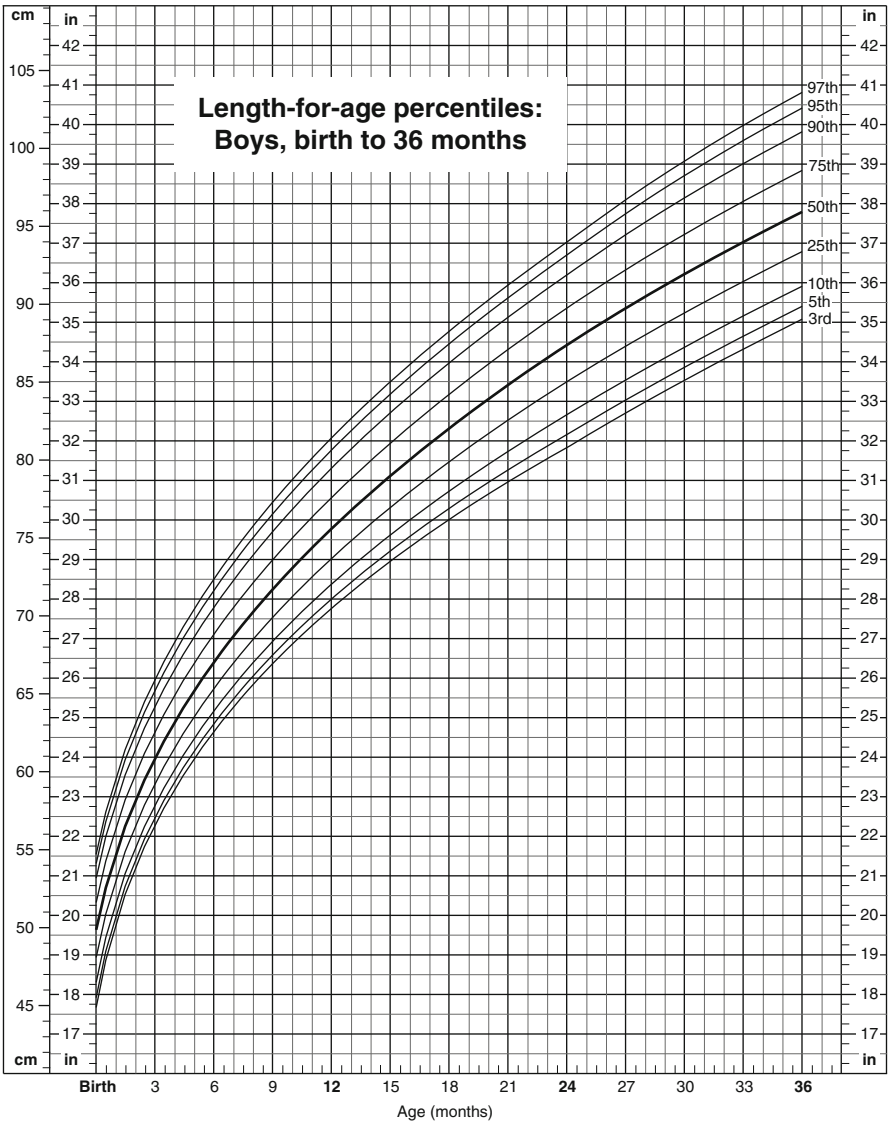
Age (months)	Brain	Heart	Thymus	Liver	R Lung	L Lung	Spleen	R Kidney	L Kidney
1	482.4(69.3)	23.4(4.2)	22.3(6.93)	160(28)	52.35(11.39)	44.5(10.2)	14.2(3.6)	17.1(4.1)	18.1(5.3)
2	540.4(89.1)	29.0(6.7)	29.33(11.87)	178(42)	59.11(11.64)	51.2(10.8)	16.6(5.5)	19.7(4.9)	19.1(5.6)
3	611.4(59.0)	31.2(5.7)	29.64(11.40)	197(39)	65.27(13.36)	56.7(11.7)	18.6(7.9)	19.5(5.3)	19.7(5.4)
4	680.4(68.5)	31.7(5.8)	35.38(1495)	216(32)	70.88(14.16)	59.3(12.6)	213(6.3)	22.5(5.6)	22.9(5.9)
5	775.3(91.3)	34.2(7.7)	37.47(15.39)	249(54)	71.21(15.33)	61.2(13.1)	22.6(8.2)	22.8(5.8)	23.3(6.7)
6	80.11(74.4)	35.4(6.9)	31.56(9.81)	280(130)	74.96(15.68)	63.0(14.7)	27.0(10.1)	23.9(8.4)	24.6(8.7)
7	795.1(103.8)	37.7(6.4)	32.76(11.08)	280(47)	80.21(17.58)	67.6(14.0)	28.2(10.0)	25.8(5.8)	26.6(6.3)
8	932.5(76.2)	39.3(5.4)	37.21(14.37)	311(45)	80.60(18.61)	68.6(18.0)	28.9(9.2)	27.0(6.6)	37.6(7.0)
9	935.5(99.3)	40.4(5.6)	32.83(10.49)	313(67)	87.75(17.13)	73.7(13.3)	32.5(9.3)	24.9(6.4)	26.4(6.6)
10	1010.0(155.1)	40.3(7.1)	34.92(15.08)	297(105)	84.20(11.65)	72.5(7.5)	31.4(8.4)	26.1(5.1)	24.9(3.9)
11	987.5(113.0)	43.8(7.8)	34.92(9.89)	375(178)	82.92(21.92)	70.1(16.5)	36.2(10.7)	26.3(3.8)	27.3(4.6)
12	967.0(61.9)	47.8(11.4)	40.50(20.82)	353(45)	91.17(20.62)	76.5(18.4)	33.8(10.2)	31.2(7.8)	30.8(6.9)

Source: Adapted from Fracasso T, et al. Organ weights in cases of sudden infant death syndrome: a German study. Am J Forensic Med Pathol. 2009;30:231–4

Appendix II: CDC Growth Charts

K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2,

CDC Growth Charts: United States



Published May 30, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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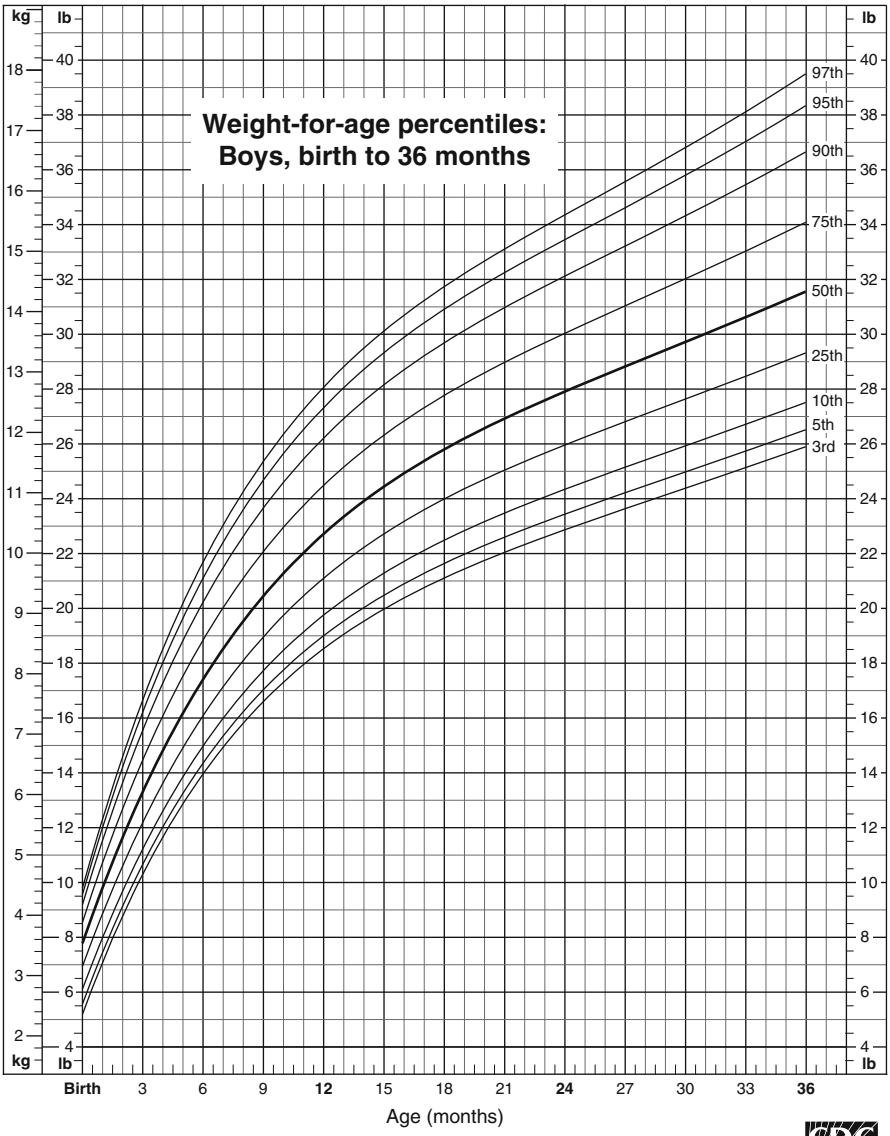
CDC Growth Charts: United States



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SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
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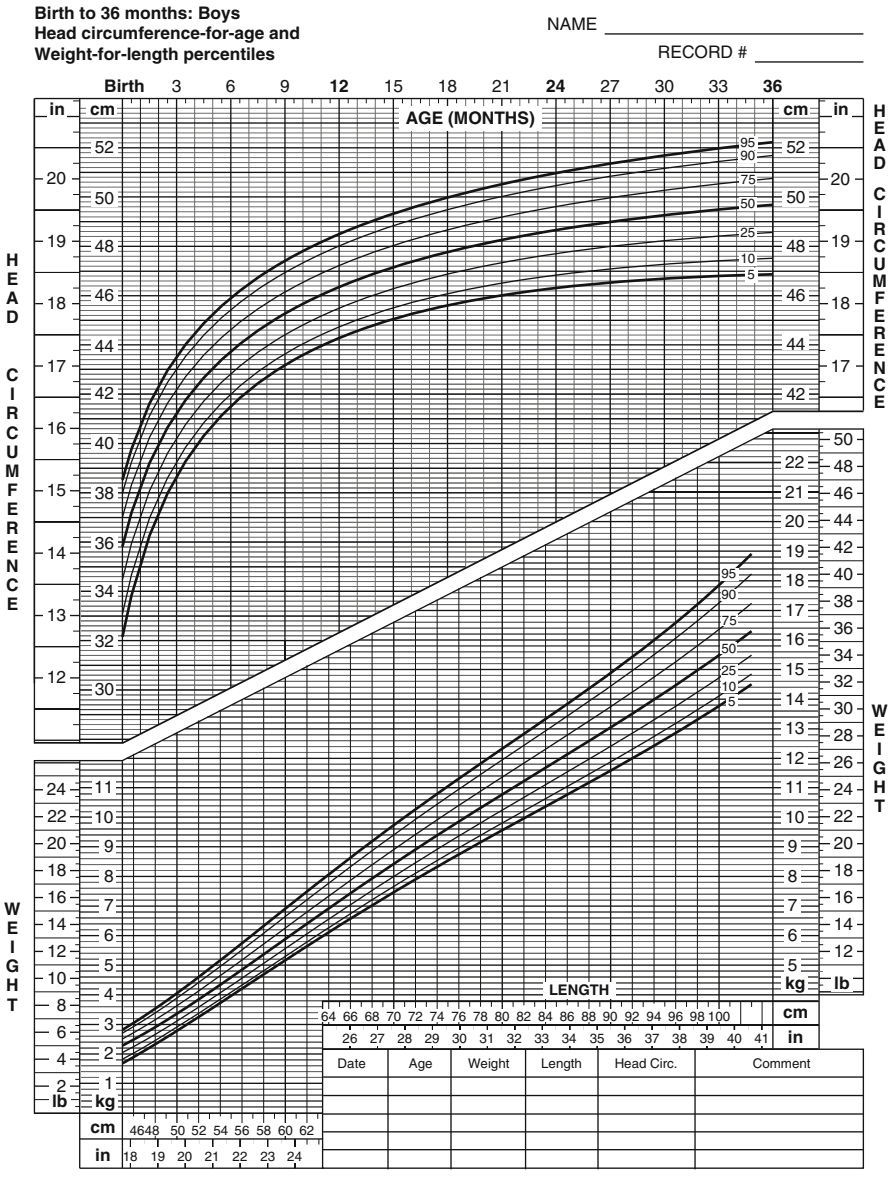
CDC Growth Charts: United States



Published May 30, 2000. (modified 10/16/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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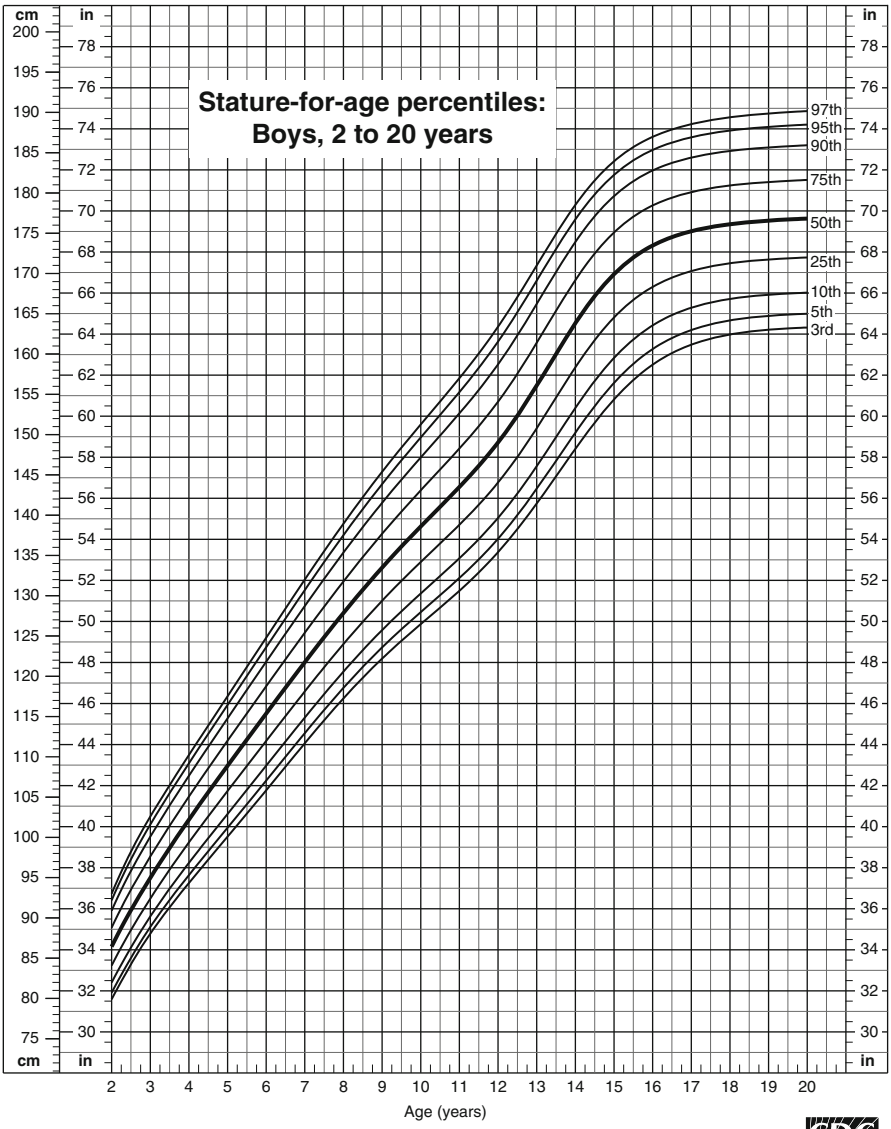
CDC Growth Charts: United States



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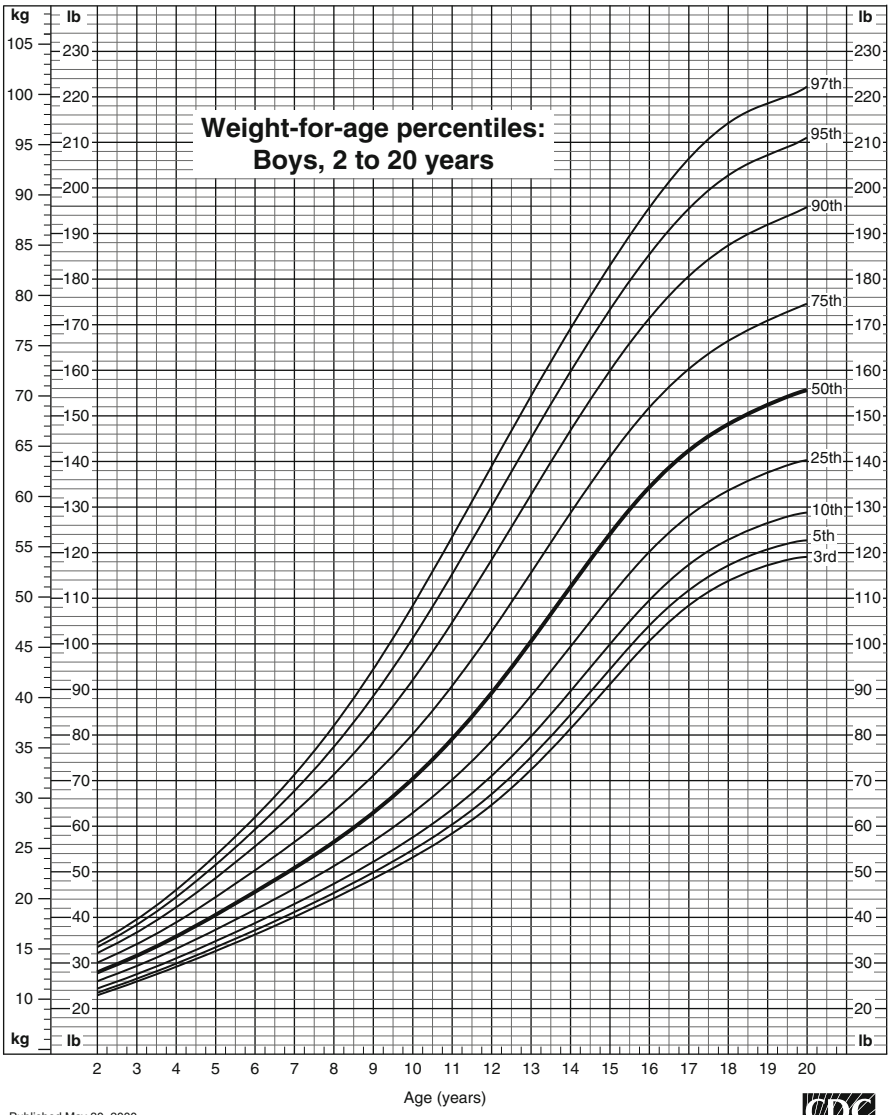
CDC Growth Charts: United States



Published May 30, 2000.

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http://www.cdc.gov/growthcharts

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CDC Growth Charts: United States

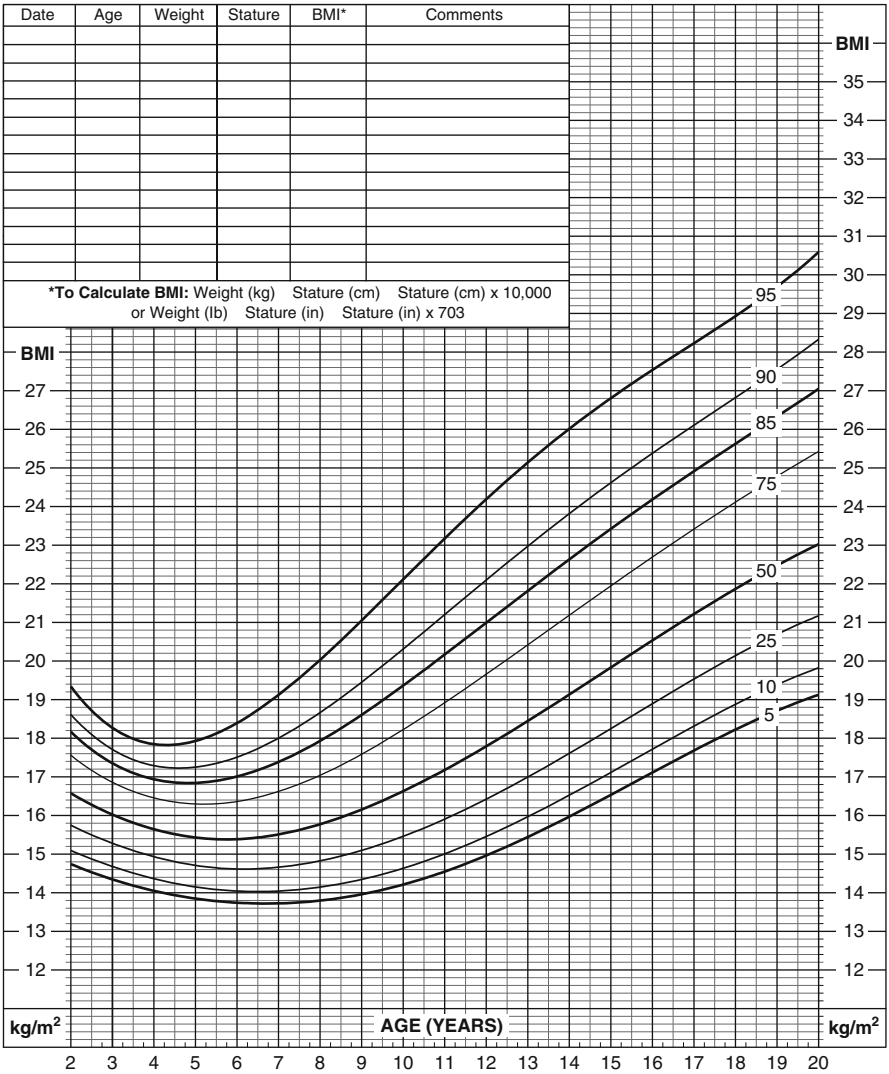
2 to 20 years: Boys
Body mass index-for-age percentiles

NAME _____

RECORD# _____

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI:** Weight (kg) Stature (cm) Stature (cm) x 10,000
or Weight (lb) Stature (in) Stature (in) x 703



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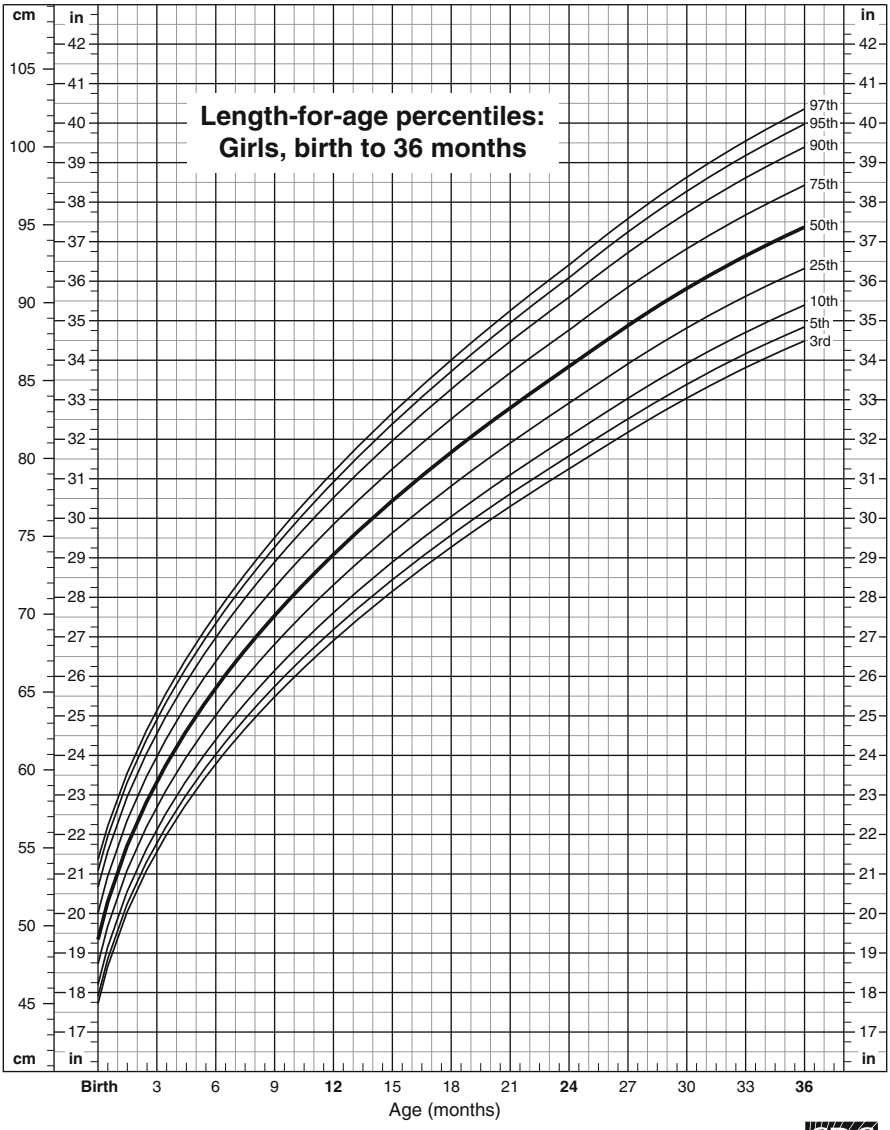
CDC Growth Charts: United States



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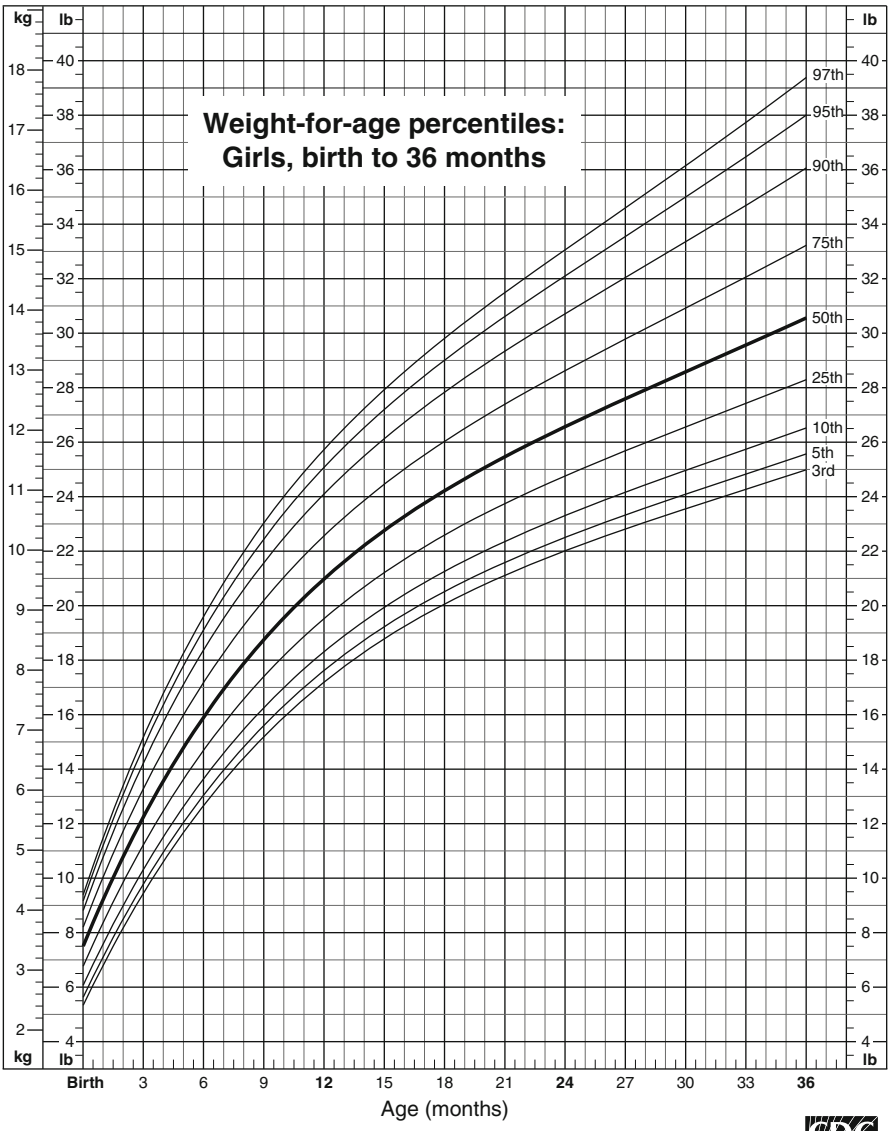
CDC Growth Charts: United States



Published May 30, 2000.

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http://www.cdc.gov/growthcharts

CDC
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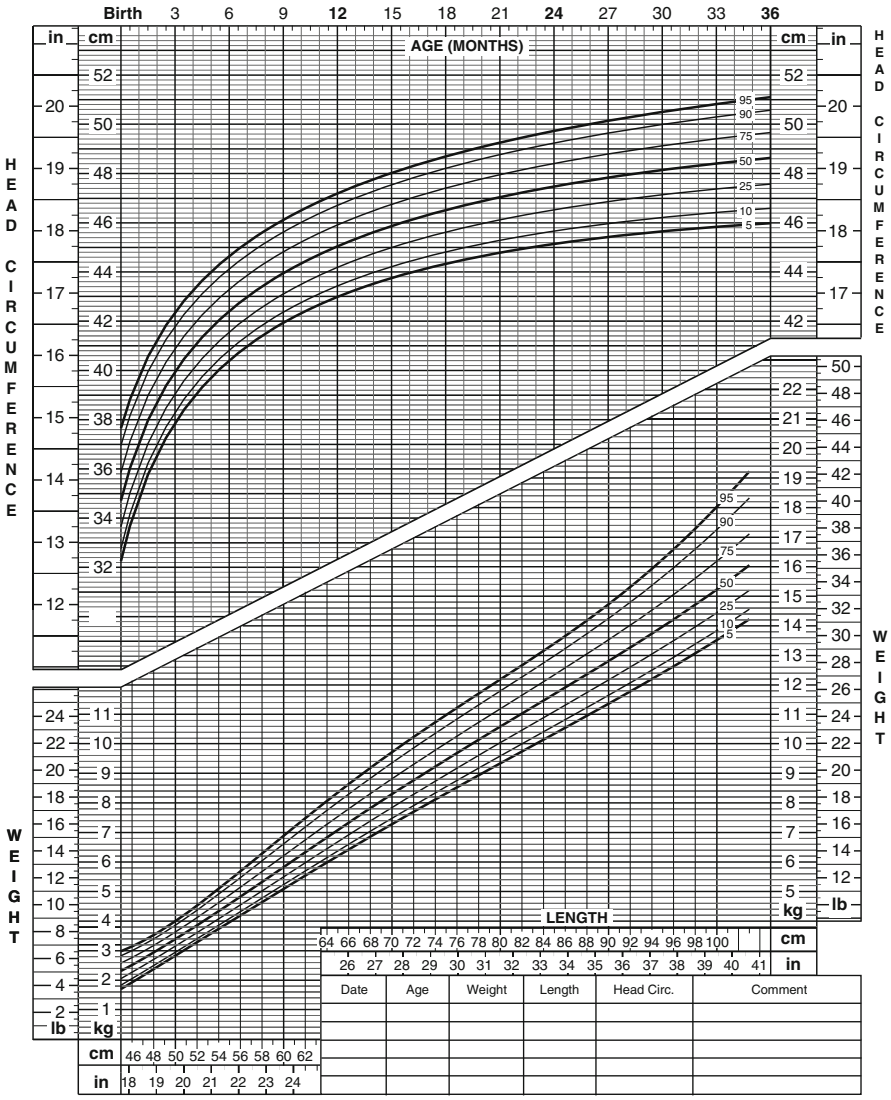
CDC Growth Charts: United States

Birth to 36 months: Girls
Head circumference-for-age and Weight-for-length percentiles

NAME _____

RECORD # _____



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SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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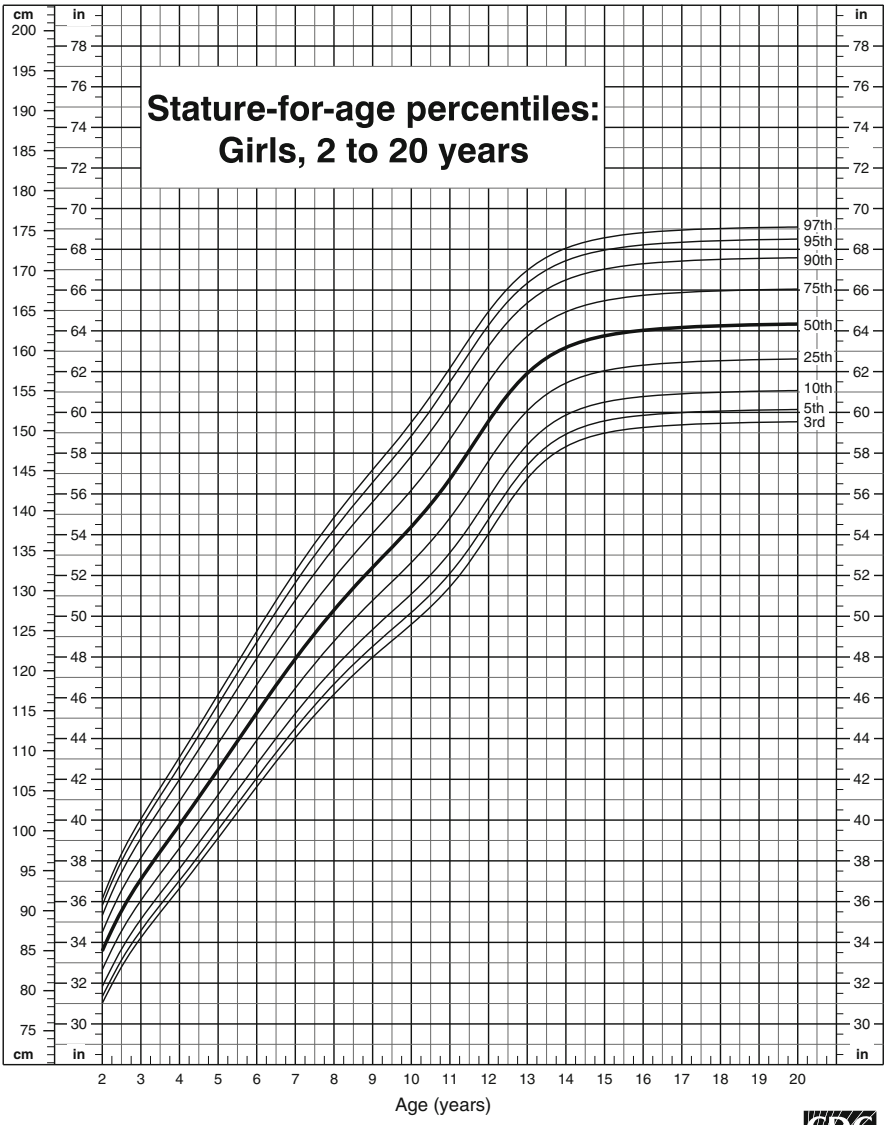
CDC Growth Charts: United States



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SOURCE: Developed by the National Center for Health Statistics in collaborati on with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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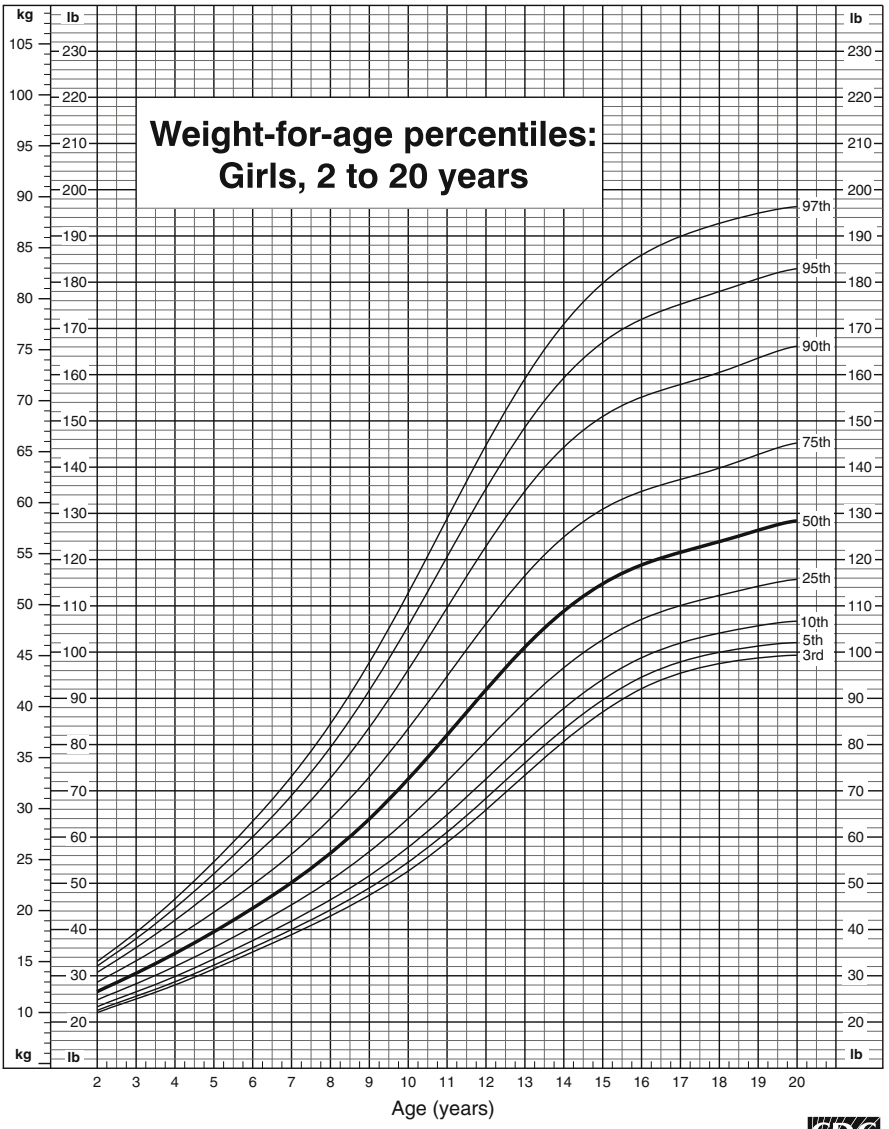
CDC Growth Charts: United States



Published May 30, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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CDC Growth Charts: United States

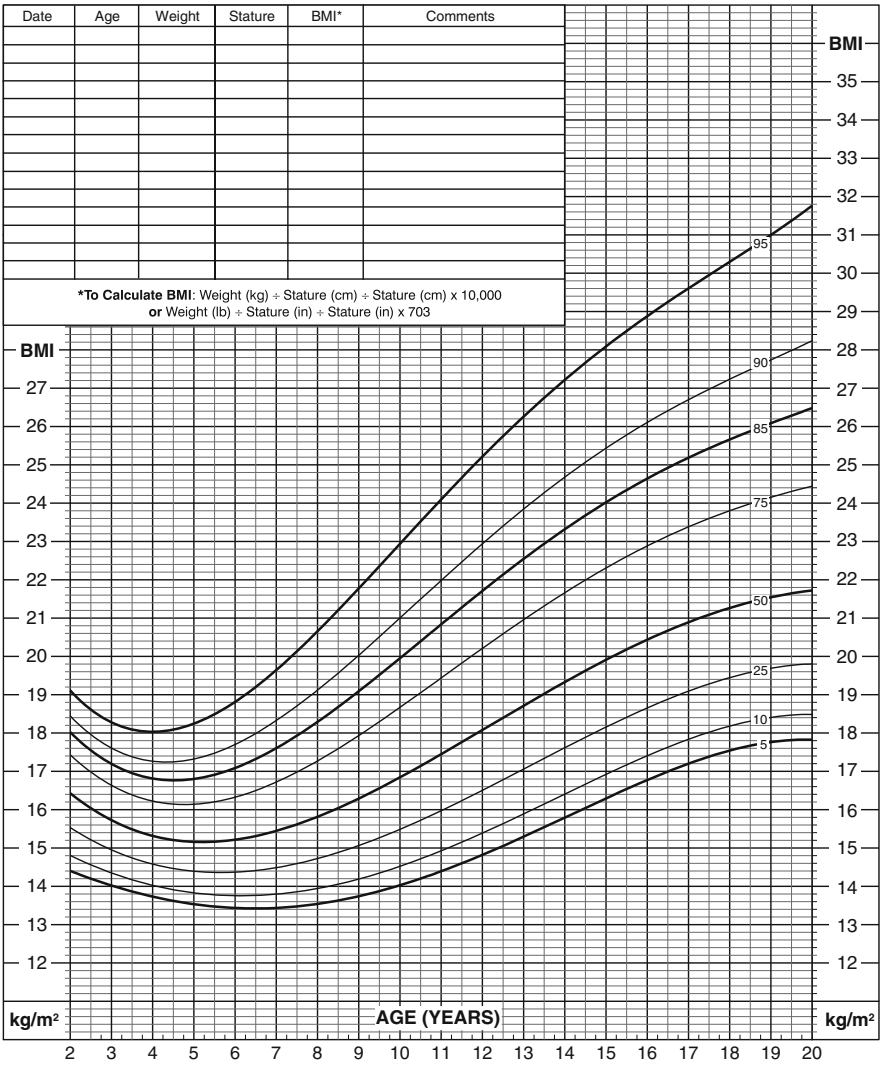
NAME _____

RECORD# _____

2 to 20 years: Girls
Body mass index-for-age percentiles

Date	Age	Weight	Stature	BMI*	Comments

***To Calculate BMI**: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 10/16/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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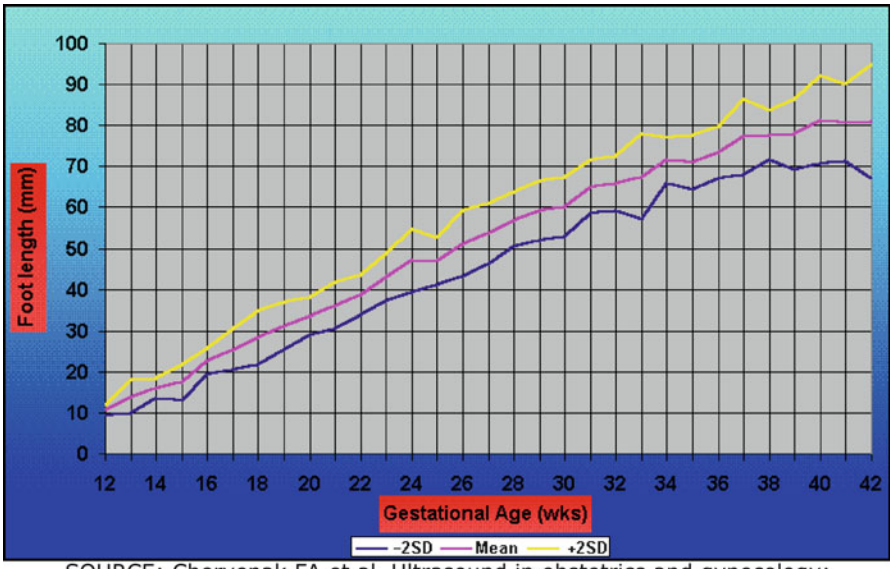
Appendix III: Foot Length

K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2,



SOURCE: Chervenak FA et al. Ultrasound in obstetrics and gynecology; 1992. Table A1-13, p. 1780.

Appendix IV: Normal Heart Weights for Body Weight for Individuals Less Than 20 Years Old

K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2,

Body weight		Heart weight (g)	
kg	lb	Male	Female
3	7	16(11–24)	19(13–29)
4	9	21(14–13)	24(16–37)
5	11	26(18–38)	29(19–44)
6	13	30(21–45)	33(22–51)
7	15	35(24–51)	38(25–58)
8	18	39(27–58)	42(28–64)
9	20	44(30–64)	46(30–71)
10	22	48(33–71)	50(33–77)
12	26	57(39–83)	58(38–89)
14	31	65(45–96)	66(43–101)
16	35	74(50–108)	74(48–113)
18	40	82(56–120)	81(53–124)
20	44	90(61–132)	88(58–135)
22	49	98(67–143)	95(62–146)
24	53	106(72–155)	102(67–156)
26	57	114(78–167)	109(71–166)
28	62	122(83–178)	116(76–177)
30	66	130(89–190)	122(80–187)
32	71	137(94–201)	129(84–197)
34	75	145(99–212)	135(88–207)
36	79	153(104–223)	142(93–216)
38	84	160(110–235)	148(97–226)
40	88	168(115–246)	154(101–236)
42	93	175(120–257)	160(105–245)
44	97	183(125–268)	166(109–254)
46	101	190(130–279)	172(113–264)
48	106	198(135–289)	179(117–273)
50	110	205(140–300)	184(121–282)
55	121	224(153–327)	199(130–199)
60	132	242(165–354)	214(140–326)
65	143	260(178–380)	228(149–348)
70	154	278(190–406)	242(158–370)
75	165	295(202–432)	256(167–391)
80	176	313(214–458)	269(176–412)
85	187	331(226–484)	283(185–432)
90	198	348(238–509)	296(194–453)
95	209	365(250–535)	309(202–473)
100	220	383(262–560)	322(211–493)

Source: Adapted from Scholz DG, et al. Age-related changes in normal human hearts during the first 10 decades of life. Part I (Growth). A quantitative anatomic study of 200 specimens from subjects from birth to 19 years old. Mayo Clin Proc 1988;63:126–36

Appendix V: The Sudden Unexplained Infant Death Investigation Report Form

How to Use SUIDI Reporting Forms

Sudden Unexplained Infant Death Investigation (SUIDI)

Each year in the United States (USA), more than 4,500 infants die suddenly of no obvious cause. Half of these sudden, unexplained infant deaths (SUIDs) are due to sudden infant death syndrome (SIDS), the leading cause of SUIDs and of deaths among infants aged 1 month to 1 year. Only sudden infant deaths that remain unexplained after a thorough examination of the death scene, a review of the clinical history, and an autopsy should be classified as SIDS. However, since 1999, some deaths due to SIDS are classified as due to an unknown cause or to accidental suffocation. Inaccurate or inconsistent classification of causes of infant deaths impedes prevention efforts because researchers cannot monitor national trends, determine risk factors, or evaluate prevention programs.

To standardize investigations of, and reports on, the causes of sudden infant deaths, the Centers for Disease Control and Prevention (CDC) collaborated with organizations who investigate infant deaths to (1) revise the 1996 Sudden, Unexplained Infant Death Investigation Reporting Form, and (2) develop a training curriculum and materials for investigators of infant deaths. We are now disseminating the reporting form and conducting train-the-trainer classes throughout the USA.

See www.cdc.gov/SIDS.

The new SUIDI Reporting Form is important for several reasons:

- It contains 25 questions that medical examiners must ask before an autopsy is done.
- It guides investigators through the steps involved in an investigation.
- It allows investigators to document their findings easily and consistently.
- It improves classification of SIDS and other SUIDs by standardizing data collection.
- It produces information that researchers can use to recognize new health threats and risk factors for infant death so that future deaths can be prevented.

This form is from http://www.cdc.gov/SIDS.

K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2,

Contents

Improvements in the SUIDI Reporting Form:

- It now contains only questions to which answers will (1) establish cause and manner of death and (2) support investigators' findings in court.
- It contains new questions about recently recognized risk factors.
- Answers to the questions can be checked off quickly, which allows for easy, consistent data collection.
- The questions are in a sequence that works well for infant-death investigations.
- The form is divided into sections, with each section being the responsibility of a particular member of the death investigation team.
- Supplemental forms for collecting information about contacts and evidence are available for jurisdictions that do not have their own.

SUIDI Reporting Form: A Guide for Investigators

The SUIDI reporting form is a guide for novice and veteran investigators of infant deaths. The form is designed to ensure that all information is collected in a consistent, sensitive manner. Training materials on how to complete the form are available.

How to Use the SUIDI Reporting Form

The form is designed as a questionnaire, that is, you can read it to the person you are interviewing. Most questions can be answered by placing an "X" in the corresponding checkbox or filling in the blank provided. The eight-page form is divided into eight sections.

Investigation Data

This section is filled out first by the person interviewing the witness.

- **Military time.** Time based on a 24-h clock which begins each day at midnight (e.g., midnight = 0000, 2 p.m. = 1400)
- SS#. Social security number.
- **DOB**. Date of birth.
- **Primary residence.** Place where the infant lived at time of their death.
- **Incident address.** Place where the infant died or where the final injury occurred.
- **Witness.** Person who knows the circumstances surrounding the infant's death. They may be the person who (1) last placed the infant in or near the area where he was found not breathing or breathing but in distress (2) last observed the infant alive, or (3) found the infant not breathing or breathing but in distress.

Witness Interview

This section is filled out by the person (e.g., coroner, death scene investigator, law enforcement office, or medical examiner) interviewing the witness.

- **Usual caregiver**. Person who took care of the infant more than 50 % of the time.
- **Placed.** Put in or near the area where he was found not breathing or breathing but in distress (e.g., placed in a crib).
- **Last known alive.** Observed to be alive (e.g., parent heard the infant cry).
- **Found.** Discovered not breathing or breathing but in distress (e.g., mom found infant not breathing).
- **Wedging.** Compression of the infant's body or face into a narrow space resulting in interference with chest wall movements and normal breathing (e.g., infant found wedged between mattress and bed frame).

Infant Medical History

This section is filled out by the person investigating the infant death. This information may be obtained from the infant's healthcare provider, medical record, or caregiver.

- **Birth defect.** A physical or functional abnormality that the infant had at birth (e.g., spina bifida, congenital heart defect, Down's syndrome).

Pregnancy History

This section is filled out by the person interviewing the biological mother or someone who knows the infant and the infant's history well (e.g., healthcare provider, medical record, or maternal grandmother).

- **Biological mother.** Woman who gave birth to the dead infant.

Incident Scene Investigation

This section is filled out by the person investigating the infant death.

Scene Diagrams

This section is filled out by the person investigating the infant death. It includes a scene diagram and a body diagram. The investigator indicates the following on the scene diagram:

- North direction
- Windows and doors
- Wall lengths and ceiling height
- Location of furniture including infant's bed or sleep surface
- Infant body location when found
- Position of other persons or animals found near infant
- Location of heating and cooling devices
- Location of other objects in the room

The Investigator Indicates the Following on the Body Diagram

- Discoloration around face/nose/mouth
- Secretions (drainage or discharge from anywhere on body)
- Skin discoloration (livor mortis)
- Pressure mark areas (pale areas, blanching)
- Rash or petechiae (small, red blood spots on skin, membranes, or in eyes)
- Marks on body (scratches or bruises)
- Location of medical devices
- Body temperature

Summary for Pathologist

This section summarizes all the information collected during the witness interview and investigation at the incident or death scene. This section is completed last by the person investigating the infant death.

- **Asphyxia.** Condition of severely deficient supply of oxygen to the body that can rapidly lead to unconsciousness and death (e.g., compression of infant's chest due to wedging or a person lying on the infant).
- **Overlying.** Situation where someone or something is placed on or over the infant.
- **Hyperthermia.** Condition where core body temperature is abnormally high (e.g., above 40 °C (104 °F) is considered life-threatening).
- **Hypothermia.** Life-threatening condition where core body temperature falls below 35 °C (95 °F).

INVESTIGATION DATA

Infant's Information: Last:_____ First:_____ M._____ Case#_____

Sex: ☐ Male ☐ Female Date of Birth _____Month/_____Day/_____Year Age_____ SS#_____

Race: ☐ White ☐ Black/African Am. ☐ Asian/Pacific Islander ☐ Am. Indian/Alaskan Native ☐ Hispanic/Latino ☐ Other

Infant's Primary Residence Address:
Address _____ City _____ Zip _____

Incident Address:

Address _____ City _____ Zip _____

Contact Information for Witness:

Relationship to the deceased: ☐ Birth Mother ☐ Birth Father ☐ Grandmother ☐ Grandfather
☐ Adoptive of Foster Parent ☐ Physician ☐ Health Records ☐ Other:

Last _____ First _____ M. _____ SS# _____
Home Address _____ City _____ State _____ Zip_____
Place of Work _____ City _____ State _____ Zip_____
Phone (H) _____ Phone (W)_____ Date of Birth_____

WITNESS INTERVIEW

1 Are you the usual caregiver? □ Yes □ No _____

2 Tell me what happened:
_____
_____
_____

3 Did you notice anything unusual or different about the infant in the last 24 hrs? □ No □ Yes ⇒ Describe:_____

4 Did the infant experience any falls or injury whitin the last 72 hrs? □ No □ Yes ⇒ Describe:_____

5 When was the infant LAST PLACED? _____Month/_____Day/_____Year ____:____Military Time Location (room) : _____

6 When was the infant ***LAST KNOWN ALIVE (LKA)***?_____Month/_____Day/_____Year ____:____Military Time Location (room) : _____

7 When was the infant ***FOUND?*** _____Month/_____Day/_____Year ____:____Military Time Location (room) : _____

8 Explain how you knew the infant was still alive _____

9 Where was the infant – (P)laced, (L)ast known alive, (F)ound (circle P, L, or F in front of appropriate response)?

P L F Bassinet	P L F Bedside co-sleeper	P L F Car seat	P L F Chair
P L F Cradle	P L F Crib	P L F Floor	P L F In a person's arms
P L F Mattress/box spring	P L F Maltress on floor	P L F Playpen	P L F Portable crib
P L F Sofa/couch	P L F Stroller/carriage	P L F Swing	P L F Waterbed

P L F Other_____

10 **In what position was the infant LAST PLACED?** □ Sitting □ On back □ On side □ On stomach □ Unknown
Was this the infant's usual position □ Yes □ No ⇒ What was the infant's usual position? _____

11 **In what position was the infant *LKA*?** □ Sitting □ On back □ On side □ On stomach □ Unknown
Was this the infant's usual position □ Yes □ No ⇒ What was the infant's usual position? _____

12 **In what position was the infant *Found?*** □ Sitting □ On back □ On side □ On stomach □ Unknown
Was this the infant's usual position? □ Yes □ No ⇒ What was the infant's usual position? _____

13	**FACE position when *LAST PLACED***	□ Face down on surface	□ Face up	□ Face right	□ Face left
14	**NECK position when *LAST PLACED?***	□ Hyperextended (head back)	□ Flexed (chin to chest)	□ Neutral	□ Turned
15	**FACE position when *LKA?***	□ Face down on surface	□ Face up	□ Face right	□ Face left
16	**NECK position when *LKA?***	□ Hyperextended (head back)	□ Flexed (chin to chest)	□ Neutral	□ Turned
17	**FACE position when *FOUND?***	□ Face down on surface	□ Face up	□ Face right	□ Face left
18	**NECK position when *FOUND?***	□ Hyperextended (head back)	□ Flexed (chin to chest)	□ Neutral	□ Turned

19 **What was the infant wearing?** *(e.x. t-shirt, disposable diaper)*_____

20 **Was the infant tightly wrapped or swaddled?** □ No □ Yes ⇒ Describe: _____

21 **Please indicate the types and numbers of layers of bedding both over and under infant (not including wrapping blanket):**

Bedding UNDER Infant,	None	Number	Bedding OVER Infant	None	Number
Receiving blankets	□	_____	Receiving blankets	□	_____
Infant/child blankets	□	_____	Infant/child blankets	□	_____
Infant/child comforters *(thick)*	□	_____	Infant/child comforters *(thick)*	□	_____
Adult comforters/duvets	□	_____	Adult comforters/duvets	□	_____
Adult blankets	□	_____	Adult blankets	□	_____
Sheets	□	_____	Sheets	□	_____
Sheepskin	□	_____	Pillows	□	_____
Pillows	□	_____	Rubber or plastic sheet	□	_____
Rubber or plastic sheet	□	_____	Other, specify:	□	_____
Other, specify: _____					

22 **Which of the following devices were operating in the infant's room?**
□ None □ Apnea monitor □ Humidifier □ Vaporizer □ Air Purifier □ Other_____

23 **What was the temperature of the infant's room?**
□ Hot □ Cold □ Normal □ Other _____

24 **Which of the following items were near the infant's face, nose, or mouth?**
□ Bumper pads □ Infant pillows □ Positional supports □ Stuffed animals □ Toys □ Other _____

25 **Which of the following items were within the infant's reach?**
□ Blankets □ Toys □ Pillows □ Pacifier □ Nothing □ Other_____

26 **Was anyone sleeping with the infant?** □ No □ Yes ⇒ Name these people._____

Name	Age	Height	Weight	Location in Relation to Infant	Impaired (intoxicated, tired)
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

27 **Was there evidence of wedging?** □ No □ Yes ⇒ Describe:_____

28 **When the infant was found, was s/he:** □ Breathing □ Not breathing

If not breathing, did you witness the infant stop breathing? □ No □ Yes

29 **What had led you to check on the infant?** _____

30 **Describe infant's appearance when found.**

	Unknown	No	Yes	Describe and specify location
a) Discoloration around face/nose/mouth	□	□	□	⇒ _____
b) Secretions (foam, froth)	□	□	□	⇒ _____
c) Skin discoloration (livor mortis)	□	□	□	⇒ _____
d) Pressure marks (pale areas, blanching)	□	□	□	⇒ _____
e) Rash or petechiae (small, red blood spots on skin, membranes, or eyes)	□	□	□	⇒ _____
f) Marks on body (scratches or bruises)	□	□	□	⇒ _____
g) Other	□	□	□	⇒ _____

31 **What did the infant feel like when found?** *(Check all that apply.)*

□ Sweaty □ Warm to touch □ Cool to touch

□ Limp, flexible □ Rigid, stiff □ Unknown

□ Other ⇒ Specify: _____

32 **Did anyone else other than EMS try to resuscitate the infant?** □ No □ Yes ⇒ Who and when?

Who _____ _____Month/_____Day/_____Year Military Time _____:_____

33 **Please describe what was done as part to resuscitation:**

_____

_____

34 **Has the parent/caregiver ever had a child die suddenly and unexpectedly?** □ No □ Yes ⇒ Explain

_____

_____

INFANT MEDICAL HISTORY

1 Source of medical information: □ Doctor □ Other healthcare provider □ Medical record
□ Mother/primary caregiver □ Family □ Other:

2 In the 72 hours prior to death, did the infant have:

	Unknown	No	Yes		Unknown	No	Yes
a) Fever	□	□	□	h) Diarrhea	□	□	□
b) Excessive sweating	□	□	□	i) Stool changes	□	□	□
c) Lethargy or sleeping more than usual	□	□	□	j) Difficulty breathing	□	□	□
d) Fussiness or excessive crying	□	□	□	k) Apnea (stopped breathing)	□	□	□
e) Decrease in appetite	□	□	□	l) Cyanosis (turned blue/gray)	□	□	□
f) Vomiting	□	□	□	m) Seizures or convulsions	□	□	□
g) Choking	□	□	□	n) Other, specify:_____			

3 In the 72 hours prior to death, was the infant injuured or did s/he have any other condition(s) not mentioned?
□ No □ Yes ⇒ Describe: _____

4 In the 72 hours prior to the infant's death, was the infant given any vaccinations or medications?
(Please include any home remedies, herbal medications, prescription medicines, over-the-counter medications.)
□ No □ Yes ⇒ List below

	Name of vaccination or medication	Dose last given	Date given (month/day/year)	Approx. time (military time)	Reasons given/comments
1.	_____	_____	_____	_____:_____	_____
2.	_____	_____	_____	_____:_____	_____
3.	_____	_____	_____	_____:_____	_____
4.	_____	_____	_____	_____:_____	_____

5 At any time in the infant's life, did s/he have a history of?

	Unknown	No	Yes	Describe
a) Allergies (food, medication, or other)	□	□	□	⇒_____
b) Abnormal growth or weight gain/loss	□	□	□	⇒_____
c) Apnea (stopped breathing)	□	□	□	⇒_____
d) Cyanosis (turned blue/gray)	□	□	□	⇒_____
e) Seizures or convulsions	□	□	□	⇒_____
f) Cardiac (heart) abnormalities	□	□	□	⇒_____
g) Metabolic disorders	□	□	□	⇒_____
h) Other	□	□	□	⇒_____

6 Did the infant have any birth defect(s)? □ No □ Yes
Describe: _____

7 Describe the two most recent times that the infant was seen by a physician or health care provider:
(Include emergency department visits, clinic visits, hospital admissions, observational stays, and telephone calls)

	First most recent visit	Second most recent visit
a) Date	_____Month/_____Day/_____Year	_____Month/_____Day/_____Year
b) Reason for visit	_____	_____
c) Action taken	_____	_____
d) Physician's name	_____	_____
e) Hospital/clinic	_____	_____
f) Address	_____	_____
g) City, ZIP	_____	_____
h) Phone number	__(____)_____ - _____	__(____)_____ - _____

8 Birth hospital name:
Street _____
City _____State_____ ZIP _____
Date of discharge _____Month/_____Day/_____Year

9 What was the infant's length at birth?_____ inches or _____ centimeters

10 What was the infant's weight at birth?_____ pounds _____ounces or _____ grams

11 Compared to the delivery date, was the infant born on time, early, or late?
□ On time □ Early–How many weeks early? □ Late–How many weeks late?_____

12 Was the infant a singleton, twin, triplet, or higher gestation?
□ Singleton □ Twins □ Triplet □ Quadruplet or higher gestation

13 Where there any complications during delivery or at birth? *(emergency c-section, child needed oxygen)*
□ No □ Yes ⇒ Describe the complications: _____
_____
_____

14 Are there any alerts to pathologist? *(previous infant deaths in family, newborn screen results)*
□ No □ Yes ⇒ Specify: _____
_____
_____

INFANT DIETARY HISTORY

1 On what day and at what approximate time was the infant last fed?

_____Month/_____Day/_____Year _____:_____ Military Time

2 What is the name of the person who last fed the infant?_____

3 What is his/her relationship to the infant?_____

4 What foods and liquids was the infant fed in the last 24 hours *(include last fed)***?**

	Unknown	No	Yes	Quantity	Specify: *(type and brand if applicable)*
a) Breast milk (one/both sides, length of time)	□	□	□	⇒_____ounces	_____
b) Formula (brand, water source – ex. Similac, tap water)	□	□	□	⇒_____ounces	_____
c) Cow's milk	□	□	□	⇒_____ounces	_____
d) Water (brand, bottled, tap, well)	□	□	□	⇒_____ounces	_____
e) Other liquids (teas, juices)	□	□	□	⇒_____ounces	_____
f) Solids	□	□	□	⇒_____	
g) Other	□	□	□	⇒_____	

5 Was a new food introduced in the 24 hours prior to his/her death?

□ No □ Yes ⇒ Describe *(ex. content, amount, change in formula, introducton of solids)*

_____

_____

_____

6 Was the infant last placed to sleep with a bottle?

□ Yes □ No ⇒ Skip to question 9 below

7 Was the bottle propped? *(i.e., object used to hold bottle while infant feeds)*

□ No □ Yes ⇒ What object was used to prop the bottle?_____

8 What was the quantity of liquid (in ounces) in the bottle?_____

9 Did death occur during? □ Breast-feeding □ Bottle-feeding □ Eating solid foods □ Not during feeding

10 Are there any factors, circumstances, or environmental concerns that may have impacted the infant that have not yet been identified? *(ex. exposed to cigarette smoke or fumes at someone else's home, infant unusually heavy, placed with positional supports or wedges)*

□ No □ Yes ⇒ Describe concerns:_____

_____

_____

_____

PREGNANCY HISTORY

1 Information about the infant's birth mother:

First name _____ Middle name _____
Last name _____ Maiden name _____
Date of birth: _____Month/_____Day/_____Year SS# _____-_____-_____
Current Address _____ City _____State_____Zip_____
How long has the birth mother been a resident at this address?
_____Years and _____ Months Previous Address_____
City _____ State_____

2 At how many weeks or months did the birth mother begin prenatal care?
_____Weeks _____ Months □ No prenatal care □ Unknown

3 Where did the birth mother receive prenatal care? *(Please specify physician or other health care provider name and address.)*
Physician/provider _____ Hospital/clinic _____ Phone (_____)_____-_____
Street _____ City _____ State _____ ZIP _____

4 During her pregnancy with the infant, did the biological mother have any complications?
(ex. high blood pressure, bleeding, gestational diabetes)
□ No □ Yes ⇒ Specify_____

5 Was the biological mother injured during her pregnancy with the infant? *(ex. auto accident, falls)*
□ No □ Yes ⇒ Specify_____

6 During her pregnancy, did she use any of the following?

	Unknown	No	Yes	Daily consumption		Unknown	No	Yes	Daily consumption
a) Over the counter medications	□	□	□	_____	d) Cigarettes	□	□	□	_____
b) Prescription medications	□	□	□	_____	e) Alcohol	□	□	□	_____
c) Herbal remedies	□	□	□	_____	f) Other	□	□	□	_____

7 Currently, does any caregiver use any of the following?

	Unknown	No	Yes	Daily consumption		Unknown	No	Yes	Daily consumption
a) Over the counter medications	□	□	□	_____	d) Cigarettes	□	□	□	_____
b) Prescription medications	□	□	□	_____	e) Alcohol	□	□	□	_____
c) Herbal remedies	□	□	□	_____	f) Other	□	□	□	_____

INCIDENT SCENE INVESTIGATION

1 **Where did the incident or death occur?** _____

2 **Was this the primary residence?** □ Yes □ No

3 **Is the site of the incident or death scene a daycare or other childcare setting?**
□ Yes □ No ⇒ Skip to question 8 below

4 **How many children were under the care of the provider at the time of the incident or death?**
_____(*under 18 years or older*)

5 **How many adults were supervising the child(ren)?** _____ *(18 years or older)*

6 **What is the licence number and licensing agency for the daycare?**
License number:_____ Agency: _____

7 **How long has the daycare been open for business?**_____

8 **How many people live at the site of the incident or death scene?**
_____ Number of adults (18 years or older) _____ Number of children (under 18 years old)

9 **Which of the following heating or cooling sources were being used? (Check all that apply.)**

□ Central air □ Gas furnace or boiler □ Wood burning fireplace □ Open window(s)
□ A/C window unit □ Electric furnace or boiler □ Coal burning furnace □ Wood burning stove
□ Ceiling fan □ Electric space heater □ Kerosene space heater
□ Floor/table fan □ Electric baseboard heat □ Other ⇒ Specify_____
□ Window fan □ Electric *(radiant)* ceiling heat □ Unknown

10 **Indicate the temperature of the room where the infant was found unresponsive:**
_____ Thermostat setting _____ Thermostat reading _____ Actual room temp._____ Outside temp.

11 **What was the source of drinking water at the site of the incident or death scene?** *(Check all that apply.)*
□ Public/municipal water source □ Bottled water □ Other ⇒ Specify _____
□ Well □ Unknown

12 **The site of the incident or death scene has: (check all that apply)**

□ Insects □ Mold growth □ Odors or fumes ⇒ Describe_____
□ Smoky smell (like cigarettes) □ Pets □ Presence of alcohol containers
□ Dampness □ Peeling paint □ Presence of drug paraphenalia
□ Visible standing water □ Rodents or vermin □ Other ⇒ Specify_____

13 **Describe the general appearance of incident scene:** *(ex. cleanliness, hazards, overcrowding, etc.)*
_____
_____

INVESTIGATION SUMMARY

1 **Are there any factors, circumstances, or environmental concerns about the incident scene investigation that may have impacted the infant that have not yet been identified?**

_____

_____

2 **Arrival times: Law enforcement at scene:** (military time) ____:____ **DSI at scene:** (military time) ____:____

Infant at hospital: (military time) ____:____

Investigator's Notes

Indicate the task(s) performed.

□ Additional scene(s)? (forms attached) □ Doll reenactment/scene re-creation □ Photos or video taken and noted

□ Materials collected/evidence logged □ Referral for counseling □ EMS run sheet/report

□ Notify next of kin or verify notification □ 911 tape

If more than one person was interviewed, does the information differ?

□ No □ Yes ⇒ Detail any differences, inconsistencies of relevant information: (ex: placed on sofa, last known alive on chair.)

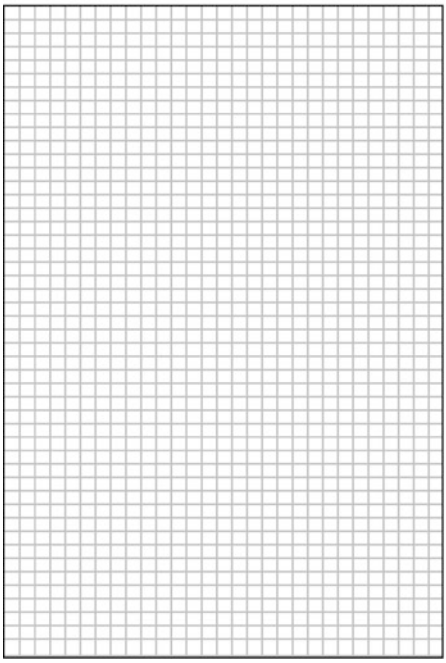
_____

_____

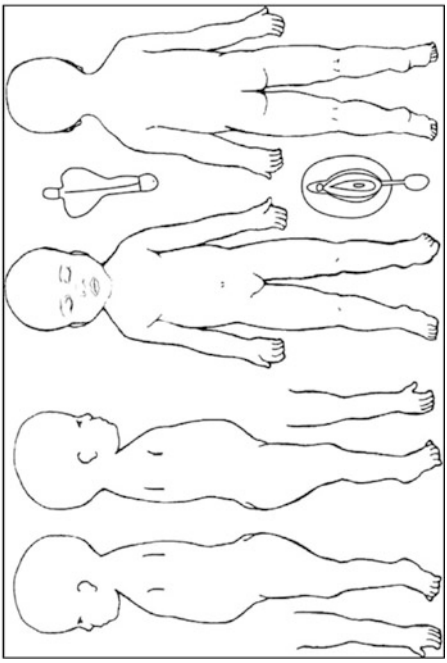
_____

INVESTIGATION DAIGRAM

a Scene Diagram



b Body Diagram



SUMMARY FOR PATHOLOGIST

Case Information

Investigator Information: Name_____Agency_____Phone_____

Investigated: _____Month/_____Day/_____Year Pronounced dead: _____Month/_____Day/_____Year
_____:_____(military time) _____:_____(military time)

Infant's Information: Last_____First_____M._____Case #_____

Sex: □ Male □ Female Date of Birth _____Month/_____Day/_____Year Age (in months) _____

Race: □ White □ Black/African Am. □ Asian/Pacific Islander □ Am. Indian/Alaskan Native □ Hispanic/Latino □ Other

Sleeping Environment

1 Indicate whether preliminary investigation suggests any of the following:

Yes	No	
□	□	Asphyxia *(ex. overlying, wedging, choking, nose/mouth obstruction, re-breathing, neck compression, immersion in water)*
□	□	Sharing of sleeping surface with adults, children, or pets
□	□	Change in sleeping condition *(ex. unaccustomed stomach sleep position, location, or sleep surface)*
□	□	Hyperthermia/Hypothermia *(ex. excessive wrapping, blankets, clothing,or hot or cold environments)*
□	□	Environmental hazards *(ex. carbon monoxide, noxious gases, chemicals drugs, devices)*
□	□	Unsafe sleeping conditions *(ex. couch/sofa, waterbed, stuffed toys,pillows, soft bedding)*

Infant History

□	□	Diet *(ex. solids introduction etc.)*
□	□	Recent hospitalization
□	□	Previous medical diagnosis
□	□	History of acute life-threatening events *(ex. apnea, seizures, difficulty breathing)*
□	□	History of medical care without diagnosis
□	□	Recent fall or other injury
□	□	History of religious, cultural, or ethnic remedies
□	□	Cause of death due to natural causes other than SIDS *(ex. birth defects, complications of preterm birth)*

Family Info

□	□	Prior sibling deaths
□	□	Previous encounters with police or social service agencies
□	□	Request for tissue or organ donation
□	□	Objection to autopsy

Exam

□	□	Pre-terminal resuscitative treatment
□	□	Death due to trauma (injury), poisoning, or intoxication

Investigator Insight

□	□	Suspicious circumstances
□	□	Other alerts for pathologist's attention

Any "Yes" answers should be explained and detailed.

Brief description of circumstances:_____

_____

_____

_____

_____

_____

_____

Pathologist

2 Pathologist Information:

Name _____ Agency _____

Phone (_____)_____-_____ Fax (_____)_____-_____

Appendix VI: International Standardized Autopsy Protocol

The International Standardized Autopsy Protocol for cases of unexpected infant death represents the first attempt to provide an international protocol aimed at standardizing autopsy practices and diagnoses. The protocol was developed by a working group set up by SIDS International and the NICHD in the 1990s (Krous 1995, Krous and Byard 2001). It aims to:

- Standardize autopsy practices and improve diagnostic accuracy
- Provide additional information to supplement information obtained from the clinical history review and death scene examination
- Enhance opportunities to further reduce infant death rates and enable more meaningful comparisons of infant death rates to be made between populations
- Improve the quality of research into unexpected infant death

The protocol has been endorsed by the National Association of Medical Examiners (NAME) and the Society for Pediatric Pathology (SPP) in the United States and has been implemented in a number of countries.

K.A. Collins, R.W. Byard (eds.), *Forensic Pathology of Infancy and Childhood*,
DOI 10.1007/978-1-61779-403-2,

International Standardized Autopsy Protocol for Sudden Unexpected Infant Death

Decedent's name		Local Accession Number
Age/Sex	Ethnicity	
Date of Birth	Date/Time of Death	
Date/Time of Autopsy	Pathologist	
County/District	Country	

Final Anatomic Diagnoses

MICROBIOLOGY RESULTS:

TOXICOLOGY RESULTS:

CHEMISTRY RESULTS:

PATHOLOGIST_____

DECEDENT'S NAME_____

ACCESSION NUMBER_____

COUNTY & COUNTRY_____

PATHOLOGIST_____

	YES	NO
MICROBIOLOGY Date/Time		
Done before autopsy		
VIRUSES trachea, stool		
BACTERIA blood, CSF, fluids		
FUNGI discretionary		
MYCOBACTERIA discretionary		
Done during autopsy		
BACTERIA liver, lung and myocardium		
VIRUSES liver, lung and myocardium		
PHOTOGRAPHS include		
Name, Case number, County,		
Country, Date		
Measuring device color reference		
Consider front and back		
Gross abnormalities		
RADIOGRAPHIC STUDIES consider		
Whole body		
Thorax and specific lesions		
EXTERNAL EXAMINATION		
Date and Time of autopsy		
Sex (circle) Male, Female		
Observed race (circle)		
White Black		
Asian Arab		
Pacific Islander Hispanic		
Other (specify)		
Rigor mortis: describe distribution		
Livor mortis: describe distribution and if fixed		
WEIGHTS AND MEASURES		
Body weight, g		
Crown-heel length, cm		
Crown-rump length, cm		
Occipitofrontal circumference, cm		
Chest circumference at nipples, cm		
Abdominal circumference at umbilicus, cm		

DECEDENT'S NAME_____
ACCESSION NUMBER_____
COUNTY & COUNTRY_____
PATHOLOGIST_____

GENERAL

APPEARANCE/DEVELOPMENT YES NO NO EXAM
Development normal
Nutritional status
Normal
Poor
Obese
Hydration
Normal
Dehydrated
Edematous
Pallor

HEAD
Configuration normal
Scalp and hair normal
Bone consistency normal
Other

TRAUMA EVIDENCE
Bruises
Lacerations
Abrasions
Burns
Other

PAST SURGICAL INTERVENTION
Scars
Other

RESUSCITATION EVIDENCE
Facial mask marks
Lip abrasions
Chest ecchymoses
ECG monitor pads
Defibrillator marks
Venipunctures
Other

CONGENITAL ANOMALIES

EXTERNAL

INTEGUMENT
Jaundice
Petechiae
Rashes
Birthmarks
Other abnormalities

EYES (remove when indicated and authorized)
Color (circle) Brown, Blue, Green, Hazel
Cataracts
Position abnormal
Jaundice
Conjunctiva abnormal
Petechiae
Other abnormalities

EARS
Low set
Rotation abnormal
Other abnormalities

NOSE
Discharge (describe if present)
Configuration abnormal
Septal deviation
Right choanal atresia
Left choanal atresia
Other abnormalities

MOUTH
Discharge (describe if present)
Labial frenulum abnormal
Teeth present
Number of upper
Number of lower

TONGUE
Abnormally large
Frenulum abnormal
Other abnormalities

PALATE
Cleft
High arched
Other abnormalities

MANDIBLE
Micrognathia
Other abnormalities

NECK
Abnormal

CHEST
Abnormal

ABDOMEN
Distended
Umbilicus abnormal
Hernias
Other abnormal

EXTERNAL GENITALIA
Abnormal

ANUS
Abnormal

EXTREMITIES
Abnormal

INTERNAL EXAMINATION
Subcutis thickness 1 cm below umbilicus
Subcutaneous emphysema
Situs inversus

PLEURAL CAVITIES
Abnormal
Fluid, describe if present
Right, mL
Left, mL

PERICARDIAL CAVITY
Abnormal
Fluid, describe if present, mL
Other abnormalities

PERITONEAL CAVITY
Abnormal
Fluid, describe if present, mL

RETROPERITONEUM
Abnormal
PETECHIAE (indicate if dorsal and/or ventral)
Parietal pleura
Right
Left
Visceral pleura
Right
Left
Pericardium
Epicardium
Thymus
Parietal peritoneum
Visceral peritoneum
UPPER AIRWAY OBSTRUCTION
Foreign body
Mucus plug
Other
NECK SOFT TISSUE HEMORRHAGE
HYOID BONE
Abnormal
THYMUS
Weight, g
Atrophy
Other abnormalities
EPIGLOTTIS
Abnormal
LARYNX
Abnormal
Narrowed lumen
TRACHEA
Abnormal
Stenosis
Obstructive exudates
Aspirated gastric contents
ET tube tip location
MAINSTEM BRONCHI
Abnormal
Edema fluid
Mucus plugs
Gastric contents
Inflammation
LUNGS
Weight
Right, g
Left, g
Abnormal
Congestion, describe location, severity
Hemorrhage, describe location, severity
Edema, describe location
Severity (circle)
Consolidation, describe location, severity
Anomalies
Pulmonary artery
Thromboembolization
PLEURA
Abnormal
RIBS
Abnormal
Fractures
With hemorrhages
Callus formation

DIAPHRAGM
Abnormal
CARDIOVASCULAR SYSTEM
Heart weight, g
Left ventricular thickness, cm
Right ventricular thickness, cm
Septal thickness maximum, cm
Mitral valve circumference, cm
Aortic valve circumference, cm
Tricuspid valve circumference, cm
Pulmonary valve circumference, cm
Myocardium abnormal
Ventricular inflow/outflow tracts narrow
Valvular vegetations/thromboses
Aortic coarctation
Patent ductus arteriosus
Chamber blood (circle) fluid clotted
Congenital heart disease
Atrial septal defect
Ventricular septal defect
Abnormal pulmonary venous connection
Other
Location of vascular catheter tips
Occlusive vascular thrombosis locations
Other abnormalities
ESOPHAGUS
Abnormal
STOMACH
Abnormal
Describe contents and volume
SMALL INTESTINE
Abnormal
Hemorrhage
Volvulus
Describe contents
COLON
Abnormal
Congestion
Hemorrhage
Describe contents
APPENDIX
Abnormal
MESENTERY
Abnormal
LIVER
Abnormal
Weight, g
GALLBLADDER
Abnormal
PANCREAS
Abnormal
SPLEEN
Abnormal
Weight, g
KIDNEYS
Abnormal
Weight:
    Right, g
    Left, g

URETERS
Abnormal
BLADDER
Abnormal
Contents, volume
PROSTATE
Abnormal
UTERUS, FALLOPIAN TUBES, and OVARIES
Abnormal
THYROID
Abnormal
ADRENAL GLANDS
Abnormal
Right, g
Left, g
Combined, g
PITUITARY
Abnormal
CONGENITAL ANOMALIES, INTERNAL
CENTRAL NERVOUS SYSTEM
Whole brain weight
  Fresh, g
  Fixed, g
Combined cerebellum/brainstem weight
  Fresh, g
  Fixed, g
Evidence of trauma
Scalp abnormal
Galea abnormal
Fractures
Anterior fontanelle abnormal
Dimensions
Calvarium abnormal
Cranial sutures abnormal
Closed (fused)
Overriding
Widened
Base of skull abnormal
Configuration abnormal
Middle ears abnormal
Foramen magnum abnormal
Hemorrhage, estimate volumes (mL)
Epidural
Dural
Subdural
Subarachnoid
Intracerebral
Cerebellum
Brainstem
Spinal cord
Intraventricular
Other
Dural lacerations
Dural sinus thrombosis
BRAIN: IF EXTERNALLY ABNORMAL FIX
  BEFORE CUTTING
Configuration abnormal
Hydrocephalus
Gyral pattern abnormal
Cerebral edema
Herniation
Uncal
Tonsillar
Tonsillar necrosis
Leptomeningeal exudates (culture)
Cerebral contusions
Malformations
Cranial nerves abnormal
Circle of Willis/basilar arteries abnormal
Ventricular contours abnormal
Cerebral infarction
Contusional tears
Other abnormalities
SPINAL CORD
Inflammation
Contusion(s)
Anomalies – other abnormalities

DECEDENT'S NAME_____
ACCESSION NUMBER_____
COUNTY & COUNTRY_____
PATHOLOGIST_____

MANDATORY SECTIONS TAKEN **YES** **NO**

Skin, if lesions
Thymus
Lymph node
Epiglottis, vertical
Larynx, supraglottic, transverse
Larynx, true cords, transverse
Trachea and thyroid, transverse
Trachea at carnia, transverse
Lungs, all lobes
Diaphragm
Heart, septum and ventricles
Esophagus, distal 3 cm
Terminal ileum
Rectum
Liver
Pancreas with duodenum
Spleen
Kidney with capsule
Adrenal
Rib with costochondral junction
Submandibular gland
Cervical spinal cord
Rostral medulla junction
Pons
Midbrain
Hippocampus
Frontal lobe
Cerebellum
Choroid plexus

OIL RED O STAINED SECTIONS, IF INDICATED

Heart
Liver
Muscle

DISCRETIONARY MICROSCOPIC SECTIONS

Supraglottic soft tissue
Lung hilum
Pancreatic tail
Mesentery
Stomach
Colon
Appendix
Testes or ovaries
Urinary bladder
Psoas muscle
Palatine tonsils
Basal ganglia

METABOLIC DISORDERS – RETAIN ON FILTER PAPER IN ALL CASES

Whole blood (1 drop)
Urine (1 drop)
Hair (taped down)

TOXICOLOGY AND ELECTROLYTES – FLUID AND TISSUES SAVED FOR 1 YEAR

Whole blood and serum, save at −70 °C and +4 °C
Liver, save 100 g at −70 °C
Frontal lobe, save at −70 °C
Urine, save at −70 °C
Bile
Vitreous humor
Serum
Gastric contents

Analyses performed, but not limited to:

Cocaine and metabolites
Morphine and metabolites
Amphetamine and metabolites
Ethanol and volatiles
Other indicated by history and exam

FROZEN TISSUES, SAVE AT −70 °C

Lung
Heart
Liver
Lymph nod

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Page references in italics indicate an illustration; 't' following a page reference indicates material presented in tabular format.

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