Pediatric Neurosurgery for Clinicians

Georgios Alexiou
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Editors

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Preface

Pediatric Neurosurgery is a constantly developing specialty that keeps evolving due to technological advancements and the gradual improvement of understanding of disease processes that affect the central nervous system.

This book includes nine sections: general topics, congenital and developmental cranial anomalies, congenital and developmental spinal anomalies, tumors, trauma, cerebrovascular disorders, functional, infections, and modern concepts and practices. Book chapters were written by experts in the field from all over the world and we would like to express our gratitude to all contributors for their efforts.

This book is specially compiled and illustrated not only for neurosurgeons but also for medical students, residents, pediatricians, radiologists, pathologists, oncologists, intensivists, and nurses. We hope that this book would help improve awareness and care of different pediatric neurosurgical disorders.

Ioannina, Greece — Georgios A. Alexiou
Athens, Greece — Neofytos Prodromou

Contents

Part III Congenital and Developmental Spinal Anomalies

Part IV Tumors

Part V Trauma

Part VI Cerebrovascular Disorders

Part VII Functional

Part I
General Topics

Chapter 1
History of Pediatric Neurosurgery

Amalia Christopoulou

Wherever the art of Medicine is loved, there is also a love of Humanity
Hippocrates (460–375 BC)

1.1 The Evolution of Neurosurgery from Ancient Greece to Modern Times

The history of neurosurgery must start when the human being first appeared on earth, and according to the history of medicine it is synchronous with the history of surgery. The first account of traumatic brain injury is found early in the Holy Bible, when Cain inflicted a fatal head injury on his brother Abel with the jawbone of an ass [1]. According to Greek mythology, and specifically cosmogony, the genesis of the Greek gods, Hephaestus struck Zeus on his forehead with an axe to relieve him of headaches. Immediately afterwards, Athena, the goddess of wisdom, emerged from her father's head. Pindar makes a clear reference to the genesis of goddess Athena in this way, inadvertently providing the first description of a neurosurgical intervention [2].

The Holy Bible provides two clear references to successful cardiopulmonary resuscitation, dating back to around 850 BC. The first is a description of how the prophets Elijah and Elisha gave life back to a boy who had apparently died, using the method of blowing air through his mouth and warming the boy with their own bodies [3]. Also in the Bible, the same method of blowing air through the mouth is used by the Jewish midwives Foa and Sephora to get newborn infants to cry [4].

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The technique of cranial trepanation has been known since prehistoric times. Its use was based on the belief that skull opening let out demonic elements that caused various neuro-psychiatric symptoms. The first documented evidence of such surgery in Greece dates back to the Minoan era findings (2000 BC), on the island of Crete, where skull drilling was performed for ritual and religious purposes [5]. In Ancient Greece, the use of analgesic techniques was widespread. During the Bronze Age, in the Aegean, a mixture of raw opium and anhydrous morphine with a maximum content of 20% was used as a primitive anesthetic, and as an analgesic to treat toothache in infants by rubbing it on their gums [6].

Pediatric reports can be widely found in the works of both Hippocrates and Galens. Hippocrates used a method similar to today's intubation to save sick children suffering from diphtherial membranes that blocked their air flow. This disease is rare today, as children now receive antidiphtherial vaccine in infancy, but in the past it was a common cause of respiratory distress in children. Hippocrates used thin tubes to relieve the young patients who were suffering from severe shortness of breath; he inserted these tubes between the jaws into the pharynx, so that the lungs could pump air, in a method very similar to modern intubation [7]. Regarding the treatment of hydrocephalus, he proposed a therapeutic approach through a cranial incision [8].

On traumatic brain injury, a famous quote of Hippocrates is "*No head injury is too trivial to be ignored*". He reported that midline head trauma is associated with increased mortality. In cases of skull fractures with hematoma, Hippocrates used a therapeutic approach through cranial perforation in order to remove the blood and create space for the brain. He recommended that the intervention be performed with maximun attention in children, because their skull bones are thinner than those of adults. In his works, Hippocrates described three cases of cranial procedures in children: (a) on a boy who had a head injury and developed a fever 12 days later due to wound infection. The inflammation spread to the surrounding tissues, and the boy had his skull drilled to improve his clinical picture, (b) on an 11-year-old boy, who suffered a fracture of the frontal bone and, because of bleeding, had his skull drilled, which resulted in improvement, and (c) on a 12-year-old girl, who suffered a compressed fracture and was treated immediately with skull drilling. In the following days, the trauma got infected and the patient developed focal convulsions [9].

As treatment for spinal disorders, Hippocrates recommended forciblet stretching in a horizontal position or hanging the patient by the armpits in order to stretch the spine. Today we know that spinal abnormalities represent the most common non-traumatic musculoskeletal disorders in childhood. Myelomeningocele is a congenital malformation, and the skeletal remains of people suffering from myelomeningocele dating back at least 3,000 years have been found in archaeological excavations. Myelomeningocele was described by both Hippocrates and Aristotle [10]. In Ancient times, medical care for infants with congenital abnormalities was almost non-existent, and infanticide was recommended, with most infants who were born with severe deformities being left to die unattended.

During the Roman period, the famous Greek doctor Asklipiadis, a friend of Cicero, Crassus and Marcus Aurelius, was the first to report a tracheotomy on a young man who was being carried in a funeral procession. Asklipiadis noticed that the youth appeared to be still alive and resuscitated him by this method [11].

Soranos the Ephesian (98–138 A.D.) would deal systematically with pediatrics; in his work, there is extensive reference to the nutrition and hygiene of infants and descriptions of pediatric diseases [12]. During the Byzantine era, which began with the establishment of the capital of the Eastern Roman Empire in Constantinople in 324 AD, Paul of Aegina (625–690 AD) made an important contribution to neurosurgery with his work on nerve injuries, hydrocephalus, and the diagnosis and treatment of skull and spinal fractures [13].

In spite of the fact that the ancient Greeks and Byzantines made significant contributions to medicine and surgery [13], in modern Greece, Pediatrics was recognized as a separate specialty only in 1878, and the first pediatric hospital operated on the premises of the Municipal Nursery of Athens. The first reference to pediatric neurosurgery in modern Greece is in 1882, when a 7-year-old boy was injured in the frontal area and underwent surgery, performed by a surgeon of that time who removed bone fragments and left the wound to heal.

At the beginning of the twentieth century, The "Aghia Sophia" Children's Hospital, founded in 1900, was the only pediatric hospital in Greece. At that time, child mortality was very high, and the Pediatric specialty in Greece was still at its very beginnings. Christos Daskalakis from Smyrna reported the excision a meningocele in the cervical spine of a 52-day-old infant on April 18, 1903 [14]. Christidis from Monastiri, reported the case of congenital encephalomyelomeningocele in a 5-month-old infant, presenting with a mass in the occipital region equal in size to the infant's head, which he operated on under general anesthesia. At a meeting of the Medical Society of Athens in 1925, Konstantinos Mermigas described in detail the treatment of a 2.5-year-old child suffering from spina bifida ("meningocele"): "*sac excision, the liquid had formed a mass at the child's head, his neck was stitched, the soft tissues were rearranged in order to close the surgical wound*" [15]. In the early 1960s, Stamatios Komninos established the first pediatric neurosurgery department at the 'Aghia Sofia" Children's Hospital in Athens. Neofytos Prodromou was the following Director for 30 years.

1.2 The Evolution of Neurosurgery in Europe

In 1517, a European surgeon, Hans von Gersdorff, described a cranioplasty, constructed with a mixture of oil and wine on wood, which was compressed until it hardened. Gersdorff rightly noted that it should not be pressed hard, because that would become fatal [16]. The first printed paper on head injuries was "*Tractatus de fractura calve sive cranei*", written by Jacopo Berengario da Carpi (1460–1530). In

this text, published in 1518, Berengario proposed several methods of treating fractured skulls, the relevance of which can be debated today: "*When large parts of the skull are removed, the wound should be sprinkled with chopped dried pumpkin (Frustulum cucurbitae siccae), which accelerates healing. The smaller defects are covered with "flesh" [carne].*" [17].

The Englishman James Yong (1647–1721) described the case of a child who survived a severe traumatic brain injury that presented with a compound skull fracture and brain tissue issuing from the wound [18]. In 1667, Thomas Willis reported the first case of a stroke in a child "Pediatric hemiplegia", after which a series of cases of pediatric stroke was reported by Osler, Sachs, Peterson and Freud [19]. The predictive method, the first modern (twentieth century) evaluation of children with ischemic stroke, was written by Ford and Schaffer, who focused on causes, outcome and quality of life in children that survived. [20]

In 1800, Samuel T. Söemmerring (1755–1830) was the first to describe the sutures of the skull. He argued that the role of skull sutures was to allow the brain to grow, and that if sutures close prematurely, abnormal growth of the head would occur. In fact, he described a case of lambdoid synostosis [21]. Later, in 1894, Wheaton first described two infants with craniosynostosis associated with fusion of the toes and feet. The Carpenter syndrome was first described by Carpenter in 1901 and later published in 1909 [22]. It is characterized by craniosynostosis. Heart abnormalities have been reported in one third of patients. Over the last 50 years, more than 65 syndromes, including craniofacial syndromes, have been described as craniosynostosis disorders, and the neurosurgical treatment of craniofacial syndromes has undergone many changes.

The term "syringomyelia" was coined by D'Angers, in 1827, from the Greek syrinx, or tube. In Greek mythology, Syrinx was a nymph who turned herself into a reed to save herself from Pan's amorous pursuits. From this reed, Pan shaped his music pipes. Today, syringomyelia is a wider term used for the development of a fluid-filled cyst within the spinal cord. It is usually associated with a variety of pathological conditions, but it is more commonly seen with posterior fossa brain abnormalities, such as type 1 Chiari malformation [23].

1.3 Period 1840–1940: The Century of the Most Important Changes

The first pediatric hospital in Europe was founded in Paris in 1802 and later, in 1855, the first in the USA [24]. During this period, major advances in anesthesia resulted in great changes in surgery. Pediatric anesthesia was first applied on July 3, 1842, when Crawford W. Long administered anesthesia to Jack, an 8-year-old boy, who needed to have his toe amputated. He was anesthetized with the use of diethyl ether on a towel [25]. In Russia, in 1847, F.I. Inozemtsev performed operations on two children aged 10 and 14 years whom he anesthetized using ether [26]. John Snow (1813–1858) in his book entitled "Chloroform and other anesthetics", reported

that chloroform was used in some newborns cases, and that by June 30, 1857, he had administered chloroform to 186 infants with no side effects [27]. In 1858, the method of cardiopulmonary resuscitation by Silvester and Howard was introduced in clinical practice [28].

Regarding the anatomy of neurosurgical conditions, in 1862, when autopsy was established, Freidrich Daniel Von Recklinghausen was the first to diagnose the disease named after him, on autopsy studies in people with multiple heart and brain tumors [29]. Intracranial aneurysms in children were rarely encountered. One of the first cases of pediatric aneurysm was recorded by the German pathologist Eppinger in 1871. He described a 15-year-old boy who collapsed during strenuous exercise while the "disease" gradually progressed to weakness of the lower limbs over the next 3 days, and the boy died. Postmortem examination showed rupture of an aneurysm from the right anterior cerebral artery. A few years later, Edvard Bull described the first case of death in a 17-year-old girl who presented with a severe headache. Autopsy revealed rupture of a cerebral aneurysm [30].

On the topic of head trauma, on March 20, 1879, Sir William Macewen, a Scottish surgeon, operated on and drained a subacute hematoma a in a nine-year-old boy, who had fallen from height. Six days later, the child presented with convulsions that led to loss of consciousness. This pioneer surgeon made a frontal skin incision and drilled in the area above the coronary suture, where the fracture line was visible. On July 27, 1879, the same surgeon re-operated for a local relapse of a large tumor in the orbit of a 14-year-old girl, which caused unilateral seizures. Macewen is considered a pioneering neurosurgeon. He was the surgeon who successfully combined the technique of anatomical localization and practice of neurosurgery [31].

A 22-month-old infant presented to the Glasgow Royal Infirmary, where Macewen worked, on June 24, 1887 with symptoms suggesting a brain disorder, with facial nerve palsy and ear discharge. He made an incision above the mastoid, and the surface of the brain was observed to be eroded, softened and ulcerated. The cavity was rinsed with borate solution, and a drainage tube was inserted, which was removed on the sixth day, when the wound had filled with granulation tissue. In 1893, Macewen published his book entitled: "Pyogenic infectious diseases of the brain and spinal cord: Meningitis, cerebral abscess, infectious venous thrombosis" [32]. In this book, a series of 19 patients with 82 brain abscesses, of which 21 were successfully drained by surgery was reported. He described the infectious diseases of the meninges of the brain and spinal cord. This work represented a comprehensive review of knowledge about brain abscesses in the nineteenth century. Through his work, Macewen made it clear that he had extensive insight and could diagnose these disorders accurately, despite the absence of modern diagnostic studies and surgical techniques.

Walter Dandy described how the urologist Victor Darwin, in 1910, used a cystoscope to remove the choroid plexus in two infants with hydrocephalus. One infant died, but the other lived for 5 years [33].

On the topic of spinal cord tumors Charles Elsberg in 1911 reported a strategy for surgical intervention and management of intramedullary tumors. As the first step, only myelotomy was performed, then, after waiting a long time for the tumor

to partially come out through the myelotomy and separate to some extent from the spinal cord, an extensive resection was performed. These first attempts to manage tumors surgically showed poor results, and the rate of neurological sequelae of surgery on intramedullary neoplasms was unacceptably high [34]. This led to more conservative treatment that included biopsy, decompression, and subsequent radiotherapy, regardless of the histological diagnosis. In 1922, Walter Dandy, who is considered a pioneering neurosurgeon, employed a cystoscope to visualize the ventricles, and used for the first time the term "ventriculoscopy" [35]. William Jason Mixter made the first successful endoscopic third ventriculostomy in 1923. Ventriculoscopy was mainly used for choroid plexus coagulation and third ventriculostomy for the treatment of hydrocephalus [36]. This technique met with various difficulties, such as inappropriate endoscopes, and the high morbidity and mortality rates discouraged neurosurgeons from using endoscopy.

Returning to Boston from England in 1929, Franc D. Ingraham, with his extensive clinical and research background, focused on the rapidly growing area of neurosurgery for children, together with Harvey Cushing. Ingraham created the first pediatric neurosurgical unit in the world, located at Boston Children's Hospital, and he is recognized as the founder of pediatric neurosurgery [37].

1.4 Period 1940–1960

After 1940 and following World War II, pediatric surgery developed rapidly. Surgeons started to go beyond the usual pediatric surgical procedures, such as tonsillectomy, appendectomy and simple orthopedic surgery. In parallel, bioethics made an appearance in the late 1940s, largely as a response to the atrocities committed by Nazi doctors in the concentration camps during World War II. The trials of these doctors in Nuremberg from 1946 to 1947 resulted in the formulation of the Nuremberg Code, outlining a list of requirements for ethical behavior in the field of research on humans, which have subsequently been updated [38].

The evolution of pediatric surgery necessitated a different management of anesthesia for newborn infants and children, and scientific research focused on how to prevent fear and psychological trauma in the child by administering pre-anesthesia. Not only were new techniques of anesthesiaapplied (oral, intravenous, intramuscular, rectal), but also new anesthetic drugs were discovered. A milestone in pediatric anesthesia was the withdrawal of ether, which was a flammable gas, and the introduction of halothane in 1955. A basic prerequisite was control of the child's airway and ventilation, achieved by the use of muscle relaxants and other sedatives, especially for cardiac surgery [39] Basic principles of pediatric anesthesia were established, such as the application of pediatric endotracheal tubes, the use of delivery systems and new non-explosive gases, anesthetic drugs and muscle relaxants, which enabled surgeons to perform complex surgery, even in premature neonates with congenital disorders. Concurrently, in the 1940s, vaccines for the influenza A virus and for diphtheria were developed.

Carl List, in 1941, described the neurological syndromes associated with developmental abnormalities of the occipital bone, atlas, and spinal cord. Pediatric neurosurgery was developed from that time, based on the concomitant advent of adult neurosurgery. In several countries, neurosurgeons such as Harvey Cushing, Walter Dandy, Kenneth McKenzie were operating, and their work was focused mainly on treating hydrocephalus and brain tumors. In 1949, Nulsen and Spitz revolutionized the treatment of hydrocephalus by introducing the ventricle drainage valve [40].

Progress has been particularly rapid since the 1950s. Breakthroughs of note at that time were the introduction of abdominal peritoneal drainage for hydrocephalus, and the recognition and effective treatment for the Chiari malformation and spinal cord tethering. The Society for Research into Spina Bifida and Hydrocephalus was founded in 1957.

1.5 Period 1960–1980

The anatomical, physiological and emotional differences between adults and infants and children, as well as the different pharmacodynamics of the anesthetic agents, contributed to the consolidation of pediatric anesthesia as an autonomous specialty. The administration of pre-anesthesia, the elimination of explosive anesthetic agents, mainly ether which was replaced by halothane, but also the introduction of endotracheal intubation and intravenous anesthetics and muscle relaxants, paved the way for the development of anesthesia covering all fields of pediatric surgery, including neurosurgery. Techniques of monitoring vital functions were developed, together with perioperative fluid management, which allowed major and lengthy operations to be performed.

In 1960, there was a revival of interest in neuroendoscopy, largely due to developments in visual imaging, with Harold Hopkins being a pioneer in the field. Hopkins, a British physicist, played a key role in the development of two important types of endoscopic systems [41]. Successful surgical removal of tumors from the spinal cord was established by Greenwood, and the introduction of the operating microscope, perfection of bipolar coagulation and microsurgery enabled neurosurgeons to treat intramedullary tumors. Because the majority of these tumors are histologically benign, complete or near complete resection is likely to lead to long-term survival, without serious morbidity [42].

In 1964, the German geneticist Rudolph Pfeiffer described a craniofacial syndrome of variable severity in children, which also presented wide thumbs and great toes and soft tissue syndactyly of the hands. The Pfeiffer syndrome may involve premature fusion of any combination of cranial sutures. Craniofacial surgery techniques were developed by the French surgeon Paul Tessier in 1967 at the Necker Hospital in Paris to correct the deformities of the Apert and Crouzon syndromes with favorable results [43]. Surgery to separate Siamese twins was also performed.

The European Society of Pediatric Neurosurgery (ESPN) was founded after the first European meeting of the Pediatric Neurosurgery Conference in Vienna in 1967.

The American Society of Pediatric Neurosurgeons (ASPN) was founded in 1978. Similar organizations were established in Japan (1973), Mexico (1999) and Australia (2002). The creation of these associations reflects the increasing focus on child neurosurgery all around the world [44]. During the 1970s and 1980s, pediatric neurosurgical departments appeared in most of the largest cities in the United States and Canada. Anthony J. Raimondi played a major role in founding the International Society of Pediatric Neurosurgery (ISPN) in Chicago in 1972.

In the 1970s, the use of computed tomography (CT) and later of magnetic resonance imaging (MRI) brought great changes in pediatric neurosurgery, and epilepsy surgery evolved [45]. In 1971, cortical dysplasia, which is increasingly recognized as the most important cause of intractable epilepsy in children, was first described Taylor and colleagues [46]. Hoffman identified a group of tumors that involve mainly the fourth ventricle, which had a better prognosis than the more common lesions.

1.6 Period 1980–present

The first fetal surgery was performed in the 1980s. The proposed optimal age for surgery was on fetuses ≤26 weeks of gestation. The fetal treatment of hydrocephalus was first reported in 1981 by Birnholz and Frigoletto, who performed a series of ultrasound-guided percutaneous cephalocenteses as an adjunct to delivery of a fetus with massive cranial enlargement [47]. Recent advances in surgical techniques for the management of spinal dysraphism and brain tumors are enormous. Since the introduction of CT and MRI, the development of functional MRI and MR spectroscopy have provided great improvements in imaging of the child's nervous system. The technology of surgical microscopes has greatly advanced, new shunt systems, such as programmable valves, have become available, and in the late 1980s, stereotactic radiosurgery became an important treatment option for children. New intraoperative devices, such as the ultrasonic surgical aspirator, have been introduced, and radiosurgery has provided a new therapeutic approach to the management of deep-seated malignant lesions. Baclofen pumps, vagal nerve stimulators, and deep brain stimulation are starting to be developed. All these advances hold great promise for the future of pediatric neurosurgery. During the past decades, the number of full-time pediatric neurosurgeons increased all over the world.

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Chapter 2
Neurological Examination

Theodoros Gouvias and Aikaterini Drougia

Clinical Pearls

1. Careful observation is mandatory! It gives important information about the patient's neurological status.
2. Don't forget the general physical examination, including head circumference in all your patients.
3. Be careful when interpreting the clinical findings! The neurological examination of neonates and infants varies by gestational age and maturation.
4. A comprehensive neurological examination guides the clinician in defining the locus and extent of neuropathological involvement.

2.1 Neurological Examination of the Neonate

An organized approach to the newborn is the cornerstone of the neonatal neurological evaluation; this comprises *the general assessment of the neonate* and *the formal neurological examination* [1, 2].

Clinicians who care for neonates require not only the ability to perform a thorough neurological examination but also the knowledge to understand and recognize normal and abnormal findings. Moreover, when they perform the neurological examination, must take into consideration the following: examination of the neonate requires patience, a careful watching, and minimal intrusion; the normal neurological examination changes with maturation; the examination findings may vary depending upon the infant's level of alertness; abnormalities

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are often global and non-specific (in contrast with the typical focal findings in children and adults); serial examinations are necessary to reliably establish the neurological findings and to document the evolution of neurological abnormalities [1, 3, 4].

Additionally, apart from the standard approach to the neonatal neurological examination, that is described in this chapter, there is a considerable number of neurological assessment methods (such as, Dubowitz, Amile-Tison, Prechtl neurological examination), which cope with the evaluation of neurodevelopment in infants and young children, and aim to produce valid and consistent results between examiners as well as useful information when they are repeated across time [3–5].

2.1.1 General Assessment

A thorough neonatal neurological examination includes a comprehensive *history*, an accurate *estimation of gestational age* (GA) and a general *physical examination* of the neonate. A careful initial observation is mandatory, giving important information about the neonate's neurological status [2].

2.1.1.1 History

A focused family, maternal, antepartum and intrapartum history is important in identifying risk factors that may explain the neonate's neurologic clinical presentation. The history should also include the neonate's gestational age, birth weight, clinical stability assessment (e.g., need for respiratory support, feeding difficulties, seizure history) and recent medication exposure [6, 7].

2.1.1.2 Assessment of Gestational Age

The estimation of GA is particularly important, because several aspects of the neonatal neurologic examination change with maturation, and recognition of these changes is critical in assessing the observations. Additionally, regions of the central nervous system (CNS) affected by the same insult differ based, in large part, on the neonate's GA. Gestational age is most often established by the last menstrual period or first trimester ultrasound dating. Postnatally, the birthweight, neuromuscular, and physical maturity characteristics also help establish GA. The external characteristics, reported to be particular helpful in estimating GA, are the ear cartilage, the breast tissue, the external genitalia, and the creases of the plantar surface of the foot [1, 6].

The Ballard scoring system is a validated method for clinical use that accounts for neuromuscular and physical maturity features [8].

2.1.1.3 Physical Examination

Initial observation of the neonate and careful examination of the head, face, skin and spine are all essential physical components of the neonatal neurological examination. Vital signs are also essential in assessing sick neonates [2, 6, 7].

Observation. A careful observation before handling the infant is recommended. Considerable information about the level of consciousness, cranial nerve function, and motor function can be garnered by watching the infant carefully. Observation is best performed when the neonate is in a quiet awake state, in supine lying. In this position the examiner can assess the neonate's resting posture, eye position and movement, facial symmetry and movement, head position, limb positions and onset of spontaneous movements. Obvious dysmorphic features will also be apparent [1, 6].

Head. The examination of the head includes measuring of the occipitofrontal circumference, noting the skull shape, observing for presence of abnormal hair patterns and for unusual lesions or protuberances, palpating the fontanels and the sutures. In some cases, transillumination may be useful if hydrocephalus or hydranencephaly is suspected. Auscultation of the fontanels is performed for bruits if an arteriovenous malformation is suspected (e.g., vein of Galen) [2, 7].

Head size. The occipitofrontal circumference, should be measured at its maximum circumference. Microcephaly (occipitofrontal circumference 2 standard deviations below the mean for age), may be attributable to congenital infections, chromosomal abnormalities and syndromes, congenital CNS malformations, metabolic disorders, or maternal toxic exposure. Macrocephaly (occipitofrontal circumference 2 standard deviations above the mean for age) is caused by an increase in size of any of the components of the cranium (such as the brain parenchyma, cerebrospinal fluid, blood, or bones), or may be associated with increased intracranial pressure, and rarely with mass lesions [2, 7].

Fontanels. In a quiet neonate, the fontanels should be soft and flat. A large anterior and posterior fontanel is found in neonates with hydrocephalus, hypothyroidism or intrauterine growth restriction. A tense or bulging fontanel, with the infant at rest, may indicate raised intracranial pressure (e.g., hydrocephalus, meningitis, subdural hematoma). A small anterior fontanel may be seen in cases of microcephaly and hyperthyroidism [2, 7].

Sutures. The principal sutures of the skull should be palpated. Passage through the birth canal may result in molding, a temporary asymmetry of the skull caused by overlapping or overriding of the sutures. An asymmetric skull that persists for longer than two to three weeks after birth, or a persistent palpable ridge along the suture line is abnormal and might suggest craniosynostosis [2].

Scalp swelling. Extradural fluid collections in neonates may be due to injuries that occur during delivery: caput succedaneum (diffuse edematous swelling of the presenting portion of the scalp), cephalohematoma (hemorrhage that is confined by the periosteum and therefore is bounded by the sutures) and subgaleal hematoma (hemorrhage below the epicranial aponeurosis) [2, 7].

Face. Congenital brain anomalies may be associated with dysmorphic facial features such as hypotelorism, hypertelorism, low set ears, narrow palpebral fissures, and cleft lip and/or palate. Facial asymmetry is indicative of facial nerve palsy. An inverted U-shaped appearance of the upper lip is suggestive of low tone, and may represent an underlying neuromuscular disorder [2, 7].

Skin and Spine. As the neurological system is derived from the ectoderm, the skin may provide important clues to underlying neurological disorders. Certain skin pigmentation lesions may indicate a neurocutaneous disorder; characteristic cafe au lait spots may appear in infants with neurofibromatosis, hypopigmented macules may be associated with tuberous sclerosis. A port-wine stain located over the forehead and upper lip, may signify Sturge-Weber syndrome. The spine should be examined along its entire length for findings that might suggest an underlying congenital spinal cord anomaly, such as tethered cord syndrome or spina bifida occulta (e.g., midline hair tufts, dimples, dermal sinus tract, or lipoma). A meningocele or a myelomeningocele will be readily visualized, and are often detected prenatally [2, 6, 7].

2.1.2 Formal Neurological Examination

The neonatal neurological examination framework includes the assessment of the neonate's level of alertness, the cranial nerve function, the motor and sensory examination, and the assessment of primitive neonatal reflexes (Table 2.1) [1, 6, 7].

2.1.2.1 Level of Alertness

The level of alertness is a sensitive "summary" indicator of CNS integrity and function. By assessing the level of alertness, the physician is able to evaluate the neonate's ability to respond to the environment through observation of spontaneous eye opening, spontaneous movements, and response to stimulation. It is important to take into consideration that the level of alertness in the normal infant will vary, depending particularly on time of last feed (the best time to examine a baby is between feeds), environmental stimuli, recent experiences, and GA. Before 28 weeks gestation it is difficult to identify periods of wakefulness, however with

Table 2.1 Neonatal neurological examination—essential components

Level of alertness
Cranial nerves
Motor system
Tone and posture
Motility and muscle power
Tendon reflexes and plantar response
Primitive reflexes
Sensory system

ongoing maturation there is an increasing duration, frequency, and quality of alertness. By 32 weeks, sleep-wake alternation is apparent. Term neonates should have more prolonged periods of wakefulness, they cry more often, and they are more responsive to external stimuli. An irritable neonate, cannot be soothed, is agitated, and cries with minimal stimulation [1, 2, 9].

Abnormalities of the level of alertness. Most disorders that affect the CNS disturb the level of alertness at some time. The alertness level, is based upon the neonatal response to arousal maneuvers (gentle shaking, pinch, shining of a light, ringing a bell) and to more noxious stimuli, and is classified in three states:

1. *Normal*: awake with normal arousal and noxious stimuli responses.
2. *Stupor*: slight, moderate or deep—sleepy/lethargic or asleep with diminished or absent arousal and diminished noxious stimuli responses.
3. *Coma*: unresponsive, absent arousal and noxious stimuli responses [1].

2.1.2.2 Cranial Nerves

Cranial nerve (CN) testing evaluates brainstem function. The examination of CN involves a combination of observation and specific maneuvers [1, 7].

Cranial Nerve I (Olfactory Nerve)

Although olfaction is rarely affected or even evaluated in neonates, it can be tested by using strong scents (e.g., peppermint or cloves); by 32 weeks infants respond with behavioral changes (grimacing or sucking) when exposed to these substances [1, 7].

Cranial Nerve II (Optic Nerve)

Visual responses exhibit distinct changes with maturation. By 26 weeks the infant consistently blinks to light; by 32 weeks begins to show signs of fixation. Term infants should turn toward soft lights and be able to fix and follow moving bright objects (e.g., a red ball). Optokinetic nystagmus, elicited by a rotating drum, is present consistently at term. In the fundoscopic examination the infant's optic disk has a pale, gray-white appearance. Consistent failure to demonstrate visual following in a full-term infant is a disturbing sing; most commonly this is part of a constellation of neurologic abnormalities indicative of disturbance of several levels of the CNS and not a primary lesion in the optic nerves or tracts. Absence of the red reflex should raise concerns for retinoblastoma or cataract [1, 7].

Cranial Nerves III, IV and VI (Oculomotor, Trochlear, and Abducens Nerves)

Intact CNs II and III are necessary for the pupillary light response, which begins to appear at 30 weeks and is consistently present by 32 to 35 weeks. Extraocular movements are evaluated by observation of spontaneous eye movements and symmetry or by the use of the doll's-eye maneuver; in this test, moving the head and neck from side to side normally leads to conjugate eye deviation to the opposite side, which demonstrates intact eye adduction (III) and abduction (VI), [1, 7, 9]. *Papillary abnormalities* in neonates are not of great value in the localization of pathological events, as it occurs in older infants and children. A bilateral increase in pupillary size is seen in the course of hypoxic-ischemic-encephalopathy (reactive early, unreactive late) and in massive intraventricular hemorrhage (unreactive). Horner syndrome should be suspected in a neonate with branchial plexus injury and unilateral decrease in papillary size (reactive) and partial ptosis. A unilaterally dilated and poorly reactive pupil is very rare in the neonates (unlike older children and adults) and is a marker of transtentorial uncal herniation (convexity subdural hematoma is the most common cause of this syndrome in the newborn). *Transient abnormalities of ocular motility* (slightly dysconjugate eyes at rest, skew deviation, or downward deviation) may be observed in otherwise healthy term infants and mostly resolve in the neonatal period. Characteristics *abnormal eye movements* are the horizontal, and, occasionally, the vertical jerking movements that are seizures manifestations, persistent downward gaze deviation that is seen in hydrocephalus or kernicterus and nystagmus. Strabismus is frequently observed in preterm infants with white matter injury [1].

Cranial Nerve V (Trigeminal Nerve)

The motor component of the trigeminal nerve is assessed by the evaluation of sucking (masticatory power). Facial sensation (response to pinprick) is rarely tested unless there is specific concern [1, 7].

Cranial Nerve VII (Facial Nerve)

Facial symmetry and movement should be observed both at rest and during active movements (such as crying). Attention should be paid to vertical width of the palpebral fissure, the forehead wrinkling, the nasolabial fold and the position of the corner of the mouth [1, 7, 9]. Injury to the facial nerve should be suspected if there is *facial asymmetry*. Facial nerve palsy is most often traumatic, related to intrauterine nerve compression during labor or to injury from a forceps delivery. Rare cause of injury to the facial nerve involve compression from a posterior fossa hematoma. Facial nerve palsy is clinical presented as a widened palpebral fissure, flattened nasolabial fold, and depressed corner of the mouth on the affected side at rest, while there is "pulling" of the lower face toward the normal side on crying. In addition,

Fig. 2.1 Left facial paralysis: clinical appearance

sucking is less vigorous with drooling of saliva or milk from the affected side (Fig. 2.1) [1, 2, 7]. Congenital hypoplasia of the depressor anguli oris muscle is characterized by an asymmetrical crying facies; the appearance of the face during cry may lead to the mistaken notion of facial palsy on the side opposite the defect. This lesion is associated with major congenital anomalies, especially cardiac defects [10].

Cranial Nerve VIII (Vestibulocochlear Nerve)

By 28 weeks gestation, the infant startles or blinks to a sudden, loud noise. During quiet wakefulness, term infants respond to the sound of a bell, hand clap, or voice by a startle response or an increase in their state of alertness. Universal newborn hearing screening programs allows for early identification of congenital hearing loss and proper treatment and services. Vestibular function is rarely tested in the newborn period [1, 7].

Cranial Nerves IX, X and XII (Glossopharyngeal, Vagus, and Hypoglossal Nerves)

Observation of the infant's sucking and swallowing assesses CNs V, VII, XII (subserve sucking) and IX, X (subserve swallowing). Sucking and swallowing are coordinated sufficiently as early as 28 weeks gestation. By 34 weeks, however, the normal infant is able to maintain a concerted action of breathing, sucking and

swallowing for productive oral feeding. The gag reflex, subserved by CNs IX and X, can be tested by using a tongue blade or during suctioning. Tongue movement, mediated by CN XII, is assessed best during the infant's sucking on the examiner's fingertip; the size and symmetry of the muscle, and the activity at rest should also be observed [1, 7, 9]. *Disturbances of sucking and swallowing* very often coexist. Major neurological causes of impaired sucking and swallowing in the neonatal period are cerebral disorders (most common generalized depression of CNS function associated with encephalopathies), CNs nuclear lesions (hypoxic-ischemic injury, Mobius syndrome, Werdnig-Hoffman disease), CNs injuries (traumatic facial neuropathy and, rarely, posterior fossa hematoma or tumor), and neuromuscular or muscle diseases (myasthenia gravis, and congenital myotonic dystrophy are the most common). The neuronal disorders result in atrophy and fasciculations of the tongue, which can be detected reliably only with the tongue at rest (Werdnig-Hoffmann disease, hypoxic-ischemic injury) [1].

Cranial Nerve XI (Spinal Accessory Nerve)

Function of the sternocleidomastoid muscle is difficult to be assessed in the newborn. One useful maneuver with the full-term neonate, is to gently extend the head side to side with the child in supine position; the passive rotation of the head reveals the configuration and bulk of the muscle. *Abnormalities of sternocleidomastoid function*, result in disturbed flexion and lateral rotation of the head; in the newborn they occur almost exclusively as a feature of congenital torticollis [1].

2.1.2.3 Motor Examination

The neonatal motor examination includes the assessment of *posture and muscle tone*, the evaluation of *motility and muscle power*, and the elicitation of *tendon reflexes*. A key principle of the infant's motor development is that it progresses in a cephalocaudal, and proximal to distal direction. The findings of the normal neurological examination to be described next, are applicable to an infant at an optimal level of alertness and after the first day of life [1, 6].

Tone and Posture

Careful observation of the resting posture, when the infant is in a quite-awake state, is valuable for the evaluation of the symmetry and maturity of the passive tone. There is a caudal-rostral direction in the progressive maturation of muscle tone, with development of flexor predominance. At 28 weeks all limbs are passively extended and have minimal resistance to passive movement; by 32 weeks

there is distinct flexion of the legs, with some resistance to manipulation; by 36 weeks the infant develops flexion at the elbows, and the term infant assumes strong flexion of all four extremities. It is notably, that most newborn infants preferentially position their heads to the right. A thumb-in-fist position is the predominant hand posture in term neonates, while the hands intermittently loosely open spontaneously. Over the first months of life, the fists gradually become loosely closed to allow for voluntary grasping. Passive tone can be measured by evaluating the resistance of the limbs to certain passive manipulations with the neonate at rest and the head placed in the midline (e.g., arm traction, leg traction, popliteal angle or scarf sign) [1, 2, 6, 9].

Motility and Power

Observation is important to evaluate the quantity, quality and symmetry of spontaneous movements and muscle antigravity power. The motor activity is gestation depended and there are fixed developmental changes with maturation. At 28 weeks gestation, movements tend to involve the entire limb or trunk; by 32 weeks, predominantly flexor movements are seen, especially at the hips and knees, which are symmetric and smooth; by 36 weeks, active flexor movements become stronger and often occur in an alternating fashion, in addition, neck extensor power is observed when the infant is supported in the sitting position. The term awake neonate is particularly active if stimulated, the limbs move in an alternating manner and neck extensor power is still better [1, 2, 9]. Furthermore, the quality of spontaneous gross movements involving the entire body ("general movements"), is a sensitive indicator of the CNS status, but it requires training and experience of the examiner to make an interpretation. In term neonates, movements with a "writhing" quality (movements that evolve the entire limb or trunk, with a slow rotational or a fast, large-amplitude characteristic), predominate in the first 8 weeks; by 2 to 5 months of age "fidgety" pattern (small amplitude, circular movements of the neck, trunk, and extremities) are prominent. Fidgety movements normally resolve by 20 weeks of age and thereafter, rapid large-amplitude antigravity and intentional movements ("swipes and swats") are prominent [1, 2, 4, 5].

Active motor tone and strength can be measured in the axial (head and trunk) and appendicular (limb) musculature by using certain maneuvers. The maneuvers most often used in this assessment are the *pull-to-sit* reaction (the neonate is gently pulled from the supine to sitting position—head control is assessed), the *vertical suspension* (the neonate is held in an upright position, by placing the hands under the arms and around the chest with the feet unsupported) and the *ventral suspension* (the neonate is held in a suspended prone position in the air by placing a hand under the chest). The normal and abnormal responses of the term neonate in the above maneuvers are illustrated in Figs. 2.2, 2.3 and 2.4 [2, 6].

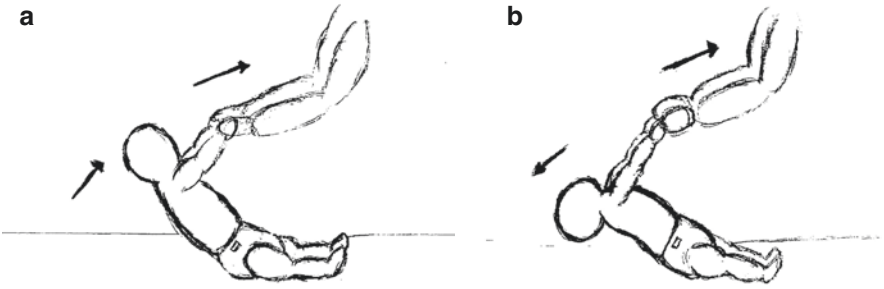

Fig. 2.2 Pull-to-sit reaction in a term neonate/infant. (**a**) Normal: The head is held in line with the trunk for several seconds. (**b**) Abnormal: The head lags behind (axial hypotonia)

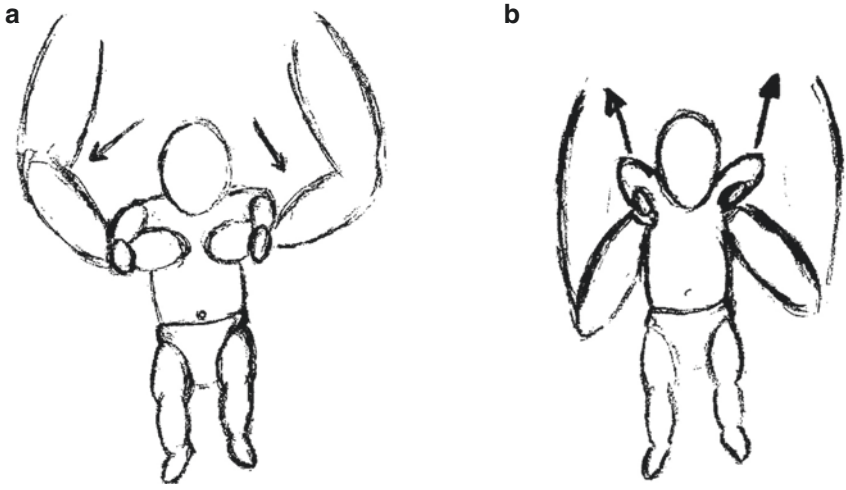

Fig. 2.3 Vertical suspension in a term neonate/infant. (**a**) Normal: The head is kept in midline momentarily; the limps are flexed. (**b**) Abnormal: The neonate/infant "slips" through the examiner's hands, the legs are extended

Tendon Reflexes and Plantar Response

The tendon reflexes that can be readily elicited in term infants are the pectoralis, biceps, brachioradialis, knee, adductor, and ankle jerks. Most of these reflexes are elicitable but less active in preterm infants. The reflexes are elicited by gentle tapping the examiner's finger placed over the tendon of the designated muscle (this permits the detection of the muscle response if the reflex is not visible). A crossed adductor response, which often accompanies the knee or the adductor jerk, is normal in the first few months of life (less than 10% of normal infants demonstrate crossed adductor responses after 8 months of age). Ankle clonus of 5 to 10 beats is also acceptable as a normal finding in neonates if no other neurological sings are

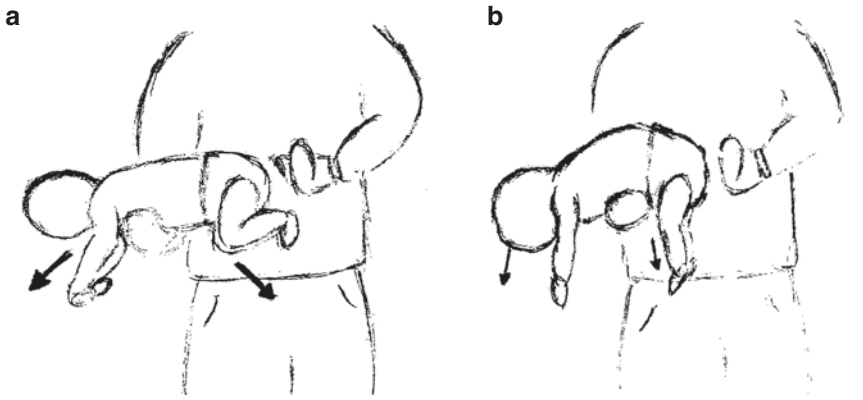

Fig. 2.4 Ventral suspension in a term neonate/infant. (**a**) Normal: The head is kept in the horizontal plane momentarily, the back is straight, the limps are flexed. (**b**) Abnormal: The head and limbs hang straight, the back is curved

present and the clonus is not distinctly asymmetrical. The plantar response is of limit value in the evaluation of the neonatal motor system, as many factors may elicit flexor or extensor responses inadvertently [1, 6].

Abnormalities of the Motor Examination

The normal maturational changes in the motility, tone, and character of reflexes in neonates, makes the delineation of motor abnormalities somewhat difficult. Observation of the posture at rest and ease of passive manipulation of the limbs must always be evaluated as a function of gestational age. Pathological hypotonia and hypertonia are detected readily with careful examination. On the contrary, subtle deficits may better detected by using specialized techniques (e.g., long-term video recordings) [1].

Hypotonia is the most common motor abnormality observed in neonatal neurological disorders. Neonatal hypotonia is caused by a variety of conditions that affect the CNS, peripheral nervous system or skeletal muscles. It is important to distinguish hypotonia and weakness; although disproportionate involvement may occur, total dissociation is rare [1, 2]. *Certain patterns of weakness* are associated with the anatomical loci of the disease. Focal injury to the cerebrum, results in contralateral hemiparesis and a tendency of the eyes to deviate to the side of the lesion (in the term neonate the upper extremity is more prominently affected than the lower, but in the preterm the opposite occurs). Parasagittal cerebral injury (hypoxic ischemic injury), in the term newborn, results in weakness of the proximal limbs, upper more than lower. Cystic periventricular leukomalacia, characteristic of the preterm infant, results initial in weakness of the lower extremities much more than the upper [1, 9]. When hypotonia is associated with *pronounced weakness*, it is suggestive of a lower motor neuron disease (flaccid weakness of all extremities, with initial relative

sparing of the face; Werdnig-Hoffmann disease is the most common), neuromuscular junction disease (generalized weakness, involvement of cranial nerve function is common; e.g., myasthenia gravis), or muscle disorders (generalized weakness, and hypotonia often more prominent in the proximal than the distal limbs; congenital myotonic dystrophy is the most frequent) [1, 2]. Finally, traumatic spinal cord injury (secondary to obstetrical disturbances), usually occurs in the cervical region, and initially results in flaccid weakness of all extremities, with sparing of the face and cranial nerves function and involvement of the sphincters [1, 9].

The *hypotonic term infant* lies supine in a "frog-like" position with his hips abducted and the limbs abnormally extended, shows decreased spontaneous activity, and abnormal response to certain maneuvers (Figs. 2.2, 2.3 and 2.4) [2].

Hypertonia is a less common feature of neonatal neurological disease than hypotonia. It may be caused by chronic (intrauterine) injury to the corticospinal or extrapyramidal system (hypoxic-ischemic lesions are the most common). Acute perinatal causes of hypertonia include meningeal inflammation (secondary to bacterial meningitis or to hemorrhage), brain stem release phenomena due to severe bilateral cerebral injury, and basal ganglia injury. Hypertonia most often has a plastic quality which increases with passive manipulation of the limbs [1].

A unilateral immobile upper extremity may be indicative of a *brachial plexus injury* (secondary to obstetrical trauma), which is the most common peripheral nervous injury in neonates. A lesion in the upper trunk of brachial plexus (Erb palsy) is the most common type; clinically the arm is adducted, internally rotated and pronated, and the wrist is flexed ("waiter's tip posture") [7].

Abnormal movements include jitteriness (frequently observed in newborns; most often related to hypoglycemia, hypocalcemia, hypoxic-ischemic encephalopathy or drug withdrawal; important its distinction from seizure), myotonia (observed in myotonic dystrophy) and fasciculations (a feature of lower motor neuron disease) [1].

Abnormalities of the tendon reflexes. Infants with lesions of the lower motor neuron exhibit diminished or absent tendon reflexes, while, in those with upper motor neuron lesions tendon reflexes are preserved, but the characteristically exaggerated responses do not develop until weeks or months later. Striking weakness accompanies disorders of the neuromuscular junction, while, in disease of muscle the decrease in tendon reflex parallels the decrease in muscle power. The existence of clonus beyond 3 months of age is considered abnormal. A distinctly asymmetrical *plantar response*, with one response being extensor, may indicate disease above the level of the lower motor neuron (especially spinal cord injury) [1].

2.1.2.4 Primitive Neonatal Reflexes

Primitive reflexes appear at a certain time during the course of brain development, are fully present at birth in term infants, and normally resolve after the first months of life when voluntary motor activity, and thus cortical inhibition emerges and takes over. Primitive reflexes provide information about brain stem and cortical function, are brainstem-mediated, automatic movement patterns and are elicited by specific

Table 2.2 Assessment of Moro reflex, Palmar Grasp, and Asymmetric Tonic Neck Reflex (ATNR)

Reflex	Age at onset (weeks of gestation)	How to elicit	Response	Age at disappearance (months postnatal)	Abnormal patterns
Moro	28–32	Sudden dropping of the head in relation to the trunk	Abduction, followed by adduction and flexion of upper extremities	6 (allows for sitting)	– asymmetrical – depressed/ absent – exaggerated
Palmar grasp	28	Placing the index finger in the palm	Flexion of fingers, fist making	2–3 (allows for voluntary grasping)	– asymmetrical – exaggerated, fixed – marked retention
ATNR	35	Rotating the head to one side	Fencing posture	6 (allows for rolling over and reaching/ grasping)	– exaggerated – obligatory – sustained

sensory stimuli. The major primitive reflexes that have been described include Moro, palmar and plantar grasp, asymmetric tonic neck reflex (ATNR), rooting, sucking, placing, stepping, Galant (truncal incurvation), crossed extensor, and others. Of those the Moro reflex, the palmar grasp, and the ATNR are the most important to perform (Table 2.2) [1, 5, 7, 9].

Abnormalities of Primitive Neonatal Reflexes. Primitive reflexes are abnormal if: (a) They are depressed or absent at an age when they should normally be present. The most common cause of a depressed or absent Moro reflex is a generalized disturbance of the central nervous system. (b) They are exaggerated, stereotyped and non-habituating, which is a feature of severe bilateral cerebral disturbance. (c) They are asymmetrical. A distinct asymmetry of the Moro reflex is most often a feature in an injury of the upper brachial plexus (Erb palsy), while in an injury of the lower brachial plexus (Klumpke palsy) the palmar grasp is absent on the involved side. (d) They persist beyond a time they should have normally resolved, which suggests impaired maturation of descending cortical inhibitory projections (Table 2.2) [1, 2, 7]. Infants with cerebral palsy have been known to demonstrate persistence of primitive reflexes or a delay in their disappearance [5].

2.1.2.5 Sensory Examination

The sensory assessment is not generally performed as a part of the usual neonatal neurological examination. The sensory examination in the neonate is limited to evaluating response to touch and to pain. It is notably that premature neonates discriminate touch and pain. When touched, infants should be alerted, and demonstrate facial expressions, or behavior change. A normal, high-level response after painful

stimuli (e.g., pinpricks) has a recognizable latency, a nonstereotyped withdrawal movement, an accompanying grimace or cry and habituation [1, 2, 7].

Abnormalities of sensation are most easily detected in the newborn period in peripheral lesions, especially those involving roots (e.g., brachial plexus injuries), and in spinal cord injury. In the latter the major sensory abnormality relates to the detection of a *sensory level* (this level corresponds to the approximate segment of cord primary affected by the injury). Detection of a sensory level is of particular value, since it strongly favors the diagnosis of a cord lesion. In contrast, abnormalities of sensory function due to cerebral lesions, are more difficult to document as such lesions disturb the quality of the response to painful stimuli [1].

2.2 Neurological Examination of the Infant and Child

The two basic elements of a complete neurologic assessment of the infant and child are focused history and detailed neurologic examination. Evaluation of the nervous system differs in infants and young children compared with older children and adults. Observation is key and patience and inventiveness are usually required.

2.2.1 History

A detailed and thorough history is a cardinal aspect of neurologic assessment and may lead, an experienced physician, to a diagnosis which can be later confirmed by physical examination and other diagnostic procedures (neuroimaging etc.) [11, 12].

Although parents may be the primary informants, most children older than 3–4 years of age are capable of giving useful first-hand history, even if their language skills are limited [11]. Furthermore, a child's inability to give a history may itself be informative [13].

Regarding the history of present illness, the physician should determine the duration of symptoms, the localization of the problem, if the process is acute or insidious, if it is focal or generalized, if the symptoms are progressive, static or they appear in episodic fashion and at what age the problem began [12, 14, 15].

Other important aspects of patient's history are current or past use of medications, family history for inherited neurological disorders, labor and delivery history and perinatal and neonatal history [12].

2.2.2 Neurological Examination

One of the most important stages of neurologic evaluation of infant, toddler and child is observation that begins the moment the child enters the examining room and during the history taking. The physician must observe how the child is playing and interacting with his/her parents or other children. For example, the patient may have abnormal facies, apparent developmental delays, abnormality of the gait, unusual posture or unusual movements or may display hyperactivity or unaware of the environment [15, 16].

During a detailed neurologic evaluation, the physician must examine the head, face, spine and extremities for abnormalities, malformations and dysmorphic appearances and assess the mental status, the integrity of the cranial nerves, the motor system, the reflexes, the sensory system as well as the coordination and gait of the patient.

2.2.2.1 Head

Measurement of the head circumference is essential and should be performed at every pediatric evaluation, especially for patients younger than 3 years. The result must be recorded on the proper head growth chart. Careful measurement of the head may reveal problems as microcephaly, macrocephaly (occipitofrontal circumference 2 standard deviations below or above the mean, respectively) or hydrocephalus.

The shape of the head should also be documented as it may reveal medical conditions such as craniosynostosis [11].

2.2.2.2 Face

Detailed examination of the face for dysmorphisms is also essential. Particular dysmorphisms are seen in chromosomal and genetic diseases like Down syndrome. Furthermore, facial features like hypertelorism or hypotelorism, amongst others, are often associated with particular malformations of the brain (agenesis of the corpus callosum and holoprosencephaly respectively). However, when a patient is thought to be dysmorphic, the physician should interpretate his/her facial features based on racial and ethnic characteristics and by looking at the parents' and siblings' faces for familial traits thar are normal [16].

2.2.2.3 Spine—Extremities

Examination of the spine should be part of a detailed neurologic evaluation at any age. The physician must search for obvious lesions such as meningocele or myelomeningocele but also for any findings suggesting of spina bifida occulta or tethered cord syndrome (hair tufts, subcutaneous lipomas, cutaneous dimples, hemangiomas, discoloration of the skin, dermal sinuses, lumps or tails) [11, 12, 15, 17]. Nervous system abnormalities may result in kyphosis or scoliosis [15].

Examination of the hands and feet may reveal abnormal creases or digits [15].

2.2.2.4 Mental Status

The assessment of the mental status, in terms of both the consciousness and the level of arousal, is one of the most important aspects of the neurologic examination of a pediatric patient [11, 18]. Consciousness represents awareness of self and environment (place and time) and reflects the function of the cerebral cortex. Arousal represents the system that initiates and maintains consciousness and is mainly a function of brainstem structures, particularly the pontine reticular activating system [13, 19].

Mental status in the infant is assessed by observation of spontaneous activities, feeding behavior, and interaction with the environment (e.g., fixate and follow an object or physicians face) [15]. The physician should note the response to tactile, visual and auditory stimuli. In toddlers and older children, observation while they are playing, telling a story or drawing, is informative about their mental status and allows a preliminary assessment of developmentally appropriate skills [11, 15]. Refined and detailed developmental tests for each age are available, such as Denver Developmental Screening Test, CDC's Developmental Milestones and Gesell Developmental Schedules [16].

The observation of language skills allows the physician to easily assess intellectual abilities. Abnormalities of language, either receptive (the ability to understand and comprehend spoken language or gestures) or expressive (the ability to speak and use gestures) are referred to as aphasias and they occur in cerebral hemispheres lesions (tumor, stroke) [15].

Memory can be evaluated briefly during the neurological examination in children older than 4 to 5 years of age, that are capable to understand and respond. At the beginning of the examination, the patient can be told by the physician to remember three unrelated objects matched with colors (e.g., red hat, orange umbrella, blue car). By asking the child to recall these items, at the end of the neurological examination, the physician has the ability to evaluate short-term memory. A simple test of long-term memory can be performed by asking the child what gift was given by parents for a birthday [16].

2.2.2.5 Cranial Nerves

The cranial nerve evaluation can reveal brain stem pathology, but it may be very difficult in a young and uncooperative child.

Cranial Nerve I (Olfactory Nerve)

Olfactory nerve is not routinely examined. The physician must keep in mind that the most common cause of anosmia is rhinitis, so it is very important to first check nostrils patency. Smell can be tested in cooperative children older than 2 years of age by using pleasant odors (e.g., chocolate). Permanent causes of anosmia are, amongst others, head trauma with damage to the ethmoid bone and frontal lobe tumors [11, 13, 15].

Cranial Nerve II (Optic Nerve)

The evaluation of optic nerve is made by testing *visual acuity, visual fields, fundoscopy* and *pupillary light response*.

Visual acuity in infants is assessed by observation of their ability to fixate and follow an object or physicians face. Standard visual charts displaying pictures instead of letters can be used to assess visual acuity in toddlers and young children [15]. Each eye should be tested separately [11].

Visual fields can be tested by bringing an object (a red toy on a string) into the visual field from behind while the child focuses on another object directly in front of him/her.

Funduscopic examination is crucial for the assessment of optic disk and retina. For example, blurring of the optic disc margins, loss of venous pulsations and loss of the optic disc cup (elevation of the optic disc) are signs of papilledema [12] while multiple retinal hemorrhages frequently occur in abusive head trauma.

The presence or absence of *pupillary light response* differentiates between peripheral and cortical blindness. A reduced or absent reflex suggests lesions of the anterior visual pathway (retina, optic nerves, and chiasm). In these lesions, amblyopia occurs in one eye and the pupil of the affected eye is not responding when stimulated with direct light. However, the pupil constricts when the other eye is illuminated (consensual pupillary response). *Marcus Gunn pupil* or relative afferent pupillary defect suggests unilateral optic nerve or retinal lesion. It is best demonstrated by the swinging flashlight test. When light is directed into the normal eye, both pupils constrict. However, when light is swung over to the abnormal eye, both pupils dilate inappropriately [11, 15, 17].

Cranial Nerves III, IV, and VI (Oculomotor, Trochlear, and Abducens Nerves)

These nerves innervate the extraocular muscles and are responsible for the eye movement. They can be examined by using a colorful toy which the child follows in the six cardinal directions of gaze. The physician should first observe the eyes at rest and then the range and nature (conjugate versus disconjugate, smooth versus choppy or saccadic) of the eye movements. Emphasis should be given to the detection of abnormal movements (e.g., nystagmus) and abnormal gaze positions like setting-sun sign (gaze held in a downward fixed position) that indicates increased intracranial pressure. For infants too young or for comatose patients the physician can assess oculocephalic vestibular reflexes (doll's eye maneuver) by rotating the infant's head [11, 15].

Cranial Nerve V (Trigeminal Nerve)

The sensory division can be tested with light touch over the face with cotton gauze and pinprick. In infant's, facial sensation can be assessed by gently stroking or gently touching the corner of his/her mouth in order to Produce the rooting reflex (seeking to nurse) [15].

The motor division of the trigeminal nerve can be tested by observation of infant while sucks and swallows [11]. In older children the physician can assess the motor division by asking the patient to open and close jaw against resistance.

In uncooperative or comatose patients, the sensory division of the trigeminal nerve can be assessed by the corneal reflex that is elicited by lightly touching the cornea with a cotton pledget and observing the degree of eye closure compared to the opposite side. The efferent (motor) arc of the corneal reflex is mediated by the facial nerve [11, 16].

Cranial Nerve VII (Facial Nerve)

The physician can easily assess the function of the facial nerve by observing face symmetry while the infant is crying or by asking the older child to smile, blow out cheeks, blink and wrinkle forehead [16].

A lower motor neuron lesion causes weakness of the muscles of the ipsilateral upper and lower face, whereas upper motor neuron lesion (tumor, stroke, abscess) is characterized by decreased voluntary movement of the lower face with drooping of the angle of the mouth and flattening of the nasolabial angle on the contralateral side of the face [15, 16].

Taste in the anterior two-thirds of the tongue is supplied by the facial nerve (Chorda tympani) and may be tested in a cooperative child by placing a small portion of sugar or saline solution on one side of the extended tongue [16].

Cranial Nerve VIII (Vestibulocochlear Nerve)

In infants, hearing can be tested by making noise with a toy or a bell. Normal infants pause sucking briefly when a bell is presented to an ear or they show an alerting response or blink [16]. By 3–4 months of age infants normally turn their hand to the direction of the sound. In older children the hearing can be assessed by whispering a word in one ear while covering the other [15].

Dysfunction of the vestibular component of the nerve causes vertigo, nausea, vomiting, diaphoresis and nystagmus.

Cranial Nerves IX and X (Glossopharyngeal and Vagus Nerves)

The physician can assess cranial nerves IX and X by observation of feeding and swallowing behavior and by asking the patient to open mouth and say "aah" in order to observe the symmetry of palatal movement. The uvula is moving toward the side of cerebral lesion in unilateral IX nerve injury. The gag (pharyngeal) reflex tests both the sensory and motor components of cranial nerves IX and X [13]. Hoarseness can be caused by cranial nerve X dysfunction [12].

Cranial Nerve XI (Spinal Accessory Nerve)

Cranial nerve XI innervates the trapezius and sternocleidomastoid muscles. Its function can be tested by shoulder shrug and by turning of the neck against resistance [13, 15].

Cranial Nerve XII (Hypoglossal Nerve)

The hypoglossal nerve innervates the tongue. The physician should inspect the tongue for atrophy, weakness, and fasciculations. Fasciculations of the tongue usually indicate a lesion of the anterior horn cells (spinal muscular atrophy). If the lesion is unilateral the tongue deviates toward the side of the lesion [15].

2.2.2.6 Motor System

The motor examination includes assessment of muscle bulk, tone, and strength, as well as observation for abnormal movements [11].

Bulk

The physician must note the symmetry of muscle bulk as some degree of asymmetry may suggest subtle hemiparesis [13]. Muscle atrophy may indicate pathology of

the lower motor neuron, nerve root, peripheral nerve or muscle. Increased muscle bulk of the calves is often found in Duchenne muscular dystrophy [11].

Tone

Muscle tone is the unconscious, continuous, low-level contraction of muscles that creates the resistance to passive movement of a joint. Decreased resistance to passive movement is called hypotonia and is found in lower motor lesions and in lesions of the cerebellum. On the other hand, an initial increased resistance followed by a sudden release is called spasticity and represents upper motor neuron pathology, whereas increased resistance to passive movement, that is equal throughout passive movement of a joint is called rigidity and is found in basal ganglia lesions [11, 15].

In infants, a good way to assess the tone is by observation of his/her posture while lying on the examination table [13]. Infants with hypotonia display the characteristic frog-leg posture (the hips are flexed, and the legs are abducted to an extent that causes the lateral thigh to rest upon the examination table). Physical examination shows head lag (Fig. 2.2), lack of shoulder and elbow muscle contraction on traction response, inability to tighten the shoulder girdle muscles (or "slipping through") when held under the axillae (Fig. 2.3), "scarf sign" (when the arm is pulled to the opposite side, the arm wraps around the neck with the elbow crossing midline), hyperdorsiflexion of the feet, easy apposition of the thumb against the forearm, feet touching the cheek with ease and without discomfort, and "inverted U sign" on ventral suspension (head, arms, and legs hanging down without elbow or knee flexion and the trunk rounded in a dome shape) (Fig. 2.4) [20].

Strength

In infants, muscle strength can be assessed by observation of spontaneous movements. Movements of the extremities must be symmetrical, and the patient must be able to move them against gravity. In infants up to 2 months of age, muscle power can be tested by eliciting the palmar grasp reflex (distal power) and the Moro reflex (proximal power) [11, 15]. In young children, muscle strength is assessed by

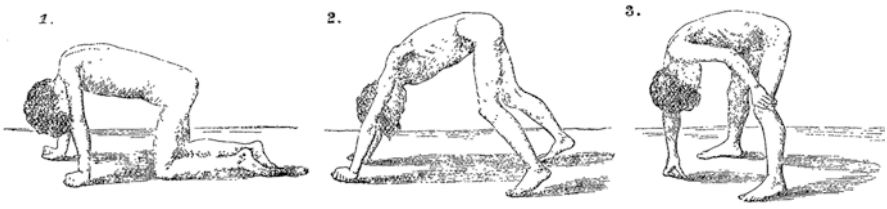

Fig. 2.5 Gower's sign. (Reproduced under kind permission of the publishers from Gowers WR. Clinical lecture on pseudohypertrophic muscular paralysis. Lancet 1879;il:73–5)

observation of activities like walking, standing up from the floor, getting up from chair, playing with objects etc. Older cooperative children can be assessed with formal strength tests that include all muscle groups. In addition, it is very important to determine the pattern of muscle weakness (proximal versus distal). Proximal muscle weakness suggests a myopathy, whereas distal muscle weakness suggests a neuropathy.

Gower's sign (the child rises by pushing hands against the legs when rising from a squatting, sitting, or supine position) (Fig. 2.5) typically occurs in cases of proximal muscle weakness (e.g., Duchenne muscular dystrophy) [21]. Muscle strength can be recorded [17] as displayed in Table 2.3.

Abnormal Movements

The physician must observe patient for any involuntary or abnormal movements such as tics, chorea, dystonia, and athetosis that indicate basal ganglia lesions or fasciculations that indicate lower motor neuron lesions [1].

2.2.2.7 Reflexes

Deep tendon reflexes can be tested in all age groups. The most common reflexes that are tested are the biceps, triceps, brachioradialis, patellar, and Achilles reflexes [17]. The response to elicitation of deep tendon reflexes [11, 17] can be reported as displayed in Table 2.4.

Hyporeflexia generally occurs in cases of lower motor neuron or cerebellar dysfunction, whilst hyperreflexia reflects upper motor neuron lesion. It is, however,

Table 2.3 Scoring system of muscle strength

5	Normal power
4	Inability to maintain position against moderate resistance
3	Inability to maintain position against slight resistance or gravity
2	Active movement with gravity eliminated
1	Trace of contraction (minimal movement)
0	No contraction (complete paralysis)

Table 2.4 Grading of tendon reflexes

0	Absent
1	Hyporeflexia (trace)
2	Normal
3	Hyperreflexic (exaggerated reflex, with spread to contiguous areas)
4	Clonus (unsustained or sustained)

important to emphasize that acute upper motor neuron injury can, initially, cause hypoactive or absent deep tendon reflexes [11].

Sustained clonus must always be considered as a pathological sign. However, infants younger than 3 months of age can normally have 5–10 beats of clonus, and older children can have 1–2 beats of clonus, provided that it is symmetric [11].

The plantar extensor response or *Babinski sign*, compromises extension of the hallux with fanning of the remaining toes [13]. It is elicited by stimulating the sole of the foot with a blunt object beginning at the heel and extending to the base of the toes [16]. A positive *Babinski sign* indicates upper motor neuron lesion but is normal below 18 months of age [13]. An asymmetric plantar extensor response must always be considered as an abnormal sign [22].

2.2.2.8 Sensory System

The evaluation of the sensory system is often difficult in infants and young children and its results are of limited diagnostic value. For that reason, sensation may need to be reexamined in a later, more appropriate time. A gross sensory examination, in this age groups, can be achieved by touching the unaware patient with a cotton swab. Normally, infants and young children respond to this stimulation by crying, withdrawing the extremity or by another alerting response [11, 12, 15].

In older children, the sensory function can be tested in the same manner as in adults. The physician should evaluate the senses of light touch, pain, temperature, vibration, and joint position (proprioception). The sense of light touch can be tested by having the patient has his/her eyes closed. The physician should touch patient's extremities (consecutively or simultaneously) and then ask him/her where he/she feels the touch. The sense of pain/temperature can be tested following the same process while using a pin or a cold fork (It is not usually necessary to test both pain and temperature; either will suffice) [23]. Vibration sense can be tested by applying a tuning fork over patients thumbs and toes and asking him/her if the vibration is felt. Proprioception is tested by moving the thumps and toes of the patient slightly up and down while his/her eyes are closed and ask him/her to identify the direction of movement. Another test the physician could use to test proprioception is the *Romberg test*. During this test the child is initial asked to stand with feet together and eyes open and then is asked to close the eyes. The physician notes if the patient can maintain balance [12].

Graphesthesia can be tested, in children old enough to cooperate, by drawing a number from 0 to 9 on his/her index finger with a ballpoint pen while his/her eyes are closed and then asking him/her to identify the number. In a similar manner, stereognosis can be tested by asking the patient to identify a small object that the physician places in his/her hand while his/her eyes remain closed. Each hand should be tested separately [23].

2.2.2.9 Coordination

Coordination is largely controlled by cerebellum. Cerebellar disorders typically manifest with ataxia which refers to a disturbance in the smooth performance of voluntary motor acts. Lesions of cerebellar vermis tend to affect midline, causing truncal ataxia (unsteadiness while sitting, standing or walking, tandem gait). On the other hand, lesions of cerebellar hemispheres cause appendicular ataxia (patient unable to perform finger-to-nose, finger-to-examiner's finger-to-nose, and heel-to-knee-to-shin stroking).

Dysdiadochokinesis (inability to perform rapid alternating movements) can be assessed by asking the patient to alternate pronate and supinate the hand on a flat surface (e.g., upper thigh), as fast as possible, whilst the contralateral hand remains stationary. The physician must test each hand separately and note if synkinesis (mirror movements) occurs. Other signs of cerebellar dysfunction are dysmetria, i.e., the inability to correctly judge the distance to a target, and intention tremor, i.e., coarse, high-amplitude tremor when approaching a target [17].

2.2.2.10 Gait

The gait examination is a cardinal aspect of the neurologic evaluation and is best performed by observing the patient walk. For more accurate observation the patient must be barefoot and wearing minimum clothing. Toddlers, normally, walk with a wide base but the base of the gait narrows with age. A cooperative child older than 6 years of age, should be asked to perform tandem gait (the toes of the back foot touch the heel of the front foot) [11, 12, 15, 17].

The physician must observe diligently for any pathologic pattern of gait. A Spastic gait is associated with cerebral palsy or other upper motor neuron lesions and is characterized by toe walking, soldier-like stiffness and scissoring of the legs. A hemiparetic gait is characterized by stiffens and circumduction of the lower extremity whilst swing of the ipsilateral arm is decreased and may be held in a flexed posture. An unsteady, wide-based gait indicates cerebellar disorder. A waddling (walking like a duck) or myopathic gait, with exaggerate of the trunk, occurs in proximal weakness due to lower motor neuron or neuromuscular disorders (e.g., Duchenne dystrophy) and is usually accompanied by lumbar lordosis. A slapping gait (the front of the foot hits the ground before the heel) implies peripheral weakness [16].

2.3 Conclusions

Neurological examination in the pediatric patient may be challenging as it is influenced by age and developmental stage, spanning from birth to adolescence. A comprehensive neurological examination can be accomplished through a systematic approach and careful observation of the neonate, infant and child. The essential value of the neurological examination in defining the locus and extent of neuropathological involvement and therefore in formulating plans of management is unequivocal.

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Part II
Congenital and Developmental Cranial Anomalies

Chapter 3
Hydrocephalus

Marcos V. D´Amato Figueiredo and Roberta Rehder

3.1 Introduction

Hydrocephalus is one of the most common neurosurgical conditions, characterized by the excessive accumulation of cerebrospinal fluid (CSF) within the ventricles of the brain. Based on the consensus definition of International Hydrocephalus Working Group, hydrocephalus can be defined as "an active distension of the ventricular system … resulting from inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation." [1] It can be developmental (primary) or acquired (secondary) to other neurological insults, such as tumors, hemorrhage, infection, and congenital malformation. The prevalence of hydrocephalus in infants is approximately one case per 1000 births [2].

Cerebrospinal fluid is produced by the choroid plexus of the lateral ventricles and the tela choroidea of the third, and fourth ventricles in a rate of 20 ml/hour [3]. It is crucial for protection and homeostasis of the neural tissue. In normal adults, the CSF volume is approximately 125 to 150 mL. It circulates through the subarachnoid space between the arachnoid mater and the pia mater and it is absorbed by the arachnoid granulations. The reabsorption is based on the pressure gradient between the sagittal sinus and the CSF and inversely proportional to flow resistance [4]. An imbalance between the production and absorption of CSF will result in an increase of the intracranial pressure.

Hydrocephalus can be classified as communicating or noncommunicating [2, 5]. In noncommunicating hydrocephalus, there is an obstruction of CSF flow within the

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ventricles. In communicating hydrocephalus, the obstruction of CSF flow or its absorption occurs in the subarachnoid spaces [6]. is observed in cases in which the ventricular cavities are dilated uniformly. In cases of non-communicating hydrocephalus, there is an obstruction of the CSF flow, either proximal (at the third ventricle or aqueduct) or distal (at the fourth ventricle fourth ventricular outflow tracts, or foramen magnum).

In this chapter, the authors will describe the causes of hydrocephalus, diagnosis, management, and prognosis.

3.2 History

In 1910, Victor Darwin Lespinasse (1878–1946), a urologist from Chicago, performed the first endoscopic neurosurgical procedure on two infants using a rigid cystoscope as an effort to treat hydrocephalus [7]. Later, Walter Dandy (1886–1946) in 1918 introduced the concept of choroid plexectomy to reduce CSF production [8]. Dandy reported the use of a rigid cystoscope to visualize the ventricles and named the term 'ventriculoscopy" in 1922 [9].{Dandy, 1921, An operation for the removal of pineal tumors} In the early 1940s, Putnam and Scarff improved to the endoscope to include a cauterizing electrode for choroid plexus cauterization [10]. {Scarff, 1935, Third ventriculostomy as the rational treatment of obstructive hydrocephalus;Scarff, 1936, Treatment of hydrocephalus: description of ventriculoscope and preliminary report of cases}

The era of CSF diversion started after the development of valve systems to treat hydrocephalus, initially by Torkildsen, followed by Matson, Nulsen and Spitz, Pudenz and others [11–13]. Although several devices had been developed, shunt-related complications continued, including dysfunctions and infections. Shunts are associated with a high complication rate, often requiring multiple revisions during a patient's lifetime.

Few advances in neuroendoscopy were seen for nearly 50 years, until the development of the cold light generator by Fourestier and Vulmière from the optical Institute of Paris [14]. In 1963, Gerard Guiot was the first to describe its use intracranial [15]. In 1973, Takanori Fukushima introduced the ventriculofiberscope, the first modern description of intraventricular endoscopic biopsy [16].

3.3 Etiology

Based on the etiology, hydrocephalus is classified as congenital or acquired. Congenital hydrocephalus occurs in 1 in every 1,000 newborns and it can be associated with significant fetal and neonatal morbidity and mortality.{Appelgren, 2010, Long-term outcome after treatment of hydrocephalus in children}

Advances in imaging and technology have improved the diagnosis of prenatal anomalies. Signs of hydrocephalus may be visible on ultrasound scans as early as 18th and 20th gestational weeks [17]. Among the causes of congenital

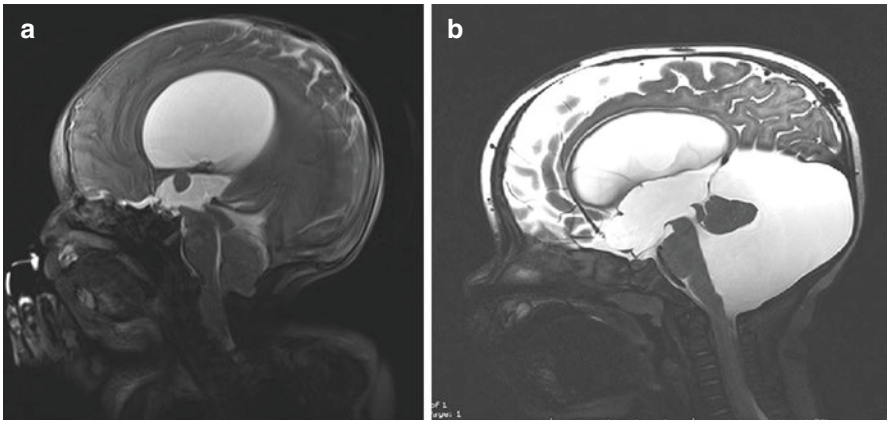

Fig. 3.1 Sagittal MRI, T2-WI, congenital hydrocephalus showing thinning of the corpus callosum, dilation of the lateral and third ventricles, bulging of the third ventricular floor. (**a**) A newborn presenting with myelomeningocele and Chiari 2 malformation. (**b**) Dandy-Walker malformation in a one-year old child, consisting of hypoplasia of cerebellar vermis, and cephalad rotation of the vermian remnant, cystic dilation of the IV ventricle, lifting of the tentorium cerebelli and enlarged posterior fossa

hydrocephalus include aqueductal stenosis, porencephalic cysts, myelomeningocele, Dandy-Walker malformation, and atresia of the foramina of Luschka and Magendie (Fig. 3.1) [18].

The most common heritable from of hydrocephalus is the X-linked hydrocephalus associated with stenosis of aqueduct of Sylvius, representing 10% of males with idiopathic hydrocephalus [2]. *L1CAM* mutations are the most important predispositions of stenosis of aqueduct of Sylvius [19]. Other mutations associated with congenital hydrocephalus include the *MPDZI* encoding MUPP-1, a tight junction protein, and the *CCDC88C*-mutations encoding DAPLE in the Wnt signalling pathway [6, 20]. Primary ciliopathies including the Meckel-Gruber and Joubert´s syndromes are also associated with congenital hydrocephalus [21].

Acquired causes of hydrocephalus can be secondary to brain or spinal tumors, trauma, CNS infection and brain hemorrhage. Intraventricular hemorrhage in premature newborns secondary to germinal matrix hemorrhage is the most common cause of acquired hydrocephalus [2, 22].The germinal matrix on the head of the caudate nucleus is a highly vascular structure. Infants with moderate-to-sever intraventricular hemorrhage are at high risk of developing hydrocephalus, mental disability, and cerebral palsy.

3.4 Clinical Manifestations

In newborns and infants, increase of head circumference, identification of superficial venous congestion of the head and fontanelle bulging are red flags signs for increased intracranial pressure. Clinical manifestations include vomiting, irritability, poor feeding, seizures, lethargy, persistent downward gaze or “sun-setting”

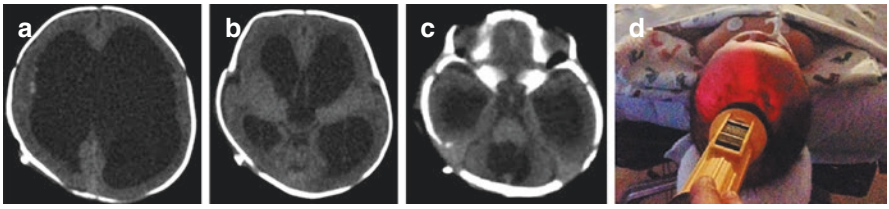

Fig. 3.2 Transillumination sign. A 3-month-old baby, presenting with bulging fontanelle, sunsetting eyes, and vomiting. (**a**) Axial CT scan showing dilation of the lateral ventricles and thinning of the adjacent parenchyma. (**b**) Axial CT scan showing dilation of the III ventricle and transependymal exudate. (**c**) Axial CT scan demonstrating communicating hydrocephalus. (**d**) Transillumination sign, preoperatively for shunt placement

eyes. Transillumination test is another diagnostic sign for hydrocephalus, in which a bright light source is applied to the anterior fontanelle (Fig. 3.2) [23].

Clinical presentation of hydrocephalus in older children include cranial nerve palsy, seizures, headache, lethargy, vomiting and gait disturbance. Papilledema is often present in these cases. Hydrocephalus is a medical emergency and if left untreated can lead to death.

3.5 Imaging

Fetal ultrasound is the method of choice of prenatal diagnosis of hydrocephalus. Transfontanellar ultrasound plays an important role in the diagnosis and management of infants with hydrocephalus. It is a noninvasive, bedside and fast method for characterization of several brain malformation in fetal and newborns.

Computed Tomography (CT) is routinely used in the emergency department in suspected cases of increased intracranial pressure, such as hydrocephalus, shunt dysfunction or hemorrhage. CT scan is a fast exam and can show imaging criteria suggesting hydrocephalus, including dilation of the ventricles, brain swelling, bowing of the corpus callosum and brain lesion (Fig. 3.3). However, recently most departments are preferring magnetic resonance to avoid excessive radiation particularly in children with shunts [24].

CT/MRI imaging criteria in the diagnosis of hydrocephalus include thinning and elevation of the corpus callosum, enlargement of the third ventricular recesses and lateral ventricular horns, normal or narrowed cortical sulci, periventricular white matter hyperintensities and the Evans coefficient greater than 30% (Fig. 3.4) [25, 26]. The Evans coefficient is calculated by ratio of the maximum width of the frontal horns of the lateral ventricles and the maximal internal diameter of the skull at the same level in axial CT and MRI images.

Other criteria include the size of both temporal horns greater than 2 mm, transependymal exudate, the “Mickey mouse” ventricles known as the ballooning of frontal horns of lateral ventricles and third ventricle (Fig. 3.5) [1, 27].

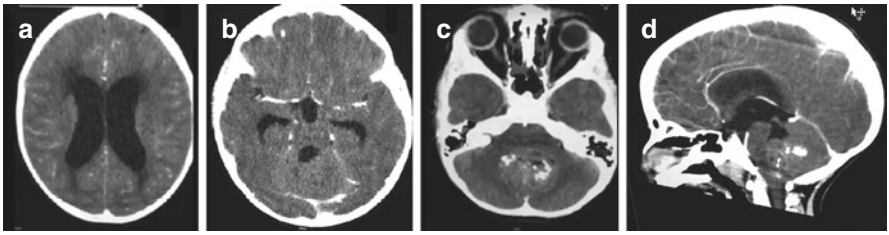

Fig. 3.3 A 6-year-old boy, presenting at the emergency department with vomiting, headache and lethargy, CT scan with contrast showing a non-communicating hydrocepahlus. (**a**) Axial CT, dilation of the frontal horns with transependymal edema. (**b**) Axial CT, dilation of the temporal horns. (**c**) Posterior fossa mass with heterogenous contrast enhancement. (**d**) Sagittal CT, enlargement of the lateral and third ventricles, thinning of the corpus callosum, large mass in the IV ventricle causing an obstruction of the CSF flow through the IV ventricle

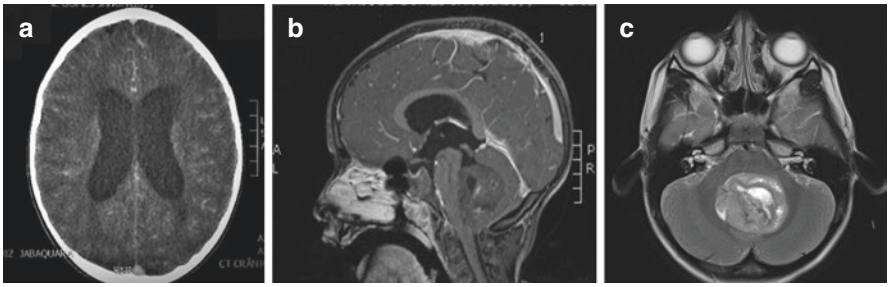

Fig. 3.4 An eleven-year-old boy presenting with headache and vomiting. Imaging exams showing a posterior fossa tumor in the IV ventricle. Pathology demonstrating medulloblastoma. (**a**) Axial CT scan showing enlargement of the lateral ventricles, Evan´s ratio greater than 30%. (**b**) Sagittal MRI T1-WI contrast enhancement demonstrating a posterior fossa mass, thinning of the corpus callosum and enlargement of the lateral and III ventricles. (**c**) Axial MRI T2-FLAIR showing a large IV ventricular mass

3.6 Treatment

Acute hydrocephalus is a neurosurgical emergency. The external ventricular drain (EVD) is a life-saving procedure as a temporary method for CSF diversion, which is often inserted in the right lateral ventricle. Among the surgical indications for EVD include acute hydrocephalus secondary intracranial hemorrhage with intraventricular extension, traumatic brain injury, meningitis, and subarachnoid hemorrhage [28].

Traditionally the implantation of shunt systems has been the most common definitive method for treating hydrocephalus, including ventriculoperitoneal, ventriculopleural and ventriculoatrial shunts [29, 30]. The reported rate of shunt malfunction is approximately 30% in the first year of placement and about 10% per year thereafter [31, 32]. Although the risk of infection per procedure is only 5% to 8%, the cumulative risk of infection approaches 20% per patient [33]. Several protocols

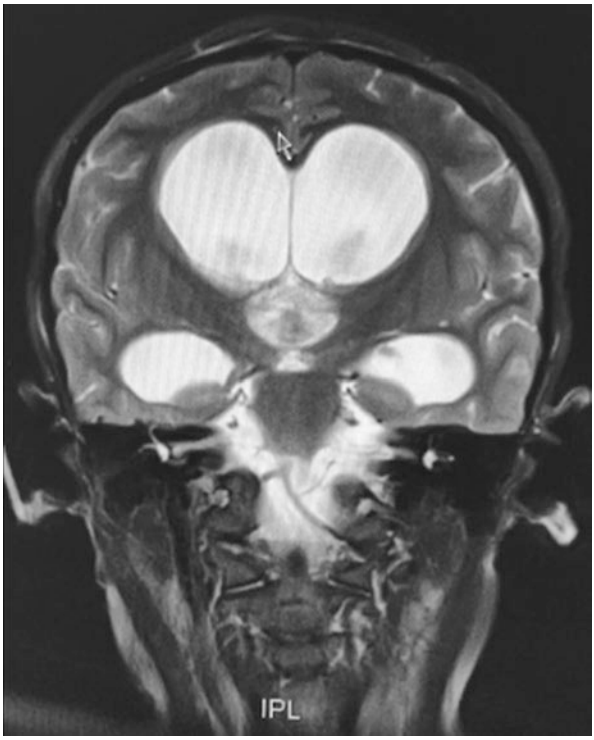

Fig. 3.5 "Mickey mouse" ventricles. An 8-year-old girl presenting with vomiting and seizures. Coronal MRI, T2-WI imaging, demonstrating ballooning of the lateral and third ventricles and dilation of the temporal horns

have been reported to reduce shunt-related surgery complications. Some of the recommendations include priority as the first surgical procedure of the day and reduced number of circulating people in the operating room.

After a long period of routine implantation of shunts, there has been an increasing interest in the performance of endoscopic third ventriculostomy (ETV) to treat hydrocephalus [34]. Advances in optics, miniaturization and computer technology have opened the door to a new field of *minimally invasive neurosurgery*. Selected procedures are now being performed through smaller exposures using microinstruments under endoscopic guidance, thereby reducing trauma to the brain and expediting patient's recovery [25]. ETV has evolved to become the treatment of choice in selected cases of non-communicating hydrocephalus. Its applications might be expanded to include selected cases of communicating hydrocephalus, shunt malfunctioning and congenital hydrocephalus. Although this and other neuroendoscopic procedures are minimally invasive, they are not risk-free and may be associated with major morbidity and mortality [35–37].

The ETV's success score is a useful scale to predict the success of ETV. This score is calculated by the sum of the age, etiology, and previous shunt, ranging from 0 (low chance of success) to 90 (high chance of ETV success) [38, 39]. According to the ETV success score, infants with hydrocephalus secondary to infection and

history of previous shunt placement most likely will not benefit from ETV procedure. The ideal candidates for ETV procedure include older children, not previously shunted, and presenting with stenosis of aqueduct or tectal lesions.

Minimally invasive neurosurgery plays an important role in the treatment of different neurosurgical pathologies, including hydrocephalus. Although the complication rates of ventricular endoscopy are low, they should not be negligible. As the field of ventricular endoscopy continues to evolve, novel techniques will be introduced to facilitate the performance of the procedure and to minimize the risks of related complications.

3.7 Conclusion

Acute hydrocephalus is a medical emergency and must be surgically treated. The clinical findings include headache, vomiting, increased head circumference in infants, sun-setting eyes, and seizures. To relieve intracranial pressure, CSF diversion is the method of choice. Shunts have been implanted for years to treat hydrocephalus. Recent advances in optics and miniaturization have enabled the development of minimally invasive techniques to treat several intracranial pathologies, including hydrocephalus. Although ETV is a minimally invasive technique, it is not risk-free. The adequate diagnosis and promptly preoperative evaluation will enable the neurosurgeon in the decision-making process of the best surgical procedure, thus reducing morbidity and mortality and optimizing prognosis and overall quality of life.

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Chapter 4
Intraventricular Hemorrhage in the Newborn

Young-Soo Park

Abbreviations

AHW	Anterior horn width
CP	Cerebral palsy
CSF	Cerebrospinal fluid
DRIFT	DRainage, Irrigation, and Fibrinolytic Therapy
ELBW	Extremely low birth weight
ETV	Endoscopic third ventriculostomy
EVD	External ventricular drainage
EVL	Endoscopic ventricular lavage
GM	Germinal matrix
IVH	Intraventricular hemorrhage
PHH	Post-hemorrhagic hydrocephalus
TOD	Thalamo-occipital dimension
TROPHY	Treatment of post-hemorrhagic hydrocephalus registry study
TVW	Third ventricular width
VAD	Ventricular access device
VLBW	Very low birth weight
VP	Ventriculo-peritoneal

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4.1 Introduction

Intraventricular hemorrhage (IVH) occurs mainly in premature infants and rarely in full-term infants. In particular, IVH occurs predominantly in very low birth weight (VLBW; <1500 g) and ELBW (<1000 g) infants within 72 h after birth [1–3]. In adults, IVH is associated with hypertensive intracerebral hemorrhage and ruptured aneurysmal subarachnoid hemorrhage. The etiology of IVH in preterm infants is completely different from that of adult IVH cases.

Advances in neonatal intensive care have dramatically improved the survival rate of VLBW and ELBW infants; however, IVH remains one of the most serious and unresolved complications [4, 5]. Severe IVH is associated with high mortality and morbidity. The main objective of treatment is to manage post-hemorrhagic hydrocephalus (PHH), but the fragilities inherent in premature infants complicates treatment considerably. Placement of a permanent ventriculo-peritoneal (VP) shunt does not necessarily solve clinical problems [6–9]. After transient treatment by various methods, successful placement of a permanent VP shunt does not completely prevent white matter damage, and shunt-related complications occur at a low, but non-negligible, rate.

This chapter describes the pathogenesis and functional outcomes of IVH, the various treatment modalities for PHH in newborns, and introduces the latest clinical studies aiming to decrease permanent shunt requirement and improve neurodevelopmental outcomes.

4.2 Pathogenesis of IVH

The pathophysiological factors of IVH in preterm infants are multifactorial and complex [1, 10]. IVH is primarily caused by unstable alterations in cerebral blood flow to the microvasculature in the germinal matrix (GM). Embryologically, GM is the source of both neurons and glial cells, and it is the most active between gestational age 8 and 28 weeks [3]. Anatomically, the GM is a highly vascularized region of the developing brain located underneath the lateral ventricles. The GM initially produces neurons and subsequently glial cells, which migrate to populate the cerebral cortex [10]. Involution of GM toward the caudothalamic groove begins late in the second trimester and is nearly complete by 32 weeks of gestation [3]. Therefore, after 34 weeks of gestation, GM hemorrhage is significantly reduced.

The GM microvasculature is fragile and easily vulnerable to hemorrhage. This fragility is derived from the anatomical feature: a single layer of surrounding endothelial cells and a scarcity of pericytes. Furthermore, it has been shown that the GM microvasculature lacks the basement membrane deposition, tight junctions, and glial end-foot investiture, all of which physiologically constitute the blood brain barrier [10].

Thus, the fragile anatomical features are affected by the fluctuations in cerebral blood flow, which is a common feature in preterm infants. Respiratory distress syndrome is inevitable, and respiratory and circulatory dynamics become unstable accordingly. In response to hypotension, hypoxia, hypercapnia, or acidosis, the cerebral blood flow increases, leading to hemorrhage within the GM [1, 10, 11]. The hemorrhaged blood easily penetrates into the lateral ventricle and is clinically recognized as IVH [11] (Fig. 4.1a). Subsequent progressive ventricular dilation after IVH causes PHH and requires neurosurgical treatment [5, 12] (Fig. 4.1b).

Furthermore, in addition to the immature anatomical features, various systemic features, including cardiorespiratory, metabolic, hematologic, and immunologic factors, are among the risk factors for IVH [1].

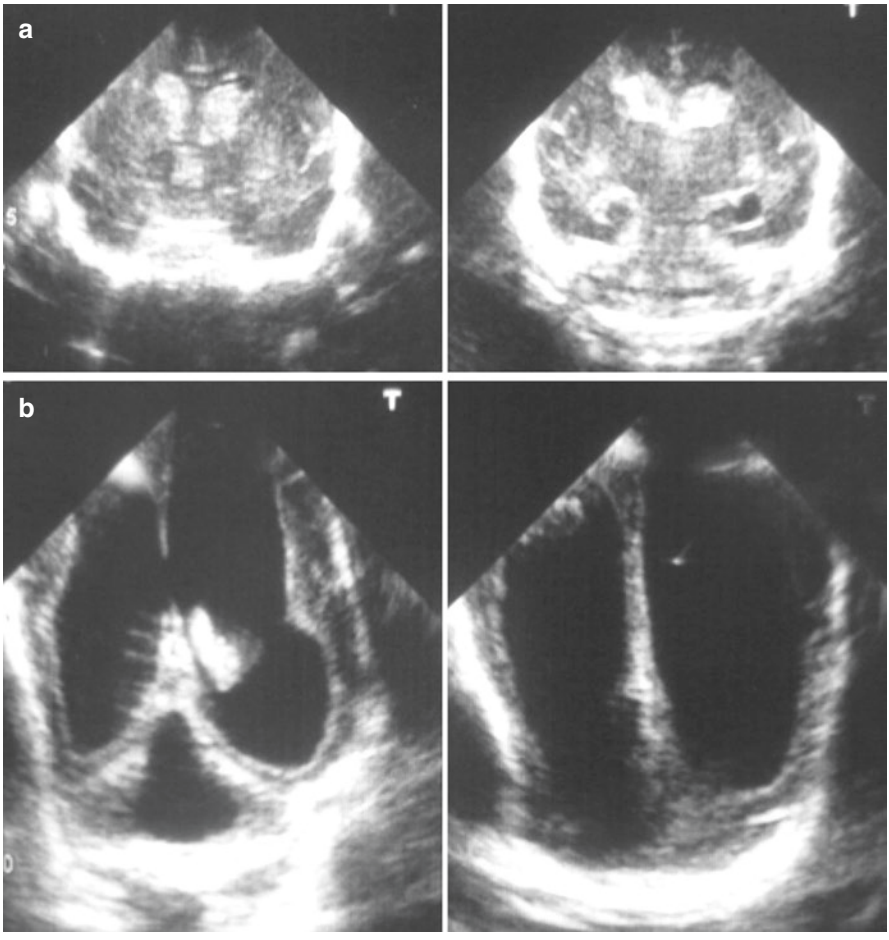

Fig. 4.1 IVH and PHH. (**a**) Geminal matrix (GM) hemorrhage easily penetrates into the lateral ventricles (onset on the second day after birth), (**b**) Subsequent progressive ventricular dilatation (42 days after birth)

4.3 Definition of IVH Grading and PHH

In principle, IVH cases in newborns are classified into Grades I to IV. The severity of IVH was initially classified based on computed tomography findings [13], and presently by ultrasound findings [14, 15] (Fig. 4.2).

Grade I: germinal matrix (GM) hemorrhage (IVH extending from the GM to the lateral ventricle, but involving <10% of the ventricle)
Grade II: intraventricular blood without distension of the ventricular system (an IVH occupying <50% of the lateral ventricle without expanding the ventricle)
Grade III: accumulation of blood and distension of the ventricular system (an IVH occupying >50% of the lateral ventricle and often expanding the ventricle)
Grade IV: parenchymal involvement, also known as periventricular venous infarction (IVH that extends into the surrounding parenchyma).
Grade IV hemorrhage is known to be caused by venous drainage occlusion occurring after venous infarction and hemorrhage into the surrounding tissue and is therefore not an extension of the original hemorrhage [12].

The prevalence of each IVH grade has been reported in several large cohort studies. According to a report of 9575 preterm infants (gestation age ≤28 weeks and weight ≤1500 g) in the nationwide registry of the USA, the incidence of Grade I hemorrhage was 10%; Grade II, 6%; Grade III, 7%; and Grade IV, 9% [16]. Overall, 16% of preterm infants had severe IVH. The Japanese national registration of

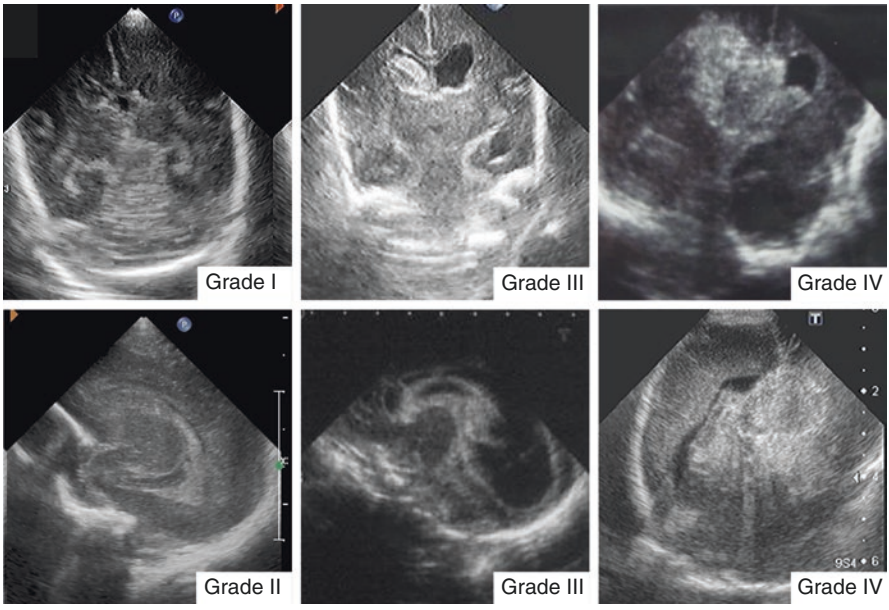

Fig. 4.2 IVH grading. Grade I-IV based on Volpe classification with ultrasound findings

preterm infants reported that 13% of the 2145 preterm infants (body weight, ≤1500 g) had IVH, and severe IVH (grade III or IV) was diagnosed in 7% of the infants [2].

The incidence of severe IVH has declined over the last decade, but it does occur at a constant rate and never totally disappears.

Progressive ventricular dilatation following IVH is diagnosed as PHH. (Fig. 4.1b) PHH is caused by obstruction of cerebrospinal fluid (CSF) circulation because of hematoma and lysate. Neuroendoscopic findings have frequently confirmed obstruction of the Sylvian aqueduct (Fig. 4.5e). Furthermore, PHH has been attributed to fibrosis of the arachnoid granulations, meningeal fibrosis, and subependymal gliosis, which add to impaired CSF resorption [1, 17].

The molecular pathogenesis of PHH remains poorly understood [18]. One hypothesis is that transforming growth factor-beta 2 (TGF-β2) in the CSF stimulates the deposition of extracellular matrix proteins in the neuropil and perivascular spaces, thus impairing CSF resorption [17, 19].

There are several indicators for the quantitative measurement of ventricular dilation. The most common one is based on reference ranges for the ventricular index (VI) according to gestational age [5, 20] (Fig. 4.3a). VI is measured as the sum of the left and right distances from the falx to the lateral wall of the ventricular body. When cases present with a distance of 4 mm over the 97th centile for ventricular index, treatment should be considered. (Fig. 4.3c) However, this reference line only exists at 27 weeks of gestation. Recently, IVH cases with gestational age <27 weeks have become common; therefore, this index alone is not a sufficient indicator of ventricular dilation.

Therefore, measurements of the anterior horn width (AHW), third ventricular width (TVW), and thalamo-occipital dimension (TOD) provide additional reference ranges. The combination of these three measurements (AHW >4 mm, TVW >3 mm, and TOD >26 mm) has been used as an alternative diagnostic index to detect PHH [5, 12, 21]. Furthermore, the severity of ventricular dilation is conveniently defined by the width of the lateral ventricle: mild, 0.5–1.0 cm; moderate, 1.0–1.5 cm; and severe, >1.5 cm [22, 23] (Fig. 4.3a, b).

Another clinical indicator is head circumference expansion. A persistent increase in the head circumference by 2 mm per day is regarded as excessive. An increase of 4 mm over 2 days is more likely to be excessive, and an increase of 14 mm over 7 days is definitely excessive [5].

4.4 Treatment Modalities for PHH

Patients with low grade IVH (Grades I and II) are usually asymptomatic and does not require treatment. In contrast, those with high grade IVH (Grades III and IV) have a high rate of progressive PHH, and require treatment and careful follow-up. In general, the aim of treatment is not to remove the hematoma itself, but to control

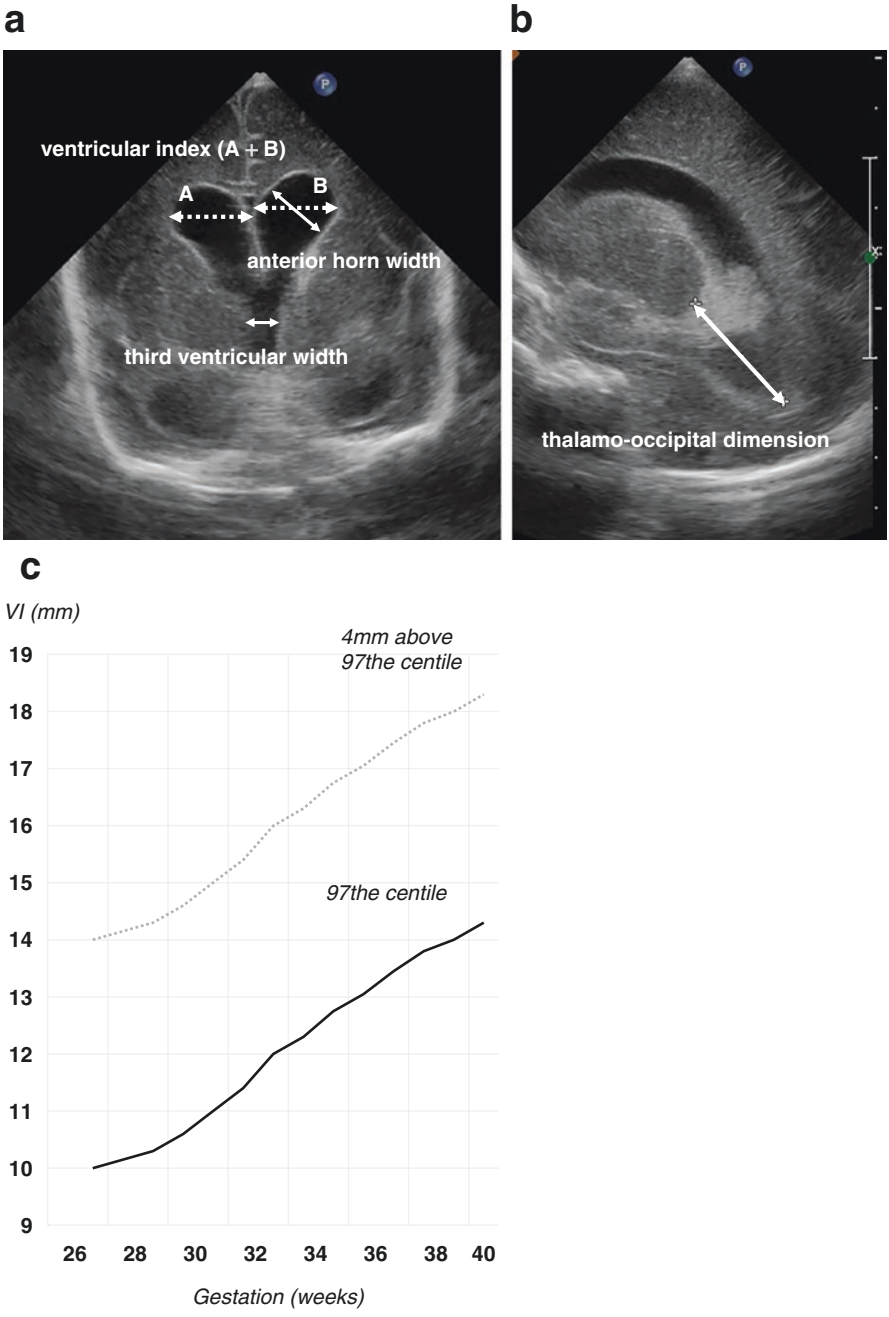

Fig. 4.3 Head ultrasound measurement. (**a**) ventricular index, anterior horn width, third ventricular width, (**b**) thalamo-occipital dimension, (**c**) reference values for ventricular index

progressive ventricular dilatation. The optimal strategy to treat PHH in the period leading up to permanent VP shunt placement is the most relevant issue in clinical practice [5, 7, 9, 16].

Several types of treatment modalities for PHH in preterm infants have been devised, with verified therapeutic effects. From the past to the present, the following treatment modalities have been applied: (1) repeated lumbar punctures and ventricular taps; (2) diuretic drug treatment; (3) CSF tap via a ventricular access device (VAD); (4) use of a ventriculo-subgaleal (VSG) shunt; (5) use of an external ventricular drainage (EVD); (6) intraventricular fibrinolytic therapy; and (7) neuroendoscopic interventions.

Repeated ventricular tap is the simplest and apparently the most effective method to remove excessively pooled CSF. However, repeated ventricular punctures can cause secondary bleeding, risk of intracranial infection, and unexpected porencephaly. Therefore, this method is rarely adopted. Although lumbar puncture is occasionally performed, this procedure is technically difficult to perform and achieving sufficient CSF evacuation is a difficult task in ELBW infants. Early lumbar or ventricular CSF tap to treat PHH was evaluated in four controlled clinical trials. Overall, there was no evidence that this approach reduced VP shunt surgery or disability, and the infection rate associated with these treatments was 7%, a non-negligible incidence rate [24].

Pharmacological treatments to reduce CSF production can be a good approach because they avoid the risk of infection associated with invasive procedures. However, the results of an international randomized controlled trial of acetazolamide and furosemide indicated that diuretic drug treatment was associated with a higher rate of shunt placement and increased neurological morbidity, and thus cannot be recommended [25].

CSF tap via VAD and VSG shunts are the two most commonly used treatment methods for PHH, with known therapeutic effects [3, 26, 27]. The former requires repeated punctures, while the latter has a rather complicated surgical procedure and risk of CSF leakage from surgical incisions other than catheter migration. In addition to these concerns, a better understanding of each infection risk and permanent VP shunt requirement rate is needed. Based on the results of a previous single-center clinical study, infection occurred in 4–11% of VAD cases and 3.3–8% in VSG shunt management. Permanent VP shunt requirement has been reported to between 69% to 90% in VAD treatment, and 60% to 86% in VSG shunt management; these results show no significant differences between treatments [7, 8, 26–29]. Further, a meta-analysis comparing the two treatment groups revealed no significant differences in the rates of infection, obstruction, VP shunt dependence, subsequent shunt infection, mortality or long-term disability. A systematic study revealed an absence of randomized controlled trials investigating this clinical equipoise. Currently, in many institutions, more familiar treatment either VAD or VSG shunt has been selected and applied [8].

EVD is the most commonly used transient method of treatment for adult hydrocephalus, but it generally avoided because of the high risk of infection and the complexity of PHH management in preterm infants. Although PHH is rarely managed by EVD alone, it has been reported as a treatment option in combination with fibrinolytic therapy.

There appear to be a negative recommendation regarding intraventricular fibrinolytic therapy, based on the results of a small number of clinical studies conducted between the 1990s and early 2000 [30]. However, the concept and purpose of fibrinolytic therapy, which aims to avoid permanent VP shunt placement, reduce white matter damage around the ventricles, and improve neurodevelopmental outcomes, should be understood [31]. The DRIFT (DRainage, Irrigation, and Fibrinolytic Therapy) study conducted by Whitelaw et al. was an epoch-making clinical study in the field of IVH treatment in preterm infants.[31] They injected tPA (tissue plasminogen activator) as a fibrinolytic agent into the lateral ventricle, and the therapeutic effect was verified in detail. The phase 1 trial reported a significant reduction in VP shunt requirements and a good neurodevelopmental outcome at postoperative 12 months.[31] However, in the phase 2 trial, a prospective randomized control study, the incidence of VP shunt surgery and death was not reduced in the DRIFT group as compared with the standard treatment group (44% vs. 50%); moreover, a high incidence of secondary IVH (35%) was reported [32]. The results of the phase 3 trial evaluating neurodevelopmental outcomes at two years of age was as follows: the incidence of death or severe disability was significantly lower in the DRIFT group than in the standard treatment group (54% vs. 72%). In addition, the incidence of severe cognitive disability was also significantly reduced (31% vs. 59%) [33]. Furthermore, they evaluated a 10-year follow-up of a randomized controlled trial and concluded that DRIFT was the first intervention for post-hemorrhagic ventricular dilatation to objectively demonstrate sustained cognitive improvement [34].

Another study of fibrinolytic therapy with urokinase by Park et al. reported that urokinase therapy could avoid permanent VP shunt placement in 86% patients and achieve a good functional outcome in 76% patients despite Grade IV IVH in ELBW infants. (Fig. 4.4a, b) They emphasize the importance of early and aggressive therapeutic interventions [35].

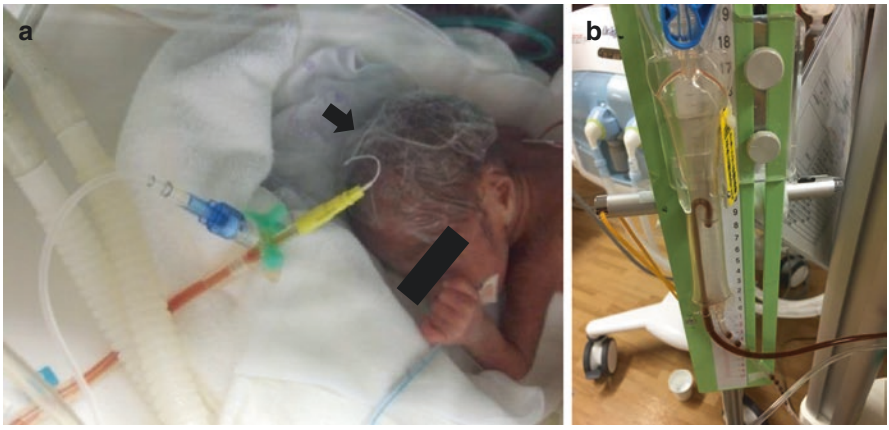

Fig. 4.4. (**a**) Ventricular lavage (VL) treatment. A very thin catheter is used for external ventricular drainage (EVD; indicated by the arrow). A urokinase (UK) infusion syringe pump is connected to a three-way cock. (**b**) Dissolution of the hematoma by fibrinolytic therapy and excretion through the cerebrospinal fluid

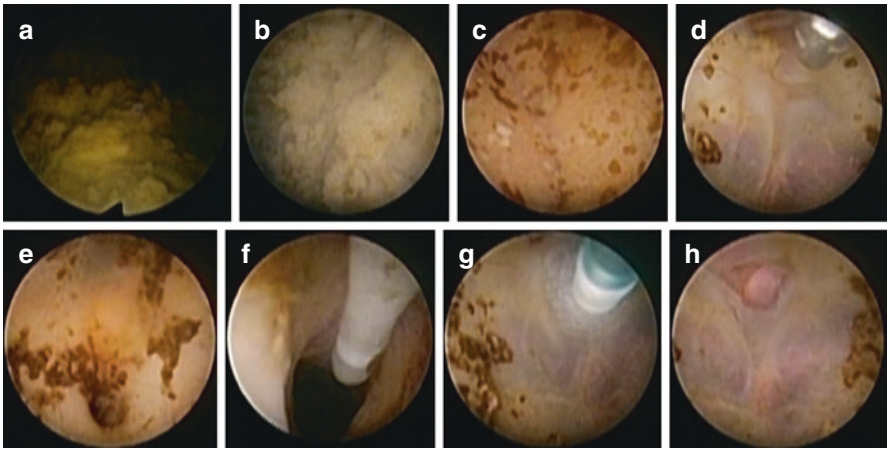

Fig. 4.5 Neuroendoscopic operation and views. (**a**, **b**) Long-lasting intraventricular hematoma before lavage. (**c**) After careful lavage, the lateral ventricle wall with hemosiderin deposits becomes visible. (**d**) Tuber cinereum at the bottom of the third ventricle. (**e**) Obstructed Sylvian aqueduct. (**f**) Aqueduct plasty with balloon catheter. (**g**) Third ventriculostomy. (**h**) Opened stoma

Finally, there are two different types of neuroendoscopic approaches to treat IVH: endoscopic third ventriculostomy (ETV) and endoscopic ventricular lavage (EVL; or neuroendoscopic lavage). (Fig. 4.5a–h) ETV has become the standard treatment for non-communicating hydrocephalus, but its success rate is defined by various clinical factors. Based on the ETV success score [36], PHH in newborns has only 30–40% success rate. Given the small head and fragile brain structures, there is no theoretical evidence and clinical benefit to take the risk and challenge ETV with such a low success rate.

Recently, EVL has been reported to be another promising treatment modality [37]. Although EVL treatment targets severe IVH cases, this new procedure reduces VP shunt requirements to 60%, and neurodevelopmental outcomes are better than that reported in historical case series [37–39]. However, it should be noted that EVL is performed in relatively large infants (mean weight at surgery, >1600 g), with infection occurring in 6–22% cases and CSF leakage occurring in 13% cases ([38, 39]). A prospective, international multi-center study (TROPHY; Treatment of post-hemorrhagic hydrocephalus registry study) is currently in progress, and the results are expected soon [40].

4.5 Prognosis

Mortality and morbidity worsen with increasing IVH grade. Low grade IVH cases (Grades I and II) are usually asymptomatic, and clinical outcomes are generally similar to those of preterm infants without IVH [41].

Recent large-scale cohort studies have investigated not only mortality but also neurodevelopmental prognosis in survivors. A population-based cohort study using the New York and Nebraska State Inpatient Databases (2005–2014) reported that all-cause inpatient mortality of 7437 premature infants born at gestational age 36 weeks or less, with a diagnosis of IVH, was 10.0%, and that the mortality stratified by IVH severity was 3.1% in grade I, 7.8% in grade II, 21.3% in grade III, and 36.1% in grade IV [41].

Over the past 20 years, mortality has steadily declined, even in patients with Grade IV IVH. Therefore, neurodevelopmental outcomes have to be investigated in survivors. According to the latest detailed report, the functional outcomes at two years of age following treatment for PHH were as follows: 16% of infants died, 88% had cerebral palsy (CP)/developmental delay, 48% were non-verbal, 55% were non-ambulatory, 33% had epilepsy, 41% had visual impairment, 9% were deaf, 5% underwent a tracheostomy and 24% required a G-tube. On comparison of outcomes based on IVH severity, 74% of Grade III infants had CP/developmental delays, 32% were non-verbal, and 37% were non-ambulatory, whereas 97% of Grade IV infants had CP/developmental delays, 59% were non-verbal, and 68% were non-ambulatory. Many infants exhibited multiple neurological deficits. Indeed, 53.3% had more than three deficits, while only 7.8% had no deficits [42]. Another population-based cohort study revealed that the overall mortality and CP were 26% and 18% in Grade III infants, respectively, and 47% and 39% in Grade IV infants, respectively [43].

Mortality in preterm infants with high grade IVH has been improving, but neurodevelopmental outcomes are still poor and have hardly improved [5]. Permanent morbidity results from periventricular white matter damage. The pathophysiology of white matter damage is complicated [44]. Certainly, white matter damage is caused by ventricular enlargement. However, the hematoma itself and its lysates also damage the white matter.

Numerous unfavorable factors are correlated with white matter damage [3, 5]. The most obvious pathology is ischemic change caused by highly dilated ventricles. The progressive accumulation of CSF changes the shape of the lateral ventricles from a slit to a balloon. Ultimately, the brain mantle becomes thin as a paper. The expanding ventricles distort the developing brain, and pressure eventually starts to rise. As the preterm skull is very compliant, the ventricles can expand without initial increment in pressure. Eventually, pressure can rise to 10–15 mm Hg [5]. The developing brain would be impaired not only by morphological damage but also by ischemic damage due to reduced cerebral perfusion pressure.

Moreover, the damaging factors of the hematoma and its lysates are also important. Free iron is a potential source of free radicals, and the presence of free iron inside the immature brain for months may be another important mechanism underlying progressive white matter injury [45]. Furthermore, proinflammatory cytokines have been implicated in white matter injury and subsequent CP [46–48].

Thus, IVH and PHH cause progressive periventricular white matter injury over several months as a consequence of pressure, distortion, free radical injury, and inflammation [4, 5, 16].

4.6 How to Reduce Periventricular White Matter Damage and Improve Neurodevelopmental Outcomes?

The previous section discussed several temporary treatments for PHH. Previous clinical studies have reported that the majority of PHH cases require permanent VP shunt placement. Does the gold-standard treatment strategy consider VP shunt placement to be inevitable? Pediatric neurosurgeons involved in neonatal care would say otherwise. VP shunt surgery and its management in fragile newborns frequently cause troublesome complications [3, 6, 9] (Fig. 4.6 a–f). Undoubtedly, shunt infection causes catastrophic brain damage. Moreover, shunt malfunction occurs frequently, and isolated fourth ventricle enlargement is known as a peculiar and difficult-to-treat complication. In some cases, VP shunt may not be possible because of gastrointestinal perforation derived from necrotizing enterocolitis [41]. In principle, the VP shunt must be delayed until the weight of the newborn increases to 1800–2000 g; during that period, PHH gradually and firmly leads to brain damage [5]. Therefore, "No shunt is the best shunt."

Key points for improving neurodevelopmental outcomes should consider the following therapeutic concepts: (1) continuous intracranial pressure control from early PHH stages; (2) recovery of brain mantle volume as soon as possible; (3) prompt

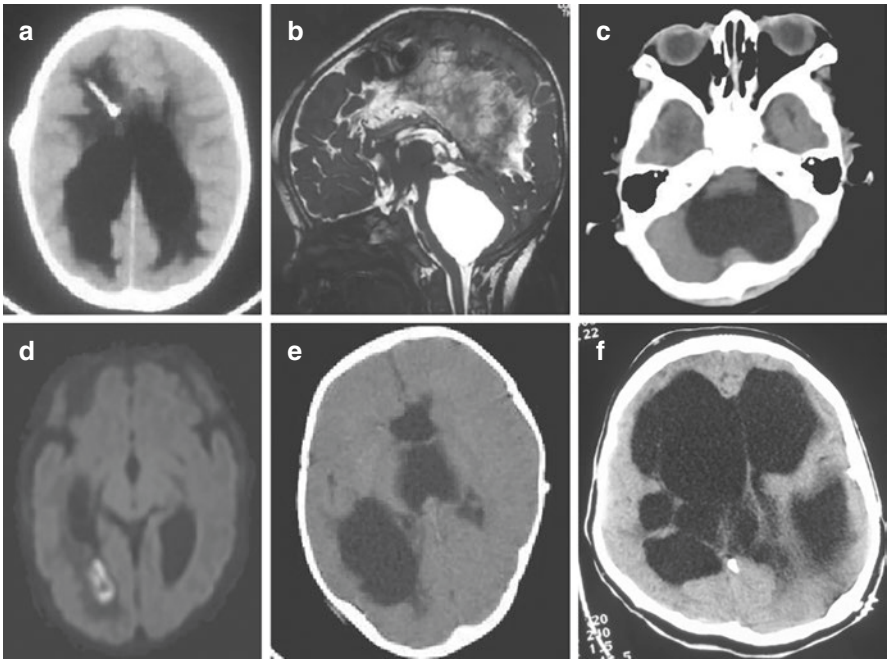

Fig. 4.6 Shunt related complications. (**a**) shunt malfunction due to ventricular catheter occlusion, (**b**, **c**) Isolated forth ventricle dilatation, (**d**) ventricle abscess associated with shunt infection, (**e**, **f**) multilobulated hydrocephalus after shunt infection

hematoma dissolution and washout; (4) inflammatory cytokines and free radical reduction; and (5) prevent of permanent VP shunt placement. These treatment approaches will contribute to minimizing white matter damage around the ventricles [5, 31, 34, 35].

4.7 Future Directions

To date, the main purpose in the treatment of IVH and subsequent PHH has been to reduce mortality as the patients were fragile premature infants; the next concern has been to prevent the need for permanent VP shunt placement. From now on, the mission of pediatric neurosurgeons is to reduce the risk of white matter damage and improve neurological functional outcomes. Thus, there is an urgent need to develop new therapeutic interventions beyond traditional treatment guidelines, such as a compromised policy of VP shunt placement and long waits for spontaneous hemolysis.

4.8 Conclusion

Treatment for IVH and subsequent PHH in preterm infants is difficult, challenging, and controversial. Although the fragile microvasculature of the GM is deeply related to IVH, the pathogenesis is complex. PHH often requires permanent VP shunt placement, but pediatric neurosurgeons must consider ways to improve neurodevelopmental outcomes.

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Chapter 5
Arachnoid Cysts

Ahmed El Damaty

5.1 Introduction

Arachnoid cysts (AC) could be located either cranial or spinal. ACs are present in around 2.6% of the population [1]. The authors reviewed 11,738 consecutive MRI studies of a pediatric population aged between 0–18 years and found in 309 arachnoid cysts to be present. The male to female ratio was 1.8:1. Most frequent was a location in middle fossa (49%), followed by posterior fossa (38%), quadrigeminal plate (6%), convexity (4%), sellar-suprasellar (2%), anterior fossa (2%), interhemispheric (1%), and intraventricular (0.3%). There was a preference noticed for side in only left middle fossa with a ratio of 1.7:1 [2]. Over a mean follow-up of 3.5 years of 111 ACs, 11 (9,9%) increased in size (three becoming symptomatic), 13 (11.7%) diminished, and 87 (78.4%) were unchanged. The younger the patient at diagnosis the more likely the need for an operation [1].

The first reports of successful treatment of spinal intradural cysts were reported by Spiller in 1903 [3] and Skoog in 1915 [4]. Later, case reports described rarities which were fatal if it located in the upper cervical medulla or at the craniocervical junction [5]. Spinal AC are very infrequent in all age groups. Age and gender do not play a role in the incidence of AC in the first two decades of life. The incidence of diagnosed AC has increased, very likely due to the better quality of magnetic resonance imaging (MRI). The introduction of 3 Tesla MRI has provided further anatomic resolution allowing better preoperative planning [6].

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5.2 Classification

5.2.1 Cranial ACs

AC can be classified as to location, size, and etiology. Location incidence, as previously mentioned mainly in the middle and posterior fossa with a wide distribution of the rest. The middle fossa AC have been classified regarding their size into small, moderate, and large (Galassi I, II and III respectively) [7]. A recent classification has been proposed for suprasellar AC [8]. Most ACs are primary. Secondary ACs are related to infection, previous operation, hemorrhage, trauma, and metastatic disease. The incidence of secondary AC is not well reported.

5.2.2 Spinal ACs

The classification of spinal ACs is more complicated, a study simplified the classification of spinal meningeal cysts into three major categories: extradural cysts without nerve root fibers (Type I) subdivided into IA-extradural arachnoid cysts and IB-sacral meningoceles or occult meningoceles; extradural cysts with nerve root fibers (Type II); and intradural cysts (Type III) [9]. Spinal meningeal cysts are most often located in the mid- to lower thoracic area [6, 10, 11], and are found predominantly in males, and tend to be symptomatic during the second decade of the patient's life [10, 11]. The arachnoid cysts in the sacral spinal canal can enlarge the bony canal, but are distinctly different from closed neural tube defects in which the dura mater extends beyond the confines of the spinal canal through a deficit in the posterior vertebral arches [12]. It is suspected that some of the intradural AC in patients with an open neural tube defect were secondary to infection. Those AC associated with a split cord malformation are more likely to be congenital.

5.3 Relation between Arachnoid Cysts and Hydrocephalus

Cranial ACs can cause blockage of the internal cerebrospinal fluid (CSF) pathways and thereby cause hydrocephalus [13]. An example is in case of suprasellar arachnoid cysts. Unlike other arachnoid cysts, these are usually associated with continuous increase in size. This occurs as the basal membrane around the basilar artery exerts a valve mechanism action and with every arterial pulsation more CSF is pushed into the cyst that may not flow out again. The growth occurs thereby slowly but continuously and takes a long time to cause compression of the third ventricle and occlusion of the aqueduct forming a classic occlusive hydrocephalus picture

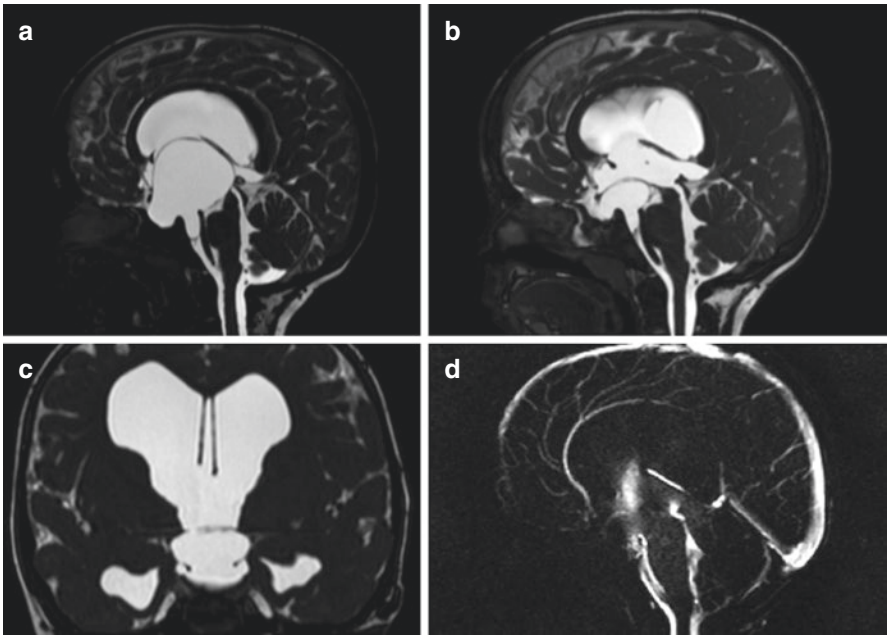

Fig. 5.1 (**a**) Midsagittal CISS MR image showing the suprasellar AC with aqueduct occlusion. (**b**) Midsagittal CISS MR image 4 years after surgery showing decrease in size of AC and free aqueduct. (**c**) Coronal CISS MR image showing the fenestration of the roof of the AC. (**d**) CINE Phase MR Image showing the flow at roof and floor of AC after successful ventriculocystocisternostomy

(see Fig. 5.1). 17–30% of all cranial ACs had an increase in intracranial pressure causing macrocephalic changes [14]. Hydrocephalus is more common with cysts of the midline and posterior fossa [15, 16]. The aim of therapy is always the fenestration of the cysts to the normal CSF spaces to achieve decompression of the cysts and at the same time a reopening of the regular CSF pathways. The implantation of a shunt should be primarily avoided as the problem is not resorptive, but rather the distorted intracranial CSF communication. For example, in cases of retrocerebellar ACs with compression of the cerebellum and 4th ventricle ventrally causing hydrocephalus, the operative choices are either a fenestration to the cisterna magna or to establish a communication to a lateral ventricle with a wide fenestration with or without stent placement. Other rare situations are septum pellucidum cysts (see Fig. 5.2) with symptoms of a periodic increase in intracranial pressure but not clearly hydrocephalic [17, 18], and intraventricular cysts [19]. In these cases, the experience of the surgeon plays a major role in the surgical decision. Basically, an endoscopic fenestration to the ventricular system is recommended, if there is local compression effect or obstruction of the CSF pathways.

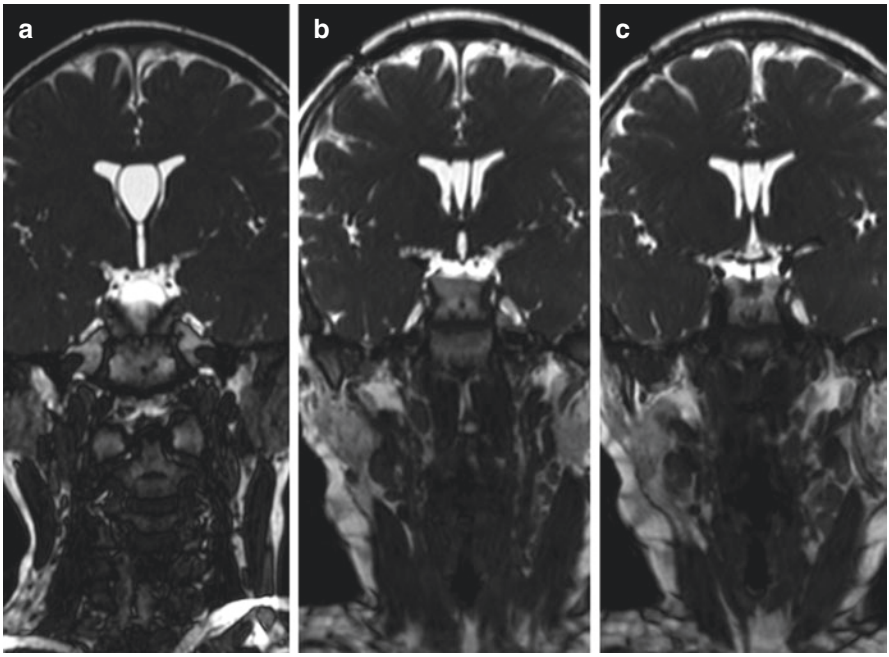

Fig. 5.2 (**a**) Coronal CISS MR image showing the septum pellucidum cyst with narrowing of both foramena of Monroi. (**b**) Coronal CISS MR image 2 years after surgery showing the fenestration of the right leaflet. (**c**) Coronal CISS MR image 2 years after surgery showing the fenestration of the left leaflet

5.4 Clinical Presentation

5.4.1 Cranial ACs

In infancy, the presence of an intracranial AC is often accompanied by an abnormal increase in head circumference secondary to enlargement of the AC or secondary to CSF flow obstruction [20]. Rare finding is an outward bowing of the calvarial bone overlying the arachnoid cyst due to chronic longstanding local pressure. The most common symptoms relate to raised intracranial pressure are headache, nausea, vomiting, lethargy, and papilledema, followed by abnormal increase in head circumference. Less common symptoms are seizures, cerebellar signs, cranial nerve deficits, hemiparesis, visual disturbances, and endocrinopathy according to its location and the nearby structures affected through local space occupying effect of the AC. A number of reports have noted that rupture or hemorrhage can occur into an AC or the adjacent subdural space spontaneously or after mild head trauma [21]. The incidence of seizures as a presenting symptom is reported to be in the range of 5%–20% [1, 22, 23]. Abnormal electrical activity if present may or may not relate to the location of the AC. Koch et al. simply stated that: “Arachnoid cysts are congenital cystic brain malformations associated with epilepsy”[24].

5.4.2 Cranial ACs and Cognitive Impairment

Eleven studies have subjected relatively large series of symptomatic AC patients to systematic neuropsychological investigations and one additional study have looked at mental functions in elderly asymptomatic patients. Ten of these studies reported significant mental impairment, mostly, but not solely, in cognition, and the seven that report both pre- and postoperative results found a clear postoperative normalization. These data highlight the importance of using neuropsychological tests in these patients, as suggested by Soukup et al. [25], that the cognitive measures may provide an alternative functional index of outcome efficacy, rather than reliance on the traditional outcome measures (i.e. anatomical decompression or resolution of clinical symptoms) as they may underestimate the efficacy of surgical intervention for these patients. The present studies indicate that ACs indeed affect mental functions and that they do so in a reversible manner. The preoperative clinical complaints seem to be not associated with the size of the cyst but with the intracystic pressure; the higher the pressure, the stronger the complaints [26]. Another common misconception is that the postoperative improvement must be correlated with the postoperative cyst volume reduction.

Most ACs are considered congenital; therefore, the effects exerted by the cyst pressure upon the surrounding brain tissue have been lifelong. There have been some prospective studies suggesting that the pressure from the cyst on the surrounding brain parenchyma does not necessarily cause a permanent destruction of brain tissue, but more likely a reversible suppression of brain functions, which probably is associated with disturbed perfusion. This explains the postoperative cognitive improvement as the perfusion of the involved brain structures is normalized after the pressure from the cyst is removed. Additionally, structural neuroimaging studies have shown that the temporal lobe adjacent to an AC is smaller and less metabolically active than the contralateral temporal region [27], that language areas within the left hemisphere is displaced by an AC, but not to the contralateral hemisphere [28], and that there is a thinning of cortical tissue around an AC [29]. Most importantly, it has also been demonstrated that a cyst may reduce the perfusion and metabolism in the surrounding cortical regions [14, 30–35], and that these changes are reversible after the cyst has been decompressed, hence explaining the cognitive improvements seen in the same patients. These findings are important, as they clearly demonstrate the association between a functional improvement and a normalized metabolism through improved perfusion in the corresponding cortical areas following cyst decompression.

5.4.3 Spinal ACs

In case of spinal AC, the usual clinical presentation is either myelopathy, radiculopathy, or both with the symptoms usually being insidious and very rarely acute. The presenting symptoms in order of decreasing frequency were: pain, lower

extremity weakness, gait disturbance, scoliosis, spasticity, sensory loss, and a neurogenic bladder [36]. An AC presenting as scoliosis is often associated with other symptoms whereas scoliosis secondary to syringomyelia more often has little or no neurological deficit. As the thoracic spinal canal is the longest and smallest in diameter, AC in this location may manifest earlier than those in the cervical or lumbosacral region.

5.5 Diagnosis

5.5.1 Cranial ACs

MRI is the gold standard for diagnosis. A very common differential diagnosis is the enlargement of the anterior temporal subarachnoid space (SAS) which is a normal common variant as is the size of the cisterna magna. Two factors help in determining whether the finding is an AC, the first being displacement of adjacent structures (i.e., mass effect), and the second is the presence of signal flow voids on MRI-T2 imaging that may indicate communication with adjacent CSF spaces. A new MRI technique, Time-SLIP, developed from modification of arterial spin labelling, has the ability, with videos, to show qualitative CSF flow between adjacent CSF spaces [37, 38]. This technique can help determine if an enlarged SAS at the anterior temporal region or a large cisterna magna is in communication with the surrounding SAS, thereby confirming the presence or absence of an AC. This MRI sequence can also establish the patency of an AC fenestration in further follow up.

As prenatal ultrasound studies are now part of routine monitoring during pregnancy, AC could be detected in utero with two-thirds of AC during the second trimester and the remaining one-third in the third [39]. The size of the AC rarely increases disproportionately to fetal growth. Unless the AC is associated with an incidental CNS malformation, the prognosis for normal neurologic development is excellent. Size and location of the AC are most often not major factors except in case of suprasellar location, in which hydrocephalus, visual impairment, and endocrinopathy can occur. It is rare for hydrocephalus to develop secondary to AC in non-suprasellar locations.

5.5.2 Spinal ACs

The use of MRI, especially with 3T machines, makes the diagnosis of spinal AC relatively clear. Contrast enhancement may be indicated in the first study only but is infrequently needed subsequently. Most useful are the T2-weighted images, as they visualize AC and delineate signal flow artifact that indicate CSF movement and signal intensity changes within the spinal cord. The recently introduced MRI

technique to visualize CSF communication to nearby CSF spaces is very beneficial. CT is infrequently needed specially in pediatric population due to long term hazards of radiation, but if done, can help delineate such bony changes as enlargement of the spinal canal, pedicle erosion, and increase in foraminal size, findings that usually are associated with extra- and not intradural AC. CT myelograms are only rarely needed, but can be useful in establishing patency between CSF spaces, especially in the presence of spinal instrumentation that produces a significant artifact on MRI and CT.

Intramedullary AC are very rare. The origin of this form of AC is not known nor is the mechanism of its enlargement. These AC are reported to present with progressive quadriparesis or paraparesis with pain not being mentioned as a prominent feature. The differential diagnosis includes syringomyelia or a spinal cord tumor associated cyst, both of which should be distinguishable by MRI.

5.6 Indications for Treatment

5.6.1 Cranial ACs

An AC can produce displacement of the adjacent brain especially in the middle fossa where an AC can become quite large. The question arises if such displacement/compression has long term effects on neurologic functions especially in an infant. If so, then diminishing the size of the AC could be postulated to improve long term neurologic function [33, 40–42].

In a recent study by Mørkve et al., adults who underwent surgery for fenestration of a middle fossa arachnoid cyst were given multiple questionnaires to evaluate if their quality-of-life improved following fenestration. Cyst size before surgery and its reduction thereafter had no correlation as to outcome. The majority of patients indicated that their quality of life was improved. The authors of this study thought that headache, dizziness, and cognitive impairment were significantly improved enough to outweigh the risk of operative intervention. We still need more studies in order to substantiate this hypothesis [40].

5.6.2 Spinal ACs

In case of spinal AC, the decision to treat is mainly depending on symptoms and the dynamic change in size noticed, if any. The decision to make surgery is therefore relatively easier in cases of spinal ACs due to the usual presentation with symptoms as well as the definite mass effect exerted on the spinal cord regarding the small spinal canal in comparison to the cranial cavity.

5.7 Operative Treatment

5.7.1 Cranial ACs

Surgical treatment of arachnoid cysts has been performed using both open [23, 26, 40, 41, 43–45], endoscopic techniques [43, 46–49] and also using various shunting procedures [43, 50, 51]. Successful treatment, regardless of approach, requires fenestration of the cyst wall creating communication between the cyst and the normal SAS (see Fig. 5.3) or an insertion of a cystoperitoneal shunt, thus relieving pressure from the cyst on the surrounding tissues. No randomized controlled trial has been undertaken to compare these different surgical approaches, and the choice of surgical procedure for a particular patient might differ from center to center based on experience and preference of the treating surgeon.

Previous decades have debated whether shunting or craniotomy was the optimal method to treat AC. Most of the current literature regarding treatment of AC is comparing craniotomy versus endoscopic techniques [23, 48, 52–54]. Taking into consideration the concept of minimally invasive neurosurgery, the less the operative manipulation the better, thus favouring the increasing use of endoscopy [55]. Despite our preference of endoscopy, recent studies comparing shunting, craniotomy, and endoscopy found no difference in outcome or complications [43, 52].

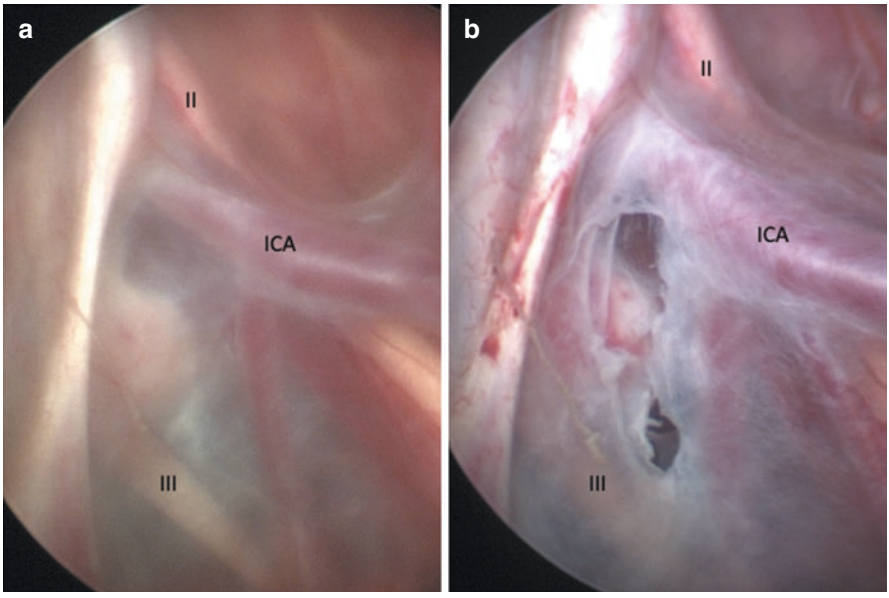

Fig. 5.3 (**a**) Endoscopic view of medial wall of perisylvian arachnoid cyst showing optic nerve (II), internal carotid artery (ICA) and oculomotor nerve (III). (**b**) Endoscopic view after successful fenestration of the cyst to the basal cisterns

Others have proven a clear-cut advantage when operating an intraventricular AC [56]. Shunting may have more long-term complications which will be discussed in this chapter later.

An individualized treatment strategy should also be applied when it comes to selecting patients for surgical treatment. Whether or not patients with arachnoid cysts should be operated, has long been a matter of controversy [40, 44, 57–61]. In these patients surgery is usually not lifesaving, but rather recommended aiming to reduce symptoms and increase quality of life, and thus should only be undertaken if the risk of complication is very low. Complication rates in surgical series have been described in 6% up to 20% [23, 40, 44, 49, 50]. This has led several authors to prefer a conservative approach [59, 60] and although most authors now would agree that symptomatic arachnoid cysts necessitate surgical treatment [40, 42–44], some reserve surgery for patients with overt symptoms of hydrocephalus, raised intracranial pressure, or other objectively verifiable symptoms [59]. A clear reduction in headache and dizziness have shown a significant improvement in patient's quality of life [40].

In case of objective symptoms of hydrocephalus, raised intracranial pressure, or focal neurological deficits that are to be expected through a potential space occupying effect, the indication and decision to offer surgical treatment is fairly straightforward. In cases where all or most symptoms are non-specific, however, it is the responsibility of the treating surgeon to identify the patients with symptoms severe enough to justify the risk of undergoing intracranial surgery. We recommend performing a neuropsychological assessment, especially in the pediatric age group, prior to surgery in order to be able to quantify an improvement after surgery if done. Regardless of which methods are applied for assessment, however, the patients and their parents in case of children must always receive unbiased and quantified information about risks and potential benefits of both surgical treatment as well as conservative management before they themselves make the final decision whether the symptoms are debilitating enough that they accept the calculated risks of undergoing surgical treatment or not.

5.7.2 Spinal ACs

As almost all extradural AC reported in the literature were dorsally located and thus, surgically accessible. Usually, the wall of the AC can be separated from the dura mater. The important feature is assuring complete closure of the communication between the SAS and the extradural cyst. This usually can be done with suturing alone and, if needed, reinforced with fat or a dural substitute. As 50% of the intradural AC are dorsally located, they are more readily fenestrated than those located anterior to the spinal cord. The other half of intradural AC is anterior to the spinal cord and more of a surgical challenge (see Fig. 5.4). Usually after opening the dura, the spinal cord bulges upward through the dural opening. The aim is to go laterally to expose the

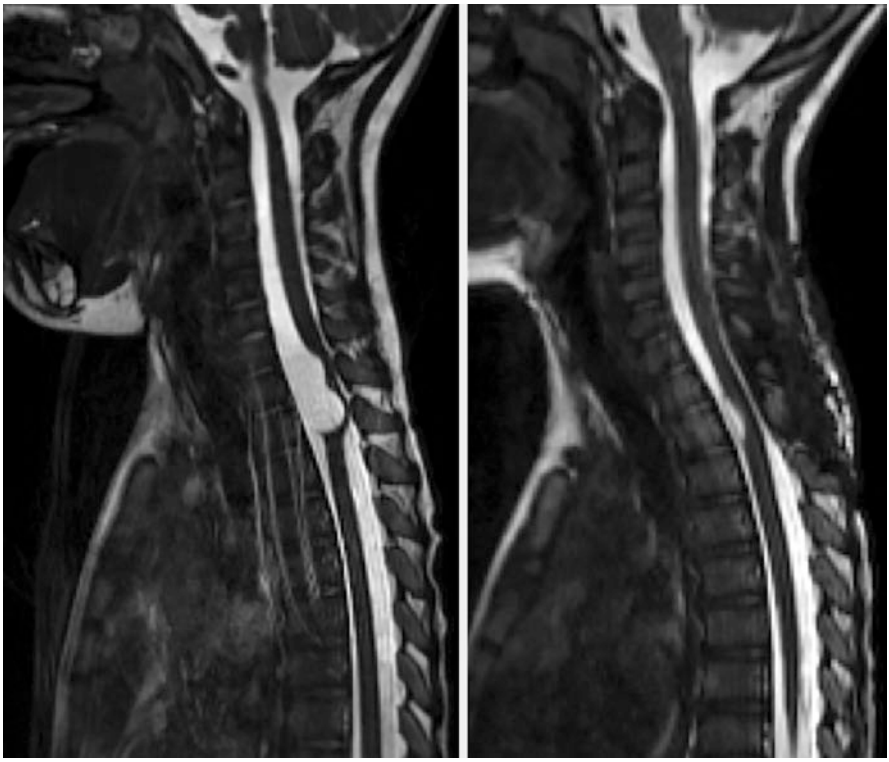

Fig. 5.4 Left: Sagittal CISS MR image of the cervical spine in a 3 years old child showing a ventrally located intradural arachnoid cyst. Right: Sagittal MR image 6 months after successful microsurgical fenestration through a 3-level laminoplasty

wall of the AC which is opened allowing drainage of CSF. After release of the pressure inside, exposure of the cyst would become easier specially after cutting the dentate ligaments and mobilising the spinal cord further medially. Additional areas should be excised on both lateral sides of the spinal cord by going between nerve roots. Intramedullary AC are almost in reality syringomyelia. If the cyst is very large and is surrounded by a thin rim of spinal cord, an approach would be to do a myelotomy in the region where the rim of spinal cord tissue is the thinnest with or without placing a stent to drain the syrinx continuously to the spinal SAS. Somatosensory and motor evoked potentials are routinely used for fenestration of AC. Nerve root stimulation might be of some benefit when dealing with AC surrounding an exiting nerve root.

5.8 Postoperative Complications

A wide spectrum of complications can occur with or following any cranial operative procedure, whether craniotomy or endoscopy, any and is dictated to a degree by the location of the AC. The most common complication related to the disease itself is impairment of CSF circulation that leads to having to do another procedure to treat

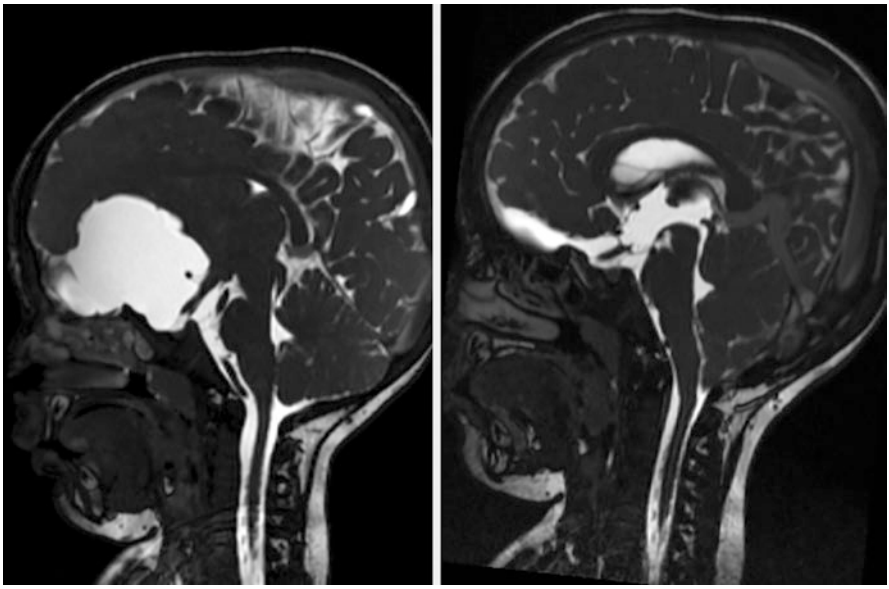

Fig. 5.5 Left: Midsagittal CISS MR image of a one-year-old child with huge perisylvian arachnoid cyst. Right: Midsagittal CISS MR image one year after insertion of a cystoperitoneal shunt showing the tonsillar herniation and the engorged venous sinuses

the hydrocephalus. A study has noted that this complication is much higher in infants under 2 years of age [20]. Other complications associated with CSF diversion via a shunt are also possible. Cystoperitoneal (CP) shunting was for decades the preferred treatment option due to its familiarity in neurosurgical practice [62]. In addition to other common complications of CSF shunting (infection, obstruction, disconnection, etc.), CP shunt insertion is also capable of producing shunt dependency [63, 64]. Current publications have clearly defined the hazards derived from CP shunt utilization, particularly those related to excessive drainage, for example, orthostatic headache, slit cyst syndrome [64], posterior fossa crowding [65], craniocerebral disproportion [65–67] and acquired (pseudo) Chiari malformation [68, 69].

Few studies tried to explain the cascade of these complications. The primary event involving overdrainage in shunted AC seems to be CSF hypotension. After cyst shunting, the cerebral ventricles initially enlarge and are displaced toward the cyst while CSF is drained. Later on, the brain aims to fill up the space left by the decompressed cyst. The intracranial venous system becomes dilated and engorged producing meningeal congestion that, in turn, will evolve to causing meningeal and sutural fibrosis. Subsequently, the skull bones thicken by inward apposition of bone and the paranasal sinuses expand to fill the gap due to volume depletion and to diminution of ICP and cerebral pulse pressure. These osseous changes also affect the posterior fossa leading to overcrowding and to tonsillar herniation (see Fig. 5.5). All these features contribute to reduce CSF reabsorption too. Finally, craniocerebral disproportion occurs when the skull becomes rigid which is usually irreversible in nature obliging the neurosurgeon to undertake more radical surgeries, such as decompressive and expanding procedures [65, 70].

To conclude, at first glance, CP shunting seems to be a safe procedure with which most neurosurgeons are familiar. However, on long terms CSF volume depletion, together with the resultant reduction in cranial capacity, leads to a cascade of events that are responsible for shunt dependency. Changes in cerebral CSF flow, brain, meninges, veins, and venous sinuses, and finally thickening of the skull bones produce a constellation of the overdrainage syndromes. All these conditions are difficult to manage and each one of them requires an individualized treatment. Hence, nowadays most neurosurgeons try to avoid placing CSF shunts and to resort to using microsurgical techniques or neuroendoscopic procedures for cyst fenestration instead.

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Chapter 6
Dandy-Walker Malformation

Georgios Alexiou and Neofytos Prodromou

6.1 Introduction

Dandy-Walker malformation (DWM) is a congenital brain anomaly affecting the posterior fossa. The hallmarks of this developmental abnormality are complete or partial agenesis of cerebellar vermis, cystic dilation of the fourth ventricle, whereas the tentorium, lateral sinuses, and torcular are displaced upward [1]. Dandy-Walker variant is a less severe form in which there is absence of posterior fossa enlargement. DWM occurs in one every 25,000 births and is slightly more common in females [2, 3]. A recent epidemiology study in Europe reported that the overall prevalence of DWM was 6.79 cases/100,000 births. The 39.2% of these cases were in livebirths, 4.3% in fetal deaths from 20 weeks gestational age and 56.5% from terminations of pregnancy following diagnosis of fetal anomaly at any gestation [4]. The prevalence of DW variant was reported to be 2.08 cases per 100,000 [4]. In about 80–90% of DWM cases there is an accompanying hydrocephalus as a consequence of the anomaly. On the other hand, DWM is present in 4% to 8% of hydrocephalus cases. Regarding treatment, shunting or endoscopic treatment has been postulated with good results.

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6.2 Etiology

The precise etiology of DWM remains largely unknown. Atresia of the Luschka and Magendie foramina was historically considered to cause DWM. Recent studies showed that abnormalities involving the roof of the rhombencephalon during development to be causative factor. The majority of DWM cases are sporadic, however Bragg et al. reported that DWM may be inherited via an autosomal fashion [5]. *FOXC1*, *ZIC1/ZIC4*, *COL4A* and *DVL2* were found to be mutated in some DWM patients [6, 7]. *DVL2* is associated with the Wnt signaling which in turn affects the normal cerebellar morphogenesis by regulating progenitor cells proliferation and migration [6]. DWM may also be associated with trisomy 13, trisomy 18 or other syndromes, such as Crouzon syndrome [8].

6.3 Imaging Findings

The most common posterior fossa abnormalities found in prenatal ultrasonography (US) are DWM and Chiari II malformation. DWM is usually associated with other neurodevelopmental anomalies and occurs in the 4th week of gestation. Thus, prenatal imaging can be diagnostic, which in turn is important for prognosis assessment and for delivery planning. DWM is usually diagnosed on ultrasound examination done during the second trimester, since the development of the cerebellar vermis is completed after the 18th week of gestation. In a European registry the median gestational age at prenatal diagnosis was 20 weeks (range 10–38) [4]. The mean maternal age was 29.8 ± 5.9 years. Usual US findings are cisterna magna measuring greater than 10 mm, absence or hypoplastic vermis and latera ventricles measuring greater than 10 mm [9]. Fetal magnetic resonance imaging (MRI) is usually the next diagnostic approach to verify the presence of DWM and to rule out other intracranial or systemic abnormalities, which may be found in up to 80% of cases. Amniocentesis for genetic assessment and exclusion of infections should be offered [9]. MRI offers discrimination of DWM from other cystic posterior fossa disorders. In posterior fossa arachnoid cysts there is normal vermis and compression of the cerebellum and 4th ventricle. In Blake's pouch cyst there is communication of the cyst with the 4th ventricle with normal cerebellum and vermis and is commonly associated with hydrocephalus. Finally, mega cisterna magna presents with intact cerebellar hemispheres and vermis with no compression on the 4th ventricle [10].

6.4 Symptomatology

DWM is usually diagnosed within the first year of life, mainly due to the increased intracranial pressure from hydrocephalus and posterior fossa cyst. Thus, bulging of the anterior fontanel, enlargement of head circumference and developmental delays

are common findings that prompt neuroimaging [2]. In older children there is usually headache, nausea and vomiting, vision disturbances, seizures and signs of cerebellar dysfunction. However, late presentation may also occur depending on the severity of structural changes. Cases presented with tremor and syringomyelia have also been reported [11]. Cognitive-behavioral symptoms and psychiatric changes, such as schizophrenia and obsessive compulsive disorder, have also been reported in patients with DWM. Disruption of the corticocerebellar tracts that produce the cerebellar cognitive affective syndrome has been considered as a causative factor [12].

6.5 Central Nervous System Abnormalities

DWM is often associated with central nervous system abnormalities (CNS) [2]. The most common malformations reported are absence or hypoplasia of the corpus callosum or a part of corpus callosum such as splenium, absence of septum pellucidum, holoprosencephaly, schizencephaly, dolichocephaly, encephaloceles, gray matter heterotopias, malformations of the brainstem, syringomyelia, Crouzon syndrome and Klippel-Feil deformity [2, 3, 8, 11]. In a study that described the morphological and morphometric alterations of neurons in a Dandy-Walker Variant there was diminished density of the dendritic spines in the cerebral cortex. In the cerebellum tonsils and vermis there was gliosis and Purkinje cells had decreased size of the cell body and of the thickness of dendritic arborization. Finally, morphometric analysis revealed a 23.77% decrease in the number of neurons in vermis and 19.4% decrease of the number of neurons in cerebral hemispheres [13].

6.6 Non-CNS Abnormalities

Several structural anomalies have been reported in association with DWM and may be found in up to 93% of patients [14]. In a study of 734 cases, 562 DWM and 172 variant cases, cardiac anomalies were the most frequent, accounting for 11.4%. These abnormalities included ventricular and atrial septal defects, patent ductus arteriosus, coarctation of aorta, stenosis of the pulmonary, tricuspid and aortic valve, tetralogy of Fallot and hypoplastic left heart [2, 4]. The second most frequent abnormalities were of the urinary system and included congenital hydronephrosis, vesicoureteral reflux, hydrocele, multicystic renal dysplasis and renal agenesis [4, 15]. Approximately 4.6% of a cases had limb abnormalities such as syndactyly, polydactyly and limb reduction defects [4]. Less frequent are anomalies from the digestive system including congenital malformations of intestinal fixation, mega rectum, esophageal and duodenal atresia. Facial anomalies commonly found are microphthalmia, congenital glaucoma and cataract, strabismus, hypertelorism, facial angioma, cleft lift and cleft palate [2, 4].

6.7 Management

The treatment of patients with DWM mainly involves hydrocephalus and posterior fossa cyst management. Common procedures described in the literature are placement of a ventriculo-peritoneal (V-P) shunt, cyst-peritoneal (C-P) shunt, combined V-P and C-P shunt, membrane excision/fenestration and endoscopic procedures including endoscopic third ventriculostomy (ETV) and fenestration [2]. Endoscopic procedures may have certain advantages over shunting, since shunt failure rates may be seen in 30–40% of cases [16]. Mohanty et al. in a large series of 72 children with DWM that were treated with the above surgical techniques, reported that aqueductal obstruction is a key-point for proper management decisions. If the aqueduct is patent ETV usually suffices. In case of ETV failure a V-P or C-P shunt may be considered. In case of aqueductal stenosis, aqueductoplasty or stent placement, in addition to ETV, is needed. However, shunt placement resulted in greater reduction of the ventricle size, and also C-P shunt in greater reduction of the cyst size [17]. In a series of 19 DWM cases, shunt was placed in all cases. In 4 cases only a V-P shunt was placed, in 10 cases a C-P shunt and 5 cases required ventricular system and posterior fossa cyst drainage, using a 3-way connector. Shunt revision was required in 4 out of 19 patients. Shunt placement proved to be a safe procedure and resulted in clinical improvement in all patients [2].

6.8 Prognosis

Congenital cerebellar malformations have been associated with several neurological, developmental, and functional disabilities in children [18]. Regarding DWM the prognosis of these patients is variable ranging from normal development to severe cognitive impairment. There are reports that nearly 50% of patients have normal cognition, whereas others never have normal intellectual development even if hydrocephalus is treated early [19]. A recent study showed that 10/10 patients had language delay and 78% had global developmental delay [18].

In a large series of 45 children, 49% of patients exhibited normal development, whereas 29% had a mild and 22% significant delay [17]. Presence of multiple congenital defects affects life expectancy.

6.9 Conclusion

DWM is a rare congenital disorder associated with several CNS and non-CNS abnormalities. Surgical treatment usually involves management of the hydrocephalus using shunts or with endoscopic procedures. Prognosis is variable and depends on the accompanying abnormalities.

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Chapter 7
Chiari Malformation

Amin Tavallaii

The term "Chiari malformation" (CM) is used to describe a complex spectrum of congenital anomalies affecting the cerebellum, brainstem, and craniocervical junction, generally in form of neural tissue herniation toward the cervical spinal canal. Reports of cerebellar tissue herniation through the foramen magnum dates back to about 130 years ago. For the first time, professor Hans Chiari, an Austrian pathologist introduced a heterogeneous spectrum of developmental anomalies affecting the cerebellum and brainstem of deceased hydrocephalic infants in autopsy series [1, 2]. These anomalies were later classified as Chiari malformation type I to III. The mildest form of the anomaly described by Chiari included the descent of cerebellar tonsils through the foramen magnum into the cervical spinal canal while the most severe form was introduced as herniation of hindbrain structures presenting as a high cervical or lower occipital encephalocele. Julius Arnold, a colleague of Chiari had a significant contribution to the introduction of a specific type of anomaly with a descent of cerebellar tonsils and vermis alongside the elongation or downward displacement of lower medulla oblongata through the foramen magnum. Therefore, this subtype of Chiari malformation was named Arnold-Chiari malformation that is also known as Chiari malformation type II (CM-II) nowadays. The evolution of this entity did not stop after the efforts of Chiari and his colleagues and up to now, many other subtypes of this developmental anomaly are identified and introduced in the literature which we try to cover all in detail throughout this chapter.

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Chiari malformation is commonly associated with other developmental and congenital anomalies of the neuroaxis such as hydrocephalus, syringomyelia, spina bifida, scoliosis, and tethered cord syndrome among many others. The long list of associated anomalies that will be presented in detail in this chapter highlights the importance of paying attention to the underlying pathophysiology and embryology of Chiari malformation as a tool for a better understanding of the etiology and the implication of these associations.

Despite the evolution of diagnostic paradigms following the advent of Magnetic Resonance Imaging (MRI) and the introduction of multiple pathophysiologic theories as the underlying cause of Chiari malformation, there are still many challenging uncertainties and controversial diagnostic, therapeutic, and prognostic aspects of this anomaly in place which we try to discuss them in-depth throughout this chapter.

7.1 Classification

When Hans Chiari in 1981 described the three subtypes of Chiari malformation probably he did not expect his classification to be expanded in such a significant manner. Today, nine various subtypes of Chiari malformation are reported in the literature. A couple of these subtypes are rare and such severe that the affected patients almost always die due to these anomalies. However, we aim to present a comprehensive classification that includes all the reported subtypes of the Chiari malformation till now (Table 7.1).

Table 7.1 A summary of the most up to date classification of CM

Type	Definition	Characteristics
0	Syringomyelia without any herniation of neural structures	Obstruction of the fourth ventricle outlet
0.5	Tonsillar wrapping around medulla and lateral medullary compression	Most recently introduced entity
1	Caudal herniation of tonsils more than 5 mm through the foramen magnum	Most common type
1.5	Caudal herniation of tonsils, vermis, brainstem, and elongation of the fourth ventricle through the foramen magnum	–
2	Caudal herniation of tonsils, vermis, brainstem, and elongation of the fourth ventricle through the foramen magnum with concomitant myelomeningocele	–
3	Hindbrain herniation into an occipital or cervical encephalocele	Severe and rare, Patients usually die
4	Cerebellar hypoplasia or aplasia	Very severe and very rare, Patients almost always die
5	Cerebellar aplasia with herniation of the occipital lobes through the foramen magnum	Most severe and rarest, Patients almost always die

7.1.1 Chiari Malformation Type 0

This type of Chiari malformation is characterized by the syrinx formation without any signs of neural tissue herniation or brainstem compression (Fig. 7.1a). The logic

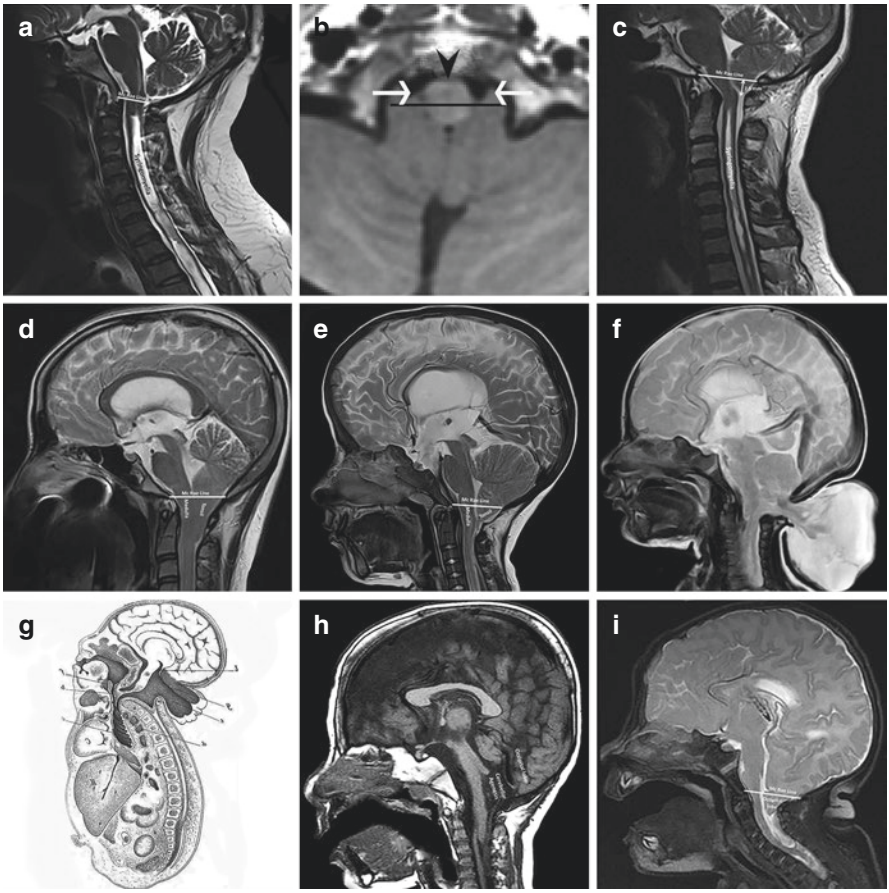

Fig. 7.1 MR images of various types of Chiari malformation. (**a**) Sagittal T2-weighted MR image of a Chiari 0 patient depicting the presence of syringomyelia without any herniation [3]. (**b**) Axial T1-weighted MR image of a Chiari 0.5 patient illustrating ventral herniation of the cerebellar tonsils (*white arrows*) and lateral compression on the medulla (*black arrowhead*) [4]. (**c**) Sagittal T2-weighted MR image of a CM-I patient showing a 7.5 mm tonsillar descent below the McRae line and presence of the concomitant syringomyelia. (**d**) Sagittal T2-weighted MR image of a patient with Chiari 1.5 depicting the tonsillar herniation and downward displacement of the medulla [5]. (**e**) Sagittal T2-weighted MR image of a patient with myelomeningocele and CM-II demonstrating the concomitant herniation of medulla and cerebellar tonsils through the foramen magnum (note the elongated fourth ventricle). (**f**) Sagittal T2-weighted MR image of a neonate with CM-III showing herniation of cerebellar tissue into a large encephalocele [6]. (**g**) Schematic illustration of Chiari malformation type 3.5 [7]. (**h**) Sagittal T1-weighted MR image of a patient with CM-IV demonstrating cerebellar agenesis and downward displacement of the tentorium. (**i**) Sagittal T2-weighted MR image of a neonate with CM-V showing complete absence of the posterior cranial fossa and herniation of occipital lobes through the foramen magnum [8]

behind this classification is the similarity of clinical presentation between these patients and patients with Chiari malformation type I (CM-I) and the observation of clinical improvement following the implementation of surgical techniques used for other types of Chiari malformation. The underlying pathophysiology seems to be a membrane or scar formation at the outlet of the fourth ventricle that disturbs the CSF flow at the craniocervical junction [3, 9, 10].

7.1.2 Chiari Malformation Type 0.5

This is the most recently introduced subtype of Chiari malformation with a clinical presentation similar to CM-I but without significant tonsillar herniation through the foramen magnum. Instead, in this subtype, the cerebellar tonsils herniate ventrolaterally and wrap around the medulla causing compression on the lateral aspects of the medulla and lower cranial nerves (Fig. 7.1b) [4].

7.1.3 Chiari Malformation Type 1

Chiari malformation type I is the most common form of Chiari malformation with herniation of the cerebellar tonsils through the foramen magnum into the cervical spinal canal (Fig. 7.1c). Multiple thresholds are reported in the literature for the tonsillar descent as the radiological diagnostic criteria of CM-I, but the most accepted one is a more than 5 mm descent for the definite diagnosis of CM-I and a 3–5 mm descent for a probable diagnosis.

7.1.4 Chiari Malformation Type 1.5

This subtype is characterized by the herniation of cerebellar tonsils, vermis, and lower medulla through the foramen magnum as well as elongation of the fourth ventricle but without associated myelomeningocele (Fig. 7.1d). This malformation can be assumed a more severe variant of CM-I given the fact that there are reports of conservatively managed CM-I patients showing radiological progression toward Chiari malformation type 1.5 gradually. However, the patients affected with this subtype present a natural history almost similar to patients with Chiari malformation type II [5, 11].

7.1.5 Chiari Malformation Type 2

This well-known subtype also called the classic Chiari malformation or Arnold-Chiari malformation includes all anomalies described in the Chiari malformation type 1.5 such as herniation of cerebellar tonsils, vermis, and lower medulla

(specifically Obex) through the foramen magnum but with the presence of concomitant spina bifida and myelomeningocele (Fig. 7.1e).

7.1.6 Chiari Malformation Type 3

This term refers to a rare form of Chiari malformation encompassing herniation of cerebellar tissue with or without brainstem structures into an occipital or high cervical encephalocele (Fig. 7.1f) [12].

7.1.7 Chiari Malformation Type 4

This was the most severe and rarest form of Chiari malformation before the introduction of Chiari malformation type 5. In this subtype, cerebellar hypoplasia or aplasia with concomitant abnormalities in the brainstem formation are seen despite the normal development of the posterior fossa (Fig. 7.1h). This malformation almost always leads to an early death.

7.1.8 Chiari Malformation Type 5

This most severe form of Chiari malformation includes cerebellar aplasia along with the herniation of the occipital lobes through the foramen magnum (Fig. 7.1i) [8].

Other than these reported types of Chiari malformation there is also an entity called Chiari malformation type 3.5 which is based on a single case report dating back to 1894, This anomaly is described as encephalomyelocystocele in a premature neonate with the absence of cervical region, presence of an occipital protruding mass connecting caudally to the scapular region and anteriorly to the abdominal viscera (Fig. 7.1g). However, due to the lack of similar reports in the literature we hesitate to include this reported anomaly in the classification of Chiari malformation [7, 13].

7.2 Embryology

Most of the available embryological explanations are developed based on Chiari malformations type I and II. Some reports advocate the impairment of paraxial mesoderm development as the underlying cause of CM-I. This maldevelopment may lead to the formation of a small and shallow posterior fossa that consequently cause overcrowding and pressure rise within the posterior fossa [14].

The formation of cerebellar tonsils happens beyond the second gestational trimester. Therefore, any increase in pressure of the posterior fossa compartment after the second trimester can lead to the caudal displacement of cerebellar tonsils and tonsillar impaction within the foramen magnum as can be seen in CM-I. If this pressure rise happens sometime within the second trimester, the herniated neural structure will be the cerebellar vermis and the resultant anomaly will be the Chiari malformation type II [15]. The presence of concomitant myelomeningocele and significant cerebrospinal fluid (CSF) loss through the defect can enhance the downward pressure gradient and exacerbate the downward displacement of posterior fossa neural structures. CSF overdrainage can also cause a low CSF pressure within supratentorial ventricles and subsequent ventricular collapse that may be the underlying cause for the presence of associated anomalies such as corpus callosum agenesis or large massa intermedia [16].

In brief, it seems that the mesodermal anomaly is the embryological process responsible for the occurrence of CM-I. On the other hand, the main embryological anomaly behind CM-II includes neuroectodermal malformation, although mesodermal maldevelopment can also play a less significant role in its pathogenesis. Moreover, Chiari malformations type III and IV are also known as neuroectodermal anomalies, although due to their rarity, the exact underlying embryological processes involved in these types of Chiari malformation are not well known till now [17].

7.3 Pathophysiology

Herniation of posterior fossa neural structures through the foramen magnum may be the result of various hereditary or acquired conditions. For instance, downward displacement of cerebellar tonsils due to the presence of space-occupying lesions within the posterior fossa such as tumors or hematomas is a known condition that can be described under the term “secondary CM-I” [18–21]. However, our focus in this chapter is on the primary Chiari malformation as a developmental and congenital anomaly and we discuss the pathophysiological processes responsible for this malformation. Many authors and researchers have tried to elucidate the cause of Chiari malformation in form of pathophysiological theories but most of these theories have failed to cover all complexities and diversity of anomalies associated with the Chiari malformation by themselves and it seems that considering a role for a combination of these theories may better overcome this challenge. Here we present the six most popular theories, the first three of them are more applicable to the CM-I and the last three better describe the underlying pathophysiology of CM-II.

7.3.1 Overcrowding Theory

A mesodermal disorder during embryonic development of the occipital bone may lead to the formation of a small and underdeveloped posterior fossa that subsequently causes overcrowding of the posterior fossa and compensatory herniation of

cerebellar tonsils through the foramen magnum to alleviate the pressure rise within the posterior fossa compartment [22–27]. As a result of this herniation, the CSF flow disturbance occurs at the craniocervical junction and the resultant development of hydrocephalus and downward pressure gradient toward the cervical spinal canal leads to exacerbation of tonsillar herniation and presentation of clinical signs and symptoms [28]. The results of an interesting study performed recently to evaluate the effects of pulsatile intracranial pressure (ICP) and pulsatile pressure gradient on the amount of tonsillar ectopia in the patients with CM-I have demonstrated the significant role of low intracranial compliance in the underlying pathophysiology of CM-I and supported the overcrowding theory [29]. This theory can also explain the pathologic process involved in cases with CM-I and concomitant craniosynostosis.

7.3.2 Growth Abnormality Theory

The key concept behind this theory is that the growth of different segments of the neuroaxis happens in different directions. The supporters of this theory believe that the collision of two growth waves, one caudally oriented wave responsible for cranial growth and another cranially oriented wave related to cervical spinal growth may cause developmental abnormalities at the craniocervical junction and be responsible for the occurrence of CM-I [30, 31].

7.3.3 Molecular Genetic Theory

In this theory, an abnormality in the genetic pathways responsible for the growth and development of the posterior cranial fossa and its neural content may play a role in the pathogenesis of Chiari malformation [32–34]. However, the vast majority of Chiari malformations do not have a hereditary background and are known to be sporadic malformations. Therefore, if we accept this theory as one of the underlying causes of CM, the occurrence of new mutations spontaneously or as the result of fetal exposure to teratogen agents is the more probable explanation. Reports of familial forms of Chiari malformation (specifically CM-I) are available in the literature, but it seems to be very rare [35–37]. Some examples of hereditary syndromes that can be associated with CM-I are hereditary connective tissue disorder (HCTD), Marfan, Ehlers-Danlos, Klippel-Feil, Pierre-Robin, Beckwith-Wiedemann, and Costello syndromes [14, 17].

7.3.4 Hydrodynamic Theory

This is the oldest theory that was presented by Hans Chiari for explaining the pathophysiology behind the caudal displacement of neural structures within the posterior cranial fossa in patients with CM-II. In this theory, the primary development of

hydrocephalus poses a downward pressure upon the posterior fossa contents and result in the herniation of these structures through the foramen magnum [2]. However, about 10–20 percent of patients with CM-II do not suffer from concomitant hydrocephalus. Moreover, fetal imaging studies usually diagnose CM-II before the presence of any radiological clues of hydrocephalus.

7.3.5 Traction Theory

With a whole mechanical view to the pathophysiology of CM-II, the supporters of the traction theory believe that the cord tethering caused by myelomeningocele may pose significant downward traction on the posterior fossa neural structures such as the brainstem and cerebellum and force the caudal displacement of these structures through the foramen magnum. But this is a simplistic view of a complex phenomenon and cannot explain most of the anomalies associated with CM-II. Moreover, it is demonstrated that the elastic characteristics of the spinal cord do not allow the transfer of traction force over so many spinal levels from the lumbosacral area to the posterior fossa [38, 39].

7.3.6 Unified Theory

As we previously mentioned, it seems that a simple theory fails to cover all the pathophysiological aspects of the Chiari malformation especially the CM-II. Therefore, we believe that the so-called "unified theory" is potentially the most relevant and acceptable in explaining the coexistence of a long list of anomalies seen in patients with CM-II. In this theory, CSF loss and leakage through the neural tube defect lead to the abnormal lowering of CSF pressure within the intracranial compartment. This intracranial hypotension results in the collapse of the ventricular system, a phenomenon that can explain the maldevelopment and inadequate growth of the posterior fossa and resultant herniation of neural structures due to the posterior fossa overcrowding. The impaction at the level of the foramen magnum disturbs the CSF flow through the outlet of the fourth ventricle and results in the development of hydrocephalus. As we know, the periventricular area plays a key role in the development and organization of the central nervous system (CNS). The ventricular collapse may disturb the normal development of cerebral structures and lead to the occurrence of various developmental anomalies seen in association with CM-II [40].

The pathophysiology behind the formation of syringomyelia in the context of Chiari malformation is another matter of debate in this entity. There are various theories available in the literature in this regard, but the most acceptable one belongs to Oldfield et al. In his theory, the piston-like movement of cerebellar tonsils within the foramen magnum during each systolic phase (hammering effect) causes an intermittent pressure rise within the spinal cord subarachnoid space and subsequent

induction of CSF permeation through the spinal cord parenchyma. On the other hand, the intermittent arterial pulsation within the closed spinal subarachnoid space enhances this CSF flow from the periphery toward the center of the spinal cord. The accumulation of CSF within spinal cord parenchyma eventually results in the formation of syringomyelia [41, 42].

7.4 Epidemiology

Chiari malformation is traditionally considered a rare anomaly. Its prevalence ranges between 0.5 and 0.7 percent based on cases diagnosed with MRI [43, 44]. However, it seems that the actual prevalence of CM is considerably higher, given the fact that a significant proportion of patients with CM remain asymptomatic throughout their life span and never receive a diagnostic evaluation with MRI. There is a lack of consensus about whether to call the CM-I or CM-II the most common type of Chiari malformation. Nevertheless, it seems that after taking the asymptomatic CM-I patients into account, the prevalence of CM-I considerably outweighs the CM-II. A range of 0.1–0.5 percent can be found throughout the literature for the prevalence of CM-I. The incidence and prevalence of other CM subtypes are not exactly known, but there is no doubt that they are far less common than CM-I and CM-II. Among these, the Chiari malformations type 3, 4, and 5 are extremely rare and almost always lead to the early death of the affected patients.

The initial presentation of CM most frequently occurs during early childhood or adulthood [43]. CM-I patients are rarely diagnosed during infancy and most of them are adolescents or young adults at the time of presentation and diagnosis [45]. Moreover, a considerable proportion of CM-I patients are asymptomatic and diagnosed incidentally. As a result of the more severe nature of the anomaly, the clinical presentation of CM-II tends to occur during infancy or early childhood [46]. However, despite the severity of developmental abnormalities seen in patients with CM-II, it is interesting that only one-third of myelomeningocele patients with the associated CM-II present the signs and symptoms related to Chiari malformation [46].

The vast majority of reports did not show any gender predominance but a few epidemiological surveys reported a slight trend toward female sex, especially among adult patients [17, 47, 48]. Despite the availability of a few case reports in the literature, there is still no high-level evidence supporting the ethnic predisposition or familial background for Chiari malformation [17, 36, 37, 49].

7.5 Signs and Symptoms

The majority of patients with CM-I remain asymptomatic throughout their life, but symptomatic patients tend to present in late childhood and early adulthood [50, 51]. On the contrary, about one-third of patients with CM-II are diagnosed during the

first 5 years of life usually following manifestation of signs and symptoms related to brainstem dysfunction and almost one-third of these symptomatic patients fail to survive [17]. This substantial difference between the clinical presentation of CM-I and CM-II is mainly due to the more complex nature of CM-II and the exacerbating effect of associated hydrocephalus on brainstem compression and cranial nerve traction [46].

An overview of clinical signs and symptoms related to CM is summarized in Table 7.2. Based on our present concept about the underlying pathophysiological mechanisms, we can classify these signs and symptoms into three distinct groups as follows:

Table 7.2 An overview of CM-related signs and symptoms classified by the underlying pathophysiology

Etiology	Sign/Symptom	Classification
CSF flow disturbance at the craniocervical junction	Irritability Over-crying Poor feeding	Infants and younger children
	Headache Cervical pain C2 dermatome dysesthesia	Older children and adults
Compression or traction on the neural structures within the posterior fossa	Ataxia Vertigo Dizziness Downbeat nystagmus	Cerebellar dysfunction
	Central sleep apnea Sinus bradycardia Blood pressure lability	Brainstem dysfunction
	Impaired Gag reflex Difficulty with swallowing Hoarseness Stridor Recurrent aspiration pneumonia Facial paresis Sensorineural hearing loss Diplopia Slurring of speech	Cranial nerve dysfunction
Spinal cord compression or syringomyelia	Sphincter dysfunction Hyperreflexia and spasticity of the lower extremities Ataxia	Spinal cord compression
	Dissociative sensory loss Atrophy of hand small muscles Central cord syndrome Progressive scoliosis	Syringomyelia

7.5.1 Signs and Symptoms Related to the CSF Flow Impairment

Pain, the most common presentation of CM (mostly CM-I) in both pediatric and adult patients lies in this group with 47% of patients complaining of a tussive headache localized to the occipital and upper cervical region and exacerbated by the Valsalva maneuvers such as straining, laughing, sneezing or coughing. This pain is usually transient and in form of short episodes coinciding with episodes of transient ICP rise and subsequent traction on the dura. The association of pain with dysesthesia in the C2 dermatome is common [52, 53]. Due to the inability to communicate, the younger pediatric patients may present with the indirect signs of pain instead, such as irritability, over crying, and poor feeding [54, 55].

7.5.2 Signs and Symptoms Related to the Brainstem and Cerebellar Compression or Traction on the Cranial Nerves

Central sleep apnea is the most common presentation of brainstem compression, especially among CM-II patients. This situation occurs in about 13 percent of pediatric patients and more frequently present in younger children [47, 56, 57]. Cranial nerve dysfunction may occur in about 20% of patients. The glossopharyngeal and vagus nerves are more frequently involved, resulting in impaired Gag reflex, difficulty in swallowing, hoarseness and stridor, and posing the risk of aspiration and subsequent pneumonia. Patients may less commonly present with signs and symptoms related to the dysfunction of other cranial nerves such as trigeminal, abducens, facial, and hypoglossal nerves [57, 58]. Manifestations of cerebellar compression and dysfunction may include downbeat nystagmus, ataxia (more frequently truncal), vertigo, and dizziness [58–60]. Autonomic dysfunction such as bradycardia or blood pressure lability may also occur due to the compression on the medulla.

7.5.3 Signs and Symptoms Related to the Spinal Cord Compression or Syringomyelia

This group consists of an array of signs and symptoms attributable to the involvement of both upper motor neurons (UMN) and lower motor neurons (LMN). UMN-related signs may present as hyperreflexia and spasticity of lower extremities while the signs related to LMN involvement include hyporeflexia and atrophy of the upper extremity musculature. CM patients with concomitant syringomyelia are usually diagnosed at a younger age and earlier in the course of the disease [60]. Syringomyelia is associated with a constellation of signs and symptoms such as (1) a distinct

pattern of a sensory disturbance called dissociative sensory loss with impairment of pain and temperature sensation and sparing of light touch and proprioception (2) central cord syndrome with motor weakness predominantly involving upper extremities (3) significant atrophy of hand small muscles and (4) progressive scoliosis [18, 61, 62]. These sensorimotor signs and symptoms usually occur asymmetrically [63]. Urinary or fecal incontinence can also be seen in CM patients due to the disturbance of pathways related to sphincter function as a result of spinal cord compression or secondary to syringomyelia.

In a different approach, we can classify the most common signs and symptoms of CM based on the patient's age at presentation, given the fact that the dominant manifestations of CM vary among pediatric and adult populations. One cause of this variation is the inability of infants and younger children to communicate and complain, which results in the more tendency of this age group to present with brainstem-related signs rather than subjective symptoms such as pain [64]. Therefore, the most common presenting signs during infancy are central apnea, quadriparesis, opisthotonos, hypotonia, developmental delay, and weak crying. Children aging 1–3 years are commonly diagnosed following the occurrence of lower cranial nerve-related signs and symptoms such as stridor, aspiration, hoarseness, choking, poor feeding, and failure to thrive. In older children, the signs and symptoms are less life-threatening, slowly progressive, and more frequently include pain and spinal cord related signs and symptoms such as motor weakness, spasticity, and disequilibrium [17].

7.6 Associated Disorders

Abnormalities associated with CM can be divided into two distinct groups. The first group consists of abnormalities caused as the result of the same underlying pathophysiological processes responsible for CM such as hydrocephalus and scoliosis. These abnormalities are in fact a presentation of the Chiari malformation and/or concomitant syringomyelia. Hydrocephalus is more commonly associated with CM-II while only 4–18% of CM-I patients demonstrate hydrocephalus. The mechanism behind the development of hydrocephalus seems to be the CSF flow disturbance at the craniocervical junction or the fourth ventricle outlet [17, 53]. Scoliosis is often diagnosed in the presence of syringomyelia and its prevalence is estimated as 18% in a large series of pediatric patients with CM-I [53]. Levoscoliosis (curve apex toward left) can be an indicator of the simultaneous presence of CM and syringomyelia while dextroscoliosis is generally thought to be idiopathic [53, 65]. In an interesting study performed to compare scoliotic features between CM-I patients with and without syringomyelia, atypical features such as levoscoliosis, severe curves, and presence of neurological deficits were significantly more common among patients with CM-I and syringomyelia [66]. There is also a long list of developmental brain anomalies associated with CM-II as the result of ventricular system collapse and subsequent compromise in the orchestrating role of the periventricular area in the process of normal brain development and organization. Callosal

agenesis, polygyria (abnormality of the cerebral cortical organization), large massa intermedia, and absence of septum pellucidum are a few examples of these associated developmental anomalies [67].

Another group of associated disorders consists of primary disorders with a probable role in the pathogenesis of CM. Such disorders are mainly associated with CM-I. Atlantoaxial instability is one of these abnormalities and there are reports of significant instability in a considerable proportion of CM-I patients acting as an underlying cause for the development of CM [68, 69]. Basilar invagination (BI) is another anomaly that is commonly associated with CM-I [25]. BI may present with underdevelopment of occipital bone that can cause posterior fossa overcrowding and development of CM-I [70]. In a different theory, the atlantooccipital instability associated with BI can lead to the occurrence of CM-I, as described earlier. However, the mechanism behind this association is still unknown and the occurrence of these two developmental anomalies can be independent and unrelated to each other [71–73]. Craniosynostosis involving lambdoid sutures can interfere with the normal development of the occipital bone and result in the formation of a small posterior fossa leading to herniation of the cerebellar tonsils. This synostosis may be nonsyndromic or occur in the context of craniosynostosis syndromes such as Crouzon, Pfeiffer, Apert, or Kleeblattschadel syndromes [17, 74]. Disorders resulting in hyperostosis such as Paget's disease and bone mineral deficiency syndromes such as familial vitamin D resistant rickets can also be associated with CM-I, as a result of anomalous skull development [75].

7.7 Diagnostic Studies

In the diagnostic evaluation of patients with suspected CM, investigations should be focused on developmental anomalies that lie within the CM-related spectrum of disorders as well as searching for space-occupying lesions or other primary causes that may cause secondary herniation of neural structures mimicking the CM. Like many other neurosurgical disorders, the diagnostic armamentarium for CM has evolved significantly throughout time especially with the advent of MRI and its derived modalities. Here, we try to briefly mention all the available diagnostic tools that can be of any help in the diagnosis of widespread abnormalities associated with CM.

7.7.1 Plain Radiography

Despite the significant role of plain radiography in the diagnosis of CM-related posterior fossa bony malformations before the advent of computed tomography (CT), today with the widespread availability of MRI it does not have a key role in the diagnosis of CM. However, static and dynamic cervical radiographs can still be of significant help in the detection of underlying craniocervical instability or associated

bony anomalies such as C1 assimilation, basilar invagination, or Klippel-Feil fusion anomaly [76, 77]. Moreover, spinal radiographic evaluation is still a mainstay in the morphological assessment and surgical planning of patients with scoliosis.

7.7.2 Ultrasound Studies

The role of ultrasonography in the diagnosis of CM is mostly during the prenatal period with some characteristic patterns described for early intrauterine detection of CM-related anomalies. The so-called "lemon sign" refers to the concave (instead of convex) formation of frontal bones due to maldevelopment of the supratentorial ventricular system and consequent resemblance of the fetal skull to a lemon (Fig. 7.2a). The classic "banana sign", is another ultrasonographic view that is seen due to the presence of a malformed and caudally displaced cerebellum and the absence of a visible cisterna magna as if a banana lies within the posterior fossa (Fig. 7.2b). These two characteristic signs are specific to CM-II [78]. Other findings such as a low-lying tentorium and torcular herophili or detection of an overcrowded and small posterior fossa can also point to the diagnosis of CM.

7.7.3 Computed Tomography (CT)

The posterior cranial fossa is surrounded by a high density of bony structures This anatomical characteristic results in a significant bone-related artifact and consequent decrease in the accuracy and reliability of CT for detection of neural

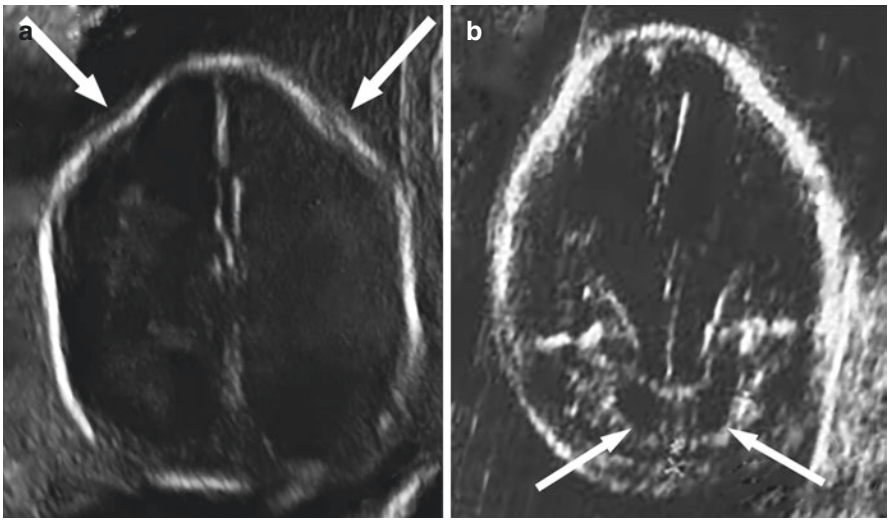

Fig. 7.2 Antenatal cranial ultrasonography depicting the lemon sign (**a**) and banana sign (**b**) in a fetus with CM-II

developmental anomalies within the posterior fossa. However, CM-associated supratentorial abnormalities such as hydrocephalus or corpus callosum agenesis can be more accurately diagnosed with CT scanning. CT can be the modality of choice for detection of CM-related bony malformations (mostly related to CM-II) such as the widening of the foramen magnum, shortening of the clivus, and Luckenschadel skull (lacunar dysplasia of cranial vault associated with CM-II) [79]. Furthermore, in the case of any contraindication or unavailability of MRI, CT-myelography with an intrathecal injection of iodinated contrast material can alternatively be used as the main tool to assess CSF spaces and the location of cerebellar tonsils at the craniocervical junction [80].

7.7.4 Magnetic Resonance Imaging (MRI)

Similar to most other disorders of the CNS, the diagnostic method of choice for CM is MRI. Cranial and spinal MRI benefiting from a high spatial resolution can effectively detect herniation of neural structures and other anomalies associated with CM such as syringomyelia, hydrocephalus, effacement of craniocervical CSF spaces, etc. Diagnosis of CM-I is based on the detection of tonsillar herniation through the foramen magnum with or without associated syringomyelia. Various amounts of tonsillar descent related to the McRae line (a line drawn anteroposteriorly at the level of foramen magnum on sagittal image) are reported as the diagnostic threshold for CM-I. The herniation of cerebellar tonsils 2 mm or less below the foramen magnum is thought to be physiologic [81]. On the other hand, it is generally accepted that a more than 5 mm descent below the foramen magnum should be labeled as CM-I, and a 3–5 mm descent can be considered as borderline [82]. Nevertheless, there are reports of the physiologic ascend of cerebellar tonsils with increasing age. Therefore, it seems that considering an age-specific threshold as the diagnostic criteria for CM-I will be more appropriate. The suggested age-specific thresholds are >6 mm before age of 10 years, >5 mm for ages 10–30 years, >4 mm for ages 30–80 years, and > 3 mm for ages more than 10 years [76, 80]. Despite the key role of quantifying the amount of tonsillar descent in the CM-I diagnostic criteria, studies have shown that there is no significant correlation between the amount of descent and the natural history or the severity of clinical presentation. Rather, the morphology of tonsillar tip seems to be significantly associated with the clinical course of CM. Tonsillar pegging with a pointed morphology of the tonsillar tip is presentative of a more severe underlying pathology and therefore is related to more severe symptomatology compared to round and blunt configuration of the tonsillar tip [83, 84].

The diagnostic landmarks for CM-II are more complex and include various CNS anomalies other than the presence of myelomeningocele. Elongation of the medulla and downward displacement of Obex (i.e., a point representative of the most caudal region of the fourth ventricle floor where the fourth ventricle potentially communicates with the central canal of the spinal cord) are among the key diagnostic criteria for CM-II. As a result of downward displacement of the medulla and relative immobility of the spinal cord due to the presence of denticulate ligaments, a medullary

kink may be seen in the upper cervical region of patients with CM-II. The presence of this sign usually coincides with a more severe clinical presentation [17]. "Tectal beaking" is another associated anomaly seen in MR images of patients with CM-II and includes the fusion of superior and inferior colliculi located on the quadrigeminal plate and the formation of a tectal beak pointing posteriorly.

Syringomyelia, as a CSF-filled cavity within the spinal cord, is more commonly associated with CM-I and can be seen in almost 65% and 40% of CM-I and CM-II cases, respectively. It is more frequently seen in the cervical or cervicothoracic spinal cord, but the formation of a holocord syrinx in the context of CM is not rare [43, 85]. Interestingly, it is shown that the amount of tonsillar descent is not correlated with the incidence and severity of syrinx formation [86].

Diffusion Tensor Imaging (DTI), a relatively newer MR-based modality, can demonstrate the compression and dysfunction of white matter tracts within the medulla and can be used to evaluate the efficacy of surgical decompression by comparing pre and post-operative status of diffusion through these tracts [87, 88].

7.7.5 CSF Flow Studies

CSF flow disturbance at the craniocervical junction plays a pivotal role in the pathophysiology and symptomatology of CM. Therefore, many efforts have been made to investigate the CSF flow patterns and use them as a guide for the optimal management of patients with CM. Cardiac-gated phase-contrast MRI (also called Cine-MRI) is a dynamic modality, which can demonstrate the presence and velocity of flow through CSF pathways in the axial and sagittal planes [89]. Despite the availability of evidence supporting the correlation between improvement of CSF flow following decompressive surgery and clinical improvement [90, 91], the role of preoperative CSF flow studies in determining the indication of surgery and the optimal surgical approach is unknown. Results of clinical studies show that there is no significant correlation between findings of Cine-MRI and clinical presentation of patients with CM [91–95]. Also, the interobserver reliability of Cine-MRI in the evaluation of CM patients is considerably low and it is only in the cases with severe disturbance of CSF flow that its reliability reaches an acceptable level [93]. Therefore, it seems that preoperative Cine-MRI is not a crucial and even beneficial step in the diagnostic pathway of CM.

7.7.6 Electrophysiological Studies

Brainstem auditory evoked potential (BAEP) evaluates the integrity and function of the auditory nerve and pathways within the brainstem and is a useful evaluation tool for CM especially CM-II. These patients usually demonstrate abnormalities of BAEP due to compression and displacement of the brainstem and resultant traction

applied to the eighth cranial nerve. The BAEP can be a landmark to determine the efficacy of surgical decompression and to follow the course of postoperative improvement, but its application as a preoperative diagnostic tool is not widely accepted [96, 97].

7.8 Management

The mainstay in the management of CM is universally accepted to be surgical intervention. Indications for surgery and management protocols vary between patients with CM-I and CM-II. It seems that the occurrence of brainstem-related signs and symptoms in patients with CM-II is more probably due to elevated ICP and intrinsic medullary dysfunction rather than direct mechanical compression of the medulla. Therefore, unlike in cases with CM-I, the surgical foramen magnum decompression (FMD) is not the first intervention in patients with CM-II [98]. The initial management step for symptomatic patients with CM-II should be relieving the underlying hydrocephalus. This could be done using different available CSF shunting techniques or by performing an endoscopic third ventriculostomy (ETV). In cases with persistence or relapse of symptoms following appropriate surgical management of hydrocephalus, a careful reevaluation should be performed to rule out any shunt malfunction of ETV failure leading to recurrence of hydrocephalus. If this was the case, a shunt revision or redo ETV should be planned. Otherwise, two different management approaches can be followed. The first approach includes providing supportive care such as performing a tracheostomy and/or gastrostomy to temporarily relieve feeding and breathing difficulties. Supporters of this more conservative approach believe that many patients with CM-II will experience a significant improvement of their symptoms over time and this approach can prevent many of these patients from being surgically treated with unnecessary FMD procedures [98, 99]. Alternatively, these patients can be managed with FMD in case of presenting severe, life-threatening signs and symptoms. The decision of which approach to proceed with should be made on a patient by patient basis.

Indications for surgical intervention in patients with CM-I is still controversial. However, there are a few more generally agreed on indications to take into account while making therapeutic decisions. The simultaneous presence of syringomyelia with CM-I seems to be one of the most accepted indications [100]. Although there are few reports of spontaneous resolution of syringomyelia in patients with CM-I, the likelihood for the development of irreversible neurological deficits following conservative management of syringomyelia is more than the probability of spontaneous syrinx resolution [51, 101, 102]. The presence of significant symptoms attributable to CM-I is another almost generally accepted indication for surgical intervention. These signs and symptoms may include tussive Valsalva-induced headaches, progressive scoliosis, neurological deficits caused by compression of neural structures at the level of the foramen magnum, and signs or symptoms related to the dysfunction of cranial nerves [103]. Therefore, asymptomatic patients or

patients presenting with mild or borderline signs or symptoms and also without radiological evidence of syringomyelia can be conservatively managed with close follow-up [47, 104]. It is shown that these conservatively managed patients have the chance to gradually improve over time with significant radiological evidence of tonsillar ascent [104]. Nevertheless, the development or exacerbation of any signs and symptoms attributable to CM-I during the follow-up period or detection of significant syringomyelia in the follow-up imaging studies is an indication for prompt surgical intervention with FMD.

In CM-I patients with concomitant hydrocephalus, it is crucial to determine whether the hydrocephalus is a primary etiology or a secondary outcome of CM-I. Clarification of this relationship between tonsillar herniation and hydrocephalus may guide the clinician to cautiously select the appropriate management approach. However, this can be a challenging matter without having the patient's complete clinical and radiological history arranged in chronological order.

The main goal of surgery in CM is alleviating the compression and restoring the normal CSF flow at the craniocervical junction [105]. FMD is thought to eventually lead to tonsillar ascent and reversal of pathological processes responsible for the syrinx formation through the restoration of normal CSF pulsations at the craniocervical junction and the enlargement of cisterna magna [106]. One of the challenging entities for neurosurgeons who manage patients with CM is the selection of the most appropriate surgical technique for FMD with the highest efficacy in relieving patient symptoms and least recurrence and complication rates [55, 107]. Traditionally, the most widely accepted and known technique is FMD followed by dura opening and eventually performing an expansile duraplasty using pericranial autograft, allograft, or synthetic dura substitutes. Other intradural interventions such as reduction, coagulation or subpial resection of cerebellar tonsils, arachnoid adhesiolysis, or fenestration of arachnoid webs compromising CSF outflow through the outlet of the fourth ventricle may also be performed during this approach based on the neurosurgeon's preference and intraoperative observations. In an attempt to provide a list of abnormal intradural findings in CM patients who underwent FMD, Dlouhy et al. presented an array of intradural abnormalities that may have a significant role in the CSF flow disturbance and may need to be addressed during FMD. Almost all of these abnormalities eventually cause significant obstruction of foramen Magendie as the main outlet of the fourth ventricle and include (but are not limited to) adhesion of tonsils to each other by arachnoid bands, medial displacement of bilateral posterior inferior cerebellar arteries (PICAs), and presence of arachnoid veils [108]. Manipulation of intradural structures with the aim of restoring normal CSF flow is of paramount importance in these cases.

Given the fact that FMD with duraplasty can be associated with significant complications (mostly CSF-related such as CSF leakage, pseudomeningocele formation, and aseptic meningitis), more conservative dura-sparing surgical techniques are introduced by neurosurgeons with the aim to reduce the complication rates. In these non-dura-opening approaches, foramen magnum bony decompression may be performed alone or in conjunction with resection of atlantooccipital ligament or dura-splitting (i.e., resection of the outer layer of dura while leaving the inner layer

intact). A neurosurgeon should weigh the risks of missing and therefore not alleviating an intradural pathology against the potential benefit of less complication rate while choosing these less invasive approaches. There are original studies as well as reviews available in the literature that compared the benefits and drawbacks of these more minimal approaches with conventional FMD plus duraplasty technique [105, 109–113]. In a metanalysis, FMD alone without any manipulation of dura was associated with lower complication rates, but also significantly higher recurrence rate and need for reoperation compared to FMD plus duraplasty approach among pediatric patients [114]. Considerable efforts are made to better identify patients with more probability of recurrence following the implementation of these dura-sparing techniques such as using preoperative CSF flow studies and/or utilization of intraoperative ultrasonography to ensure the adequacy of decompression. Despite some reported benefits of these evaluation techniques, they yet failed to form a standard diagnostic approach to be generally used by neurosurgeons during the selection of surgical technique [109, 115–118]. There are some reports of more favorable outcomes for foramen magnum bony decompression with or without dura-splitting among pediatric patients compared to their adult counterparts. Different characteristics of pediatric tissue, such as more elasticity of dura matter, allowing it to expand and form an enlarged cisterna magna may be the underlying cause of this finding [119–122]. We have performed a systematic review and meta-analysis of the available data in the literature regarding the clinical and radiological outcomes following implementation of the dura-splitting technique in the management of pediatric patients with CM-I and compared these outcomes to the ones for conventional FMD plus duraplasty technique, but the results are not published yet and we present our findings here for the first time [123]. After performing data extraction on eight eligible studies including a total number of 615 pediatric CM-I patients, the meta-analysis revealed no statistically significant difference between two surgical techniques regarding recurrence rate and clinical or radiological outcome measures. Moreover, the use of the dura-splitting technique was significantly associated with less complication rate, shorter hospital stay, and also less operation duration. These interesting findings highlights the effectiveness and safety of less invasive surgical approaches, especially the less known dura-splitting technique in the management of pediatric patients with CM-I. As we previously mentioned, there is more resistance among neurosurgeons against the implementation of non-dura-opening techniques in the management of adult CM-I patients due to the availability of reports regarding more recurrence and reoperation rates related to these techniques in the adult population [124]. Despite this significant tendency toward implementation of FMD plus duraplasty technique in the adult population, the available evidence in the literature does not support the superiority of the duraplasty technique in adult patients. The results of our recently published systematic review and meta-analysis on adult patients with CM-I revealed that clinical and radiological outcomes of the dura-splitting technique are similar to the conventional duraplasty technique. Interestingly, the complication rates (both CSF-related and infections), intraoperative blood loss, and operation duration were all significantly in favor of the dura-splitting technique [125]. Therefore, it seems that neurosurgeons should be more

open to newer, less invasive surgical techniques such as dura-splitting technique even for the management of the adult patients.

A completely different surgical management of patients with CM-I is suggested by Goel et al. based on the proposed theory that C1/C2 instability plays an important pathophysiological role in the development of CM-I. This theory suggests that herniation of the tonsils through the foramen magnum happens as a natural response to the intrinsic atlantoaxial instability to protect the spinal cord from getting damaged at the level of instability by forming a so-called "nature's airbag". Therefore, stabilization of the C1/C2 facet joint via instrumentation and fusion without performing any posterior fossa decompression may reverse this process and result in the clinical and radiological improvement of CM-I. Although few studies support this surgical approach and the theory behind it, more high-level evidence is still needed to approve and accredit this therapeutic approach [126–128].

Syringomyelia usually regresses following management of CM with FMD [55]. In rare cases in which there is no significant clinical and radiological improvement following FMD and thinning of spinal cord parenchyma and/or obliteration of spinal subarachnoid space is evident in the follow-up studies, a direct surgical approach to the syrinx such as fenestration of syrinx cavity or placement of a syrinx-subarachnoid shunt should be considered as an option [129].

Although the technical details of FMD are out of the scope of this chapter, we tried to provide a brief explanation of our surgical technique here. This operation is best performed in a prone position. We prefer to place the head on a horseshoe headrest for patients younger than 2 years old and fixating the head in a 3-pin Mayfield head holder for older patients in a slightly flexed position. The incision extends from the inion to the palpable spinous process of the C2 vertebra. Dissection between bilateral musculature continues through the avascular plane at the midline. After adequate exposure of the occipital bone and C1 posterior arch, a small craniectomy measuring about 2 × 2 cm in diameters is made using a high-speed drill. The posterior margin of the foramen magnum and a 2 cm wide midline portion of the posterior arch of C1 is then resected using a small-tip rongour. We prefer using the dura-splitting technique in the management of CM-I patients. We superficially incise the dura in a Y-shaped fashion and then bluntly peel and resect the outer layer of the dura away from the incision line under an operative microscope taking care not to inadvertently compromise the integrity of the inner layer of the dura. In our experience, this procedure can be performed with a minor blood loss and significantly shorter operation time compared to the more time-consuming duraplasty technique.

7.9 Complications

The most common complications following FMD decompression are CSF-related complications such as CSF leakage, pseudomeningocele formation, and aseptic meningitis. Among these, the CSF leakage through suture lines is the most common

and poses patients to a higher risk of postoperative CNS infection and therefore should be managed promptly [43]. The formation of pseudomeningocele may not be of significant clinical importance by itself, but some reports indicate the role of CSF egress into the pseudomeningocele on impairing the resolution of syringomyelia [130]. Although these complications can be prevented by meticulous dura and wound closure, these measures fail to provide an effective seal in patients with concomitant elevation of ICP and hydrocephalus. Therefore, the first step of management is to evaluate the patient for the presence of hydrocephalus and to manage it properly with the placement of a CSF shunt system or performing an ETV [28, 131, 132]. In the case of the absence of hydrocephalus, adding more skin sutures and/or placement of a lumbar drain usually stop the leakage.

Hemorrhagic complications may also occur due to inadvertent damage to arterial or venous structures and unfortunately, contamination of intradural spaces with blood may result in more subarachnoid scar formation and therefore higher recurrence/reoperation rate. Intraoperative arterial bleeding may occur as a result of injury to PICA during dissection and manipulation of cerebellar tonsils or due to injury to the vertebral artery during exposure and resection of the posterior arch of the C1 vertebra. These complications can be avoided by using careful microscopic sharp dissection techniques and by limiting the bony exposure to a 2 cm wide midline corridor [133]. Because of the common patency of dural sinuses such as occipital and circular sinuses in children, significant venous bleeding may happen in pediatric patients during dura opening. This can be avoided by applying a small-sized incision on the dura, expanding it gradually, early identification of dural sinuses, and prompt control of these sinuses using occluding sutures or by application of temporary clips.

Delayed occipitocervical instability is another complication of FMD. This complication may occur as a result of injury to the C2 lamina or disconnection of the muscular insertions to the C2 vertebra during dissection and resection of the posterior arch of C1. Therefore, care should be taken not to damage C2 and its surrounding musculature during exposure [134, 135].

The occurrence of focal neurological deficit following FMD even in the case of total resection of tonsils is rare and is not a significant concern with the availability of microsurgical tools and techniques in the modern era. The postoperative infection may still be considered as a probable cause of morbidity following FMD. There is almost no doubt that the infection rate is significantly higher among patients that undergo dura-opening surgical techniques (15% in duraplasty vs 4% in dura-splitting techniques), similar to the CSF-related complications mentioned earlier [125].

7.10 Outcomes and Prognosis

So many efforts are made to develop an objective method to standardize and quantify the preoperative and postoperative clinical and radiological status of patients with CM. The introduction of multiple scoring systems is the result of these efforts.

However, none of these scoring systems are widely utilized and thoroughly investigated and therefore their validity and consistency are still unknown [136–138].

Although most CM patients experience a favorable outcome and significant clinical improvement following FMD, there is also a probability for stabilization or worsening of clinical status. In our review, 64% of pediatric CM-I patients experienced clinical improvement while the rate of postoperative clinical deterioration was estimated at 7.4%. The most improvement is seen with headache [43, 58, 60]. Typical CM-specific headaches will improve postoperatively with a low recurrence rate, but the non-CM-related headaches tend to persist following FMD [53]. Signs and symptoms of a cranial nerve or brainstem dysfunction improve considerably over a few months in pediatric patients (73.6%) but this improvement less probably happens in adult patients [53, 125, 139]. Mild and moderate scoliosis tends to stabilize or improve following FMD in children younger than 10 years [53, 140]. Patients with CM-I have an overall lower cognitive performance compared to their healthy counterparts and this cognitive deficit usually does not significantly improve following surgical management [141]. In efforts made to predict the postoperative clinical course of CM patients, it is shown that preoperative morphology of the posterior fossa does not have a prognostic value determining the clinical outcome [142], but there is a significant correlation between the amount of increase in the posterior fossa volume or enlargement of cisterna magna and improvement of clinical symptoms especially headache [143].

There are many different rates reported in the literature for the recurrence/reoperation of pediatric patients with CM-I. Few examples of these reported rates include 43.8% for patients younger than 3 years and 12% for patients less than 6 years old [45, 64, 144]. A reason for this wide range of recurrence rates reported in the literature is that due to the relative rarity of CM-I in younger children, most of these rates are derived from small case series. However, in our recent review on 615 pediatric CM-I patients with ages less than 18 years, this rate was estimated to be 8.7%.

Complete resolution or size reduction of syringomyelia occurs in 73–85% of patients following surgical decompression. Nevertheless, even in these cases, there is a probability of recurrence over years and therefore a long-term follow-up is necessary to sooner diagnose these late recurrences [53, 145, 146]. As the results of our recent review indicate, postoperative stabilization or progression of syringomyelia may occur in 25% and 21% of cases, respectively. This failure in radiological improvement is probably due to the presence of any occlusion at the outlet of the fourth ventricle that is not addressed during FMD [147].

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Chapter 8
Encephaloceles

Elie Hammam, Sarut Chaisrisawadisuk, Mark H. Moore, and Stephen Santoreneos

8.1 Definition/Introduction

Encephalocele is a herniation of the brain and meninges through a cranial defect, occurring in 0.8–5.6 per 10,000 live births [1] and whilst uncommon, it represents a common form in the family of neural tube defects.

The terms **cephalocele** and **encephalocele** are used almost interchangeably in the neurosurgical literature. Nevertheless it is important to understand the differences between the two. **Cephalocele**, is an umbrella term that defines a congenital defect in the cranium with variability of herniated intracranial contents. If the pathological contents of the cephalocele consist of arachnoid and cerebrospinal fluid, it is referred to as cranial **meningocele**. If the defect contents further include cerebral and/or cerebellar tissue, at times ventricular extension and choroid plexus, it then becomes a **meningoencephalocele** [2]. They are often sporadic, but the occipital form may be part of a genetic malformation syndrome [3]. The term **encephalocele**

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has been used to include both primary congenital defects; but is also seen in secondary causes following events such as surgery, trauma or a facial cleft [4]. In this chapter, relevant to paediatric neurosurgery we will only focus on congenital malformations.

In addition to contents, classification may be on the basis of anatomical location of the bony defect. The aperture through which the encephalocele emerges is generally situated along a suture or at a junction of several bones. However on some occasions it occurs at the junction where the ossification centres meet in forming the vault [5]. If the hernia is positioned between the bregma and the anterior margin of the ethmoid bone, it is referred to as a frontal or sincipital cephalocele (Fig. 8.1), whereas, an ethmoidal and sphenoid bone hernia is considered a basal cephalocele (Fig. 8.2). If the cephalocele falls between the lambda and the foramen magnum, it is called an occipital cephalocele and variants extending caudally to the cervical spine are then appropriately called occipitocervical (Fig. 8.3). Parietal encephalocele are those occurring between the lambda and bregma. Subclassification of each category will be further detailed below.

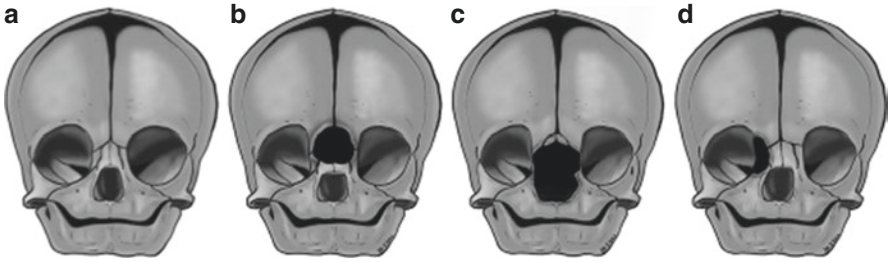

Fig. 8.1 Schematic representation of normal neonatal skull development and the three types of sincipital encephaloceles. (**a**) Normal neonatal skull with absent defects. (**b**) Frontonasal cephalocele demonstrating external defect between frontal and nasal bones. (**c**) Nasoethmoidal cephaloceles illustrating the defect between nasal bones and upper lateral cartilage. (**d**) Nasoorbital cephalocele showing the medial orbital wall defect for sac herniation. (Figures illustrated by Dr Zameer Gill)

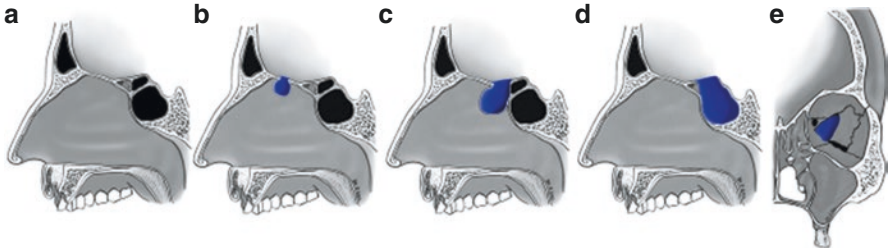

Fig. 8.2 Schematic representation of basal encephalocele. (**a**) Normal anterior cranial fossa development. (**b**) Trans-ethmoid cephalocele demonstrating external defect through the lamina cribrosa. (**c**) Spheno-ethmoidal cephalocele illustrating the defect between sphenoid and ethmoid bones. (**d**) Transphenoidal cephalocele showing the defect through the body of the sphenoid bone. (**e**) Sphenoorbital cephalocele in a coronal illustration showing the defect exiting through the medial orbital wall. (Figures illustrated by Dr Zameer Gill)

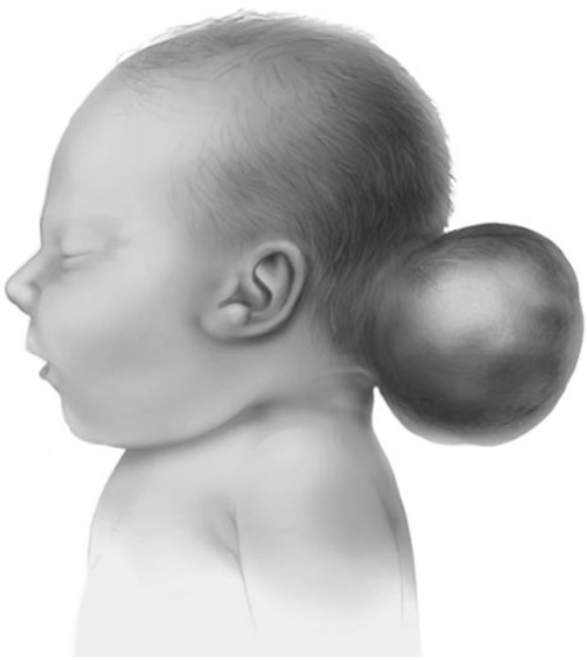

Fig. 8.3 Schematic representation of an occipital encephalocele. (Image adjusted from original illustration published by Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities)

At the external opening of the cranial defect, the dura usually blends into the periosteum of the skull. In some instances however, the cephalocele may be completely enveloped by dura. More superficially, the external surface may be protected by skin overlying the head or, based on anatomical location, the mucous membrane lining the nasal and sinus passageways.

8.1.1 Prevalence and Inheritance

The most significant difference in the prevalence of subtypes of cephaloceles are in relation to ethnicity. For example, in Australians of European heritage, majority (two-thirds) of cephaloceles were of occipital location, with only 2.2% sincipital (frontal) encephaloceles [6]. This was also true in North America and Western Europe, where approximately 85 percent of encephaloceles take the occipital form [7]. On the other hand, patients from Southeast Asia, parts of Russia, and central Africa mostly developed sincipital encephaloceles rather than the occipital type [8].

The causal relationship between maternal folate levels and incidence of encephaloceles is not evident [9, 10]. Several environmental risk factors have been proposed but most are either weakly correlated or still a matter of debate without certainty [9]. For example, low socioeconomic status, along with advanced maternal age may be associated with risk of anterior encephaloceles [11]. However, higher economic status and advanced paternal age are associated with higher incidence of occipital encephalocele [9]. To date, most studies have not found an association with maternal age [8, 9].

A role for genetic contribution is supported by its association with a number of autosomal recessive syndromes. For example, Meckel's syndrome, an autosomal-recessive disease, consisting of occipital encephalocele, polydactyly, holoprosencephaly, micro-opthalamia, and orofacial clefts amongst other systemic anomalies. Another example includes frontonasal dysplasia which manifests frontal encephaloceles. Isolated, non-syndromic encephaloceles are largely sporadic with no familial association.

Other general neurological anomalies associated with cephaloceles include agenesis of the corpus callosum, optic nerve abnormalities, craniosynostosis, Chiari malformation, Dandy-Walker Malformation and myelomeningocele. The prevalence of hydrocephalus varies with the location of the encephalocele. Whilst it has a lower incidence rate (10–15%) in the frontal type, it is relatively common in occipital encephalocele, with series reporting between 60% to 90% prevalence [12–14]; though largely occurring following hernia repair rather than a neonatal presentation.

8.1.2 Sincipital Encephaloceles

This type has been recognised since mid-nineteenth century. During the early era, Mesterton in 1855 classified the sincipital hernias of the brain into nasofrontal, naso-ethmoidal, and naso-orbital subgroups, according to the locations of the external skull defects. In 1890, von Meyer reported a case and published the same classification [15]. In 1903, Stadfeldt called all three forms of sincipital encephalomeningocele by the general name "fronto-ethmoidal" and gave the following reason: "because it is generally characteristic of all these groups that there is inside the cranium an internal orifice of the hernia distinguishable between the frontal bone and the ethmoid." However, many reports are still using the confusing nomenclature. Suwanwela et al., in 1972, studied 12 post-mortem fronto-ethomoidal encelphalomenignocele (FEEM) skulls and more clearly defined the abnormal anatomy of FEEM by its external defects [16].

The internal defect was almost always at the foramen cecum which is the junction between frontal bone and ethmoid bone, anterior to the crista galli and cribriform plate (Fig. 8.4). The encephalomeningocele mass will protrude through this hole externally causing various external defects. If the external defect is between frontal and nasal bone, it will be defined as frontonasal type. If it is between nasal bone and upper lateral cartilage, it is nasoethmoidal type. Lastly if the defect is at medial orbital wall, it is naso-orbital type (Fig. 8.1) [16].

8.1.3 Basal Encephalocele

Basal encephaloceles are malformations in skull base with neural tissue herniation. Most prevalent in South-East Asia, basal encephaloceles are the least common type, with an incidence as low as 1.5% [2, 17]. Like sinicpital encephalocele it has

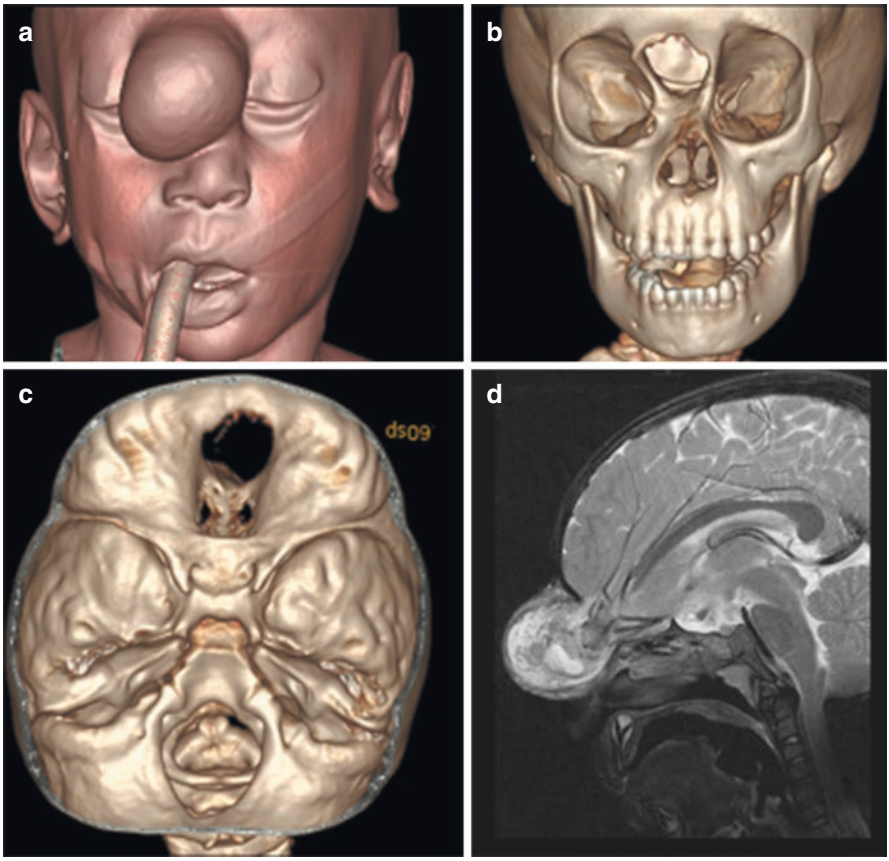

Fig. 8.4 (**a**) Soft tissue reconstruction on 3D CT of a child with sincipital encephalocele. (**b**) 3D CT reconstruction of the skull demonstrating the frontal defect and its associated medial telecanthus. (**c**) intracranial reconstruction of the same scan showing the internal defect centred between the frontal and ethmoidal bones. (**d**) Magnetic resonance imaging (MRI) sagittal section showing the frontoethmoidal meningoencephalocele with the anterior cerebral arteries in the contents of the sac

multiple subtypes, and classified based on the site of herniation [18]. The four subclassifications of basal encephalocele include:

1. *Spheno-ethmoidal*—it describes the herniation of cranial contents through the sphenoid and ethmoid bone into the posterior nasal cavity.
2. *Trans-sphenoidal*—is the herniation through the body of sphenoid bone into the sphenoid sinus or epipharynx.
3. *Spheno-orbital*—it depicts the herniation through the superior orbital fissure or osseous defect into the orbit.
4. *Trans-ethmoid*—it relates to herniation through the lamina cribrosa (cribiform plate) into the anterior nasal cavity.

Characteristic anomalies coexisting with anterior basal defect are frequently seen affecting the face, optic system and CNS. They may be associated with midline

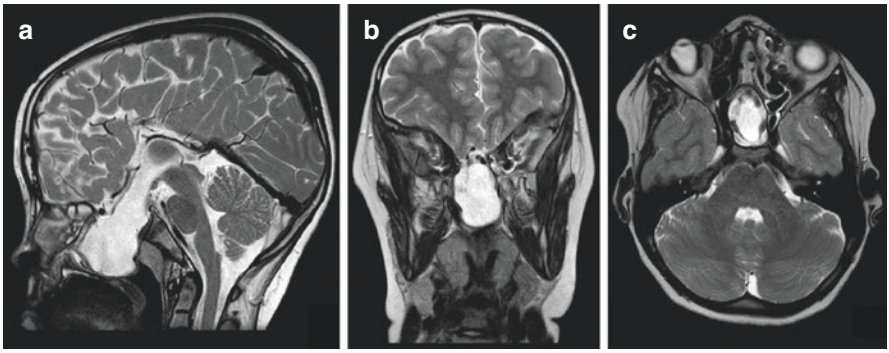

Fig. 8.5 Magnetic resonance imaging (MRI) of a child with basal encephalocele (sphenoethmoidal). (**a**) Sagittal section showing the cephalocele resting on the soft and hard palate. (**b**) Coronal view of the T2-weighted image. (**c**) Axial view of the MRI demonstrating the extent of the caudal herniation of the sac and its relationship with surrounding structures

abnormalities, including cleft palate, ocular hypertelorism, and craniosynostosis. Whilst it can largely be occult and incidentally diagnosed, symptoms vary according to site and size of location. Owing to the anatomical location, it is reasonable to expect respiratory distress; nasal obstruction (including obstructive sleep apnoea), dysphagia and failure to thrive are a consequence of direct pharyngeal pressure (Fig. 8.5). Other anomalies include pituitary dysfunction and visual disturbance.

8.1.4 Occipital Encephalocele

Occipital cephaloceles vary in size, contents and severity. Whilst the exact etiology remains unknown, it is believed to be a remnant of a separation failure between surface ectoderm and neuroectoderm creating a cranial defect allowing for herniation of intracranial elements. The defected location can vary, and may occur high up the occipital bone or suboccipitally towards the foramen magnum, or in some instances extending caudally to include the cervical spine. Absence of neural tissue is a good prognosticator. However, the sac may include cerebral, cerebellar tissue and other dysplastic neural tissue. In a case series, Simpson et al. [6] examined 34 occipital encephaloceles and reported that 32% contained recognizable cortex, 11% contained cerebellum and fourth ventricular structures, and 20% contained glial nodules. In addition, the brainstem may be partially or completely herniated, whilst the thalami were found in 20% of the cases.

Concomitant anomalies include the falx and tentorium often being in abnormal anatomical position. The intracranial contents shift postero-caudally, leading to herniated components of the diencephalon, or frontal and temporal lobes occupying middle and posterior fossa, respectively, and kinking of the brainstem. As result of the outstretched neural tissue, it creates an anomalous effect on the optic nerve causing stretching, kinking and atrophy [19]. The occurrence of lower occipital

Table 8.1 Classification of the cephaloceles based on anatomical location of the cranial defect as described by Suwanwela et al. [21]

I. Occipital encephalomeningocele
II. Encephalomeningocele of the cranial vault
A. Interfrontal
B. Anterior fontanel
C. Interparietal
D. Posterior fontanel
E. Temporal
III. Fronto-ethmoidal encephalomeningocele
A. Nasofrontal
B. Naso-ethmoidal
C. Naso-orbital
IV. Basal encephalomeningocele
A. Transethmoidal
B. Spheno-ethmoidal
C. Transsphenoidal
D. Frontosphenoidal or spheno-orbital
V. Cranioschisis
A. Cranial--upper facial cleft
B. Basal---lower facial cleft
C. Occipitocervical cleft
D. Acrania and anencephaly

lobe encephalocele with skull base defects and malformations of the cerebellum and lower brainstem characterizes Chiari type III malformations [20].

Outcomes of children with occipital encephalocele will depend significantly on the size and contents of the sac. CSF only sacs, or when containing a small nodule of dysplastic tissue will likely attain normal neurological and developmental outcome. However, the larger the sac and the more neural tissue involved the higher the likelihood of physical impairment and mental retardation. As previously mentioned, occipital encephalocele is significantly associated with hydrocephalus, with a variable rate based on the case series. The presence of hydrocephalus and its effective management may increase the severity of disability [12] (Table 8.1).

8.2 Embryology

Encephaloceles are considered a member of the family of neural tube defects (NTD). Whilst the exact mechanism is not entirely understood, it differs amongst the different types of NTDs. Normally, at approximately 18 days gestation, the central nervous system is a flat sheet of cells (the neural plate) that subsequently undergoes remarkable shape changes by approximately 28 days to form a tube of neural tissue surrounding the fluid space that will eventually become the ventricular system and spinal canal. Defect in the tube formation results in abnormalities throughout all layers, including the central nervous system, axial skeleton, and overlying skin [22].

However, closed skin-covered defects such as encephaloceles, result from aberrant development after neural tube and skin has closed. Therefore encephalocele is considered a post-neurulation disorder and likely occurs by a mechanism distinct from those of the open neural tube defects, generally mesodermal in origin, leading to protrusion of brain and meninges outside the cranial cavity.

The question remains what is the cause of the herniation? Is it primarily from an underdeveloped fusion or secondary from a brain anomaly resulting in high pressure "blow-out phenomenon" of the hernia sac through the weak point? Currently, for the anterior cranial fossa (herniation through foramen caecum), there are 2 theories proposed to explain the cause of sincipital encephaloceles.

8.2.1 Primary Defect at the Foramen Caecum

The anterior cranial base is derived from the neural crest cells. It is formed through endochondral ossification. The early embryologic precursor of the cranial base is a cartilaginous plate, also known as the chondrocranium, which will soon be replaced by bone. Normally, it undergoes progressive ossification from caudal to rostral initiating from numerous ossification centres [23]. In the human neurulation process, the anterior neuropore or primitive frontonasal region, develops in the 3rd week of foetal life. Through the 8th week of life, complex events occur. There are transient gaps. The first one is between frontal and nasal bones, called fonticulus frontalis, and second one between frontal and ethmoid bones, call foramen caecum. In the 4th to 7th week of gestation, a transient dural diverticulum extends through the plain of the foramen caecum, prenasal space and terminates at the skin of the nasal bridge, between nasal bone and upper lateral cartilage. In normal process, the herniated dura will regress. Failure of involution at these sites leads to nasal dermoid cyst, encephalocele or glioma [24].

8.2.2 Secondary to Intracranial Abnormalities

The second theory, is postulated to be pressure related, whereby a pathological process causes a rise in intracranial pressure resulting in out pouching of the dura and part of brain tissue through the weak points around skull sutures and its synchondroses. Many studies have shown the concomitant findings of intracranial anomalies and FEEM. Suwanwela et al. found 3 of 14 patients developing hydrocephalus after operation [25]. David et al. [4] report secondary increase in intracranial pressure after surgery in 2 patients causing secondary encephaloceles. Rojvachiranonda et al., in 2003, found 17% are associated with other congenital brain anomalies. Among those, arachnoid cysts were found 8.7%, ventricular dilatation 4.4%, and porencephaly 4.4% [26]. A study in Philippines showed 37% of other anomalies associated with FEEM including abnormal CSF compartment, arachnoid cysts,

gliotic changes, Chiari malformations, destruction of the orbit and globe, and pressure remodelling of the calvaria [27].

The cranial base is a fusion of the basiocciput, sphenoid, ethmoid, frontal and temporal bones. An evolution of a cartilaginous plate with multiple ossification centres fusing to form the bones. The paired sclerotome cartilages include parachordal cartilages (precursor of basioccipital), hypophyseal cartilages (precursor of basisphenoid), presphenoid (trabecular) cartilages, orbitosphenoid (precursor of the lesser wing) and alisphenoid cartilages (precursor of the greater wing). In most, the front is a single mesethmoid cartilage [28–30]. Similar to the long bone growth plates, the growth centres develop and fuse into a single basal plate—the chondrocranium—which later ossifies in numerous centres. Completion of this ossification continues postnatally.

The exact embryogenesis of the basal encephaloceles, remains unclear. However, the most favourable theory postulates, secondary failure of separation of the neuroectoderm from the surface ectoderm, preventing subsequent development of the mesodermal elements which later form the skull, as the cause of this. Other theories include failure of the ethmoid plate to close around the olfactory nerve, or development failure of ossification centres in the sphenoid bone, or increased intraventricular pressure in the embryonal stage driving the "blow-out" phenomenon through an underdeveloped bone. Finally, another postulated theory is built around the persistence of the craniopharyngeal canal leading the encephalocele through the sphenoid bone [31].

The occipital bone has four primary cartilaginous centres and one membranous centre around the foramen magnum. Occipital encephalocele is unlikely to undergo the same mechanism as the frontal or basal, given the posterior cranium is not of neural crest origin. Instead it may represent defective segmentation of the bones.

8.3 Clinical Presentation

The breadth of the cephalocele subtypes, locations and associated anomalies produces a large spectrum of presenting complaints based on severity of defect. Red flags that all clinicians should be aware of, that lead to urgent treatment include breakdown of overlying skin, CSF leak from the sac, infection and/or meningitis.

8.3.1 Frontoethmoidal Presentations

The "characteristic mass" can vary in size, site, shape, consistency and skin coverage [32]. Whilst it can be as small as 0.5 cm, the lesions are likely to increase with the growing child, resulting in an enlarged skull defect. The large or enlarging sac laterally of a FEEM displaces the orbits creating an associated telecanthus [8]. The sac may be soft, cystic and transparent reflecting the predominant CSF contents.

However, the firmer the consistency the more neural tissue it contains. Finally, the overlying skin can vary in thickness, but also in colour where it is commonly darker than the rest of the face. Lacrimal drainage dysfunction occurs secondary to the distorted and poorly or non-functioning anatomy.

Neurological presentations include seizure and hydrocephalus. Whilst mental retardation and developmental delay is notable it is important to highlight that the majority of the cases will have normal or near-normal development and intelligence. Associated intracranial findings include agenesis of the corpus callosum being frequent, along with arachnoid cysts and porencephalic cysts.

Whilst many are diagnosed at birth, it is not unusual for many to remain undiagnosed until an incidental finding later in childhood or even adulthood. For example, basal encephaloceles can remain occult until diagnosed along with the neuroendocrine dysfunction (hypothalamic and pituitary). It can be associated with visual disturbance secondary to optic chiasm or nerve displacement. Affected patients may also present primarily with respiratory distress, nasal obstruction (including obstructive sleep apnoea), dysphagia and failure to thrive as a consequence of direct pharyngeal pressure

8.3.2 Summary of Key Anterior Presentations

- *Characteristic mass*
- *Telecanthus*
- *Long mid-facial deformity*
- *Epiphora (watering eyes)*
- *Pulsatile sac*
- *Hydrocephalus*
- *Seizures*
- *Intact sense of smell*
- Airway complications

8.3.3 Occipital Presentations

Most are diagnosed either antenatally during screening ultrasound or at time of birth. These encephaloceles are characterised by a posterior midline defect. Site, size and shape, as expected will vary. Site can be high occipital, low occipital or even caudal enough to include the cervical spine. The larger size defects are more likely to be composed predominantly of neural tissue whilst smaller (<2 cm) sacs will likely contain a small nodule and CSF [8]. There is a direct relationship between size of the sac and the neurological deficits as it relates to the degree of neural dysplasia and associated sequelae of intracranial deficits. Hydrocephalus is a common feature of occipital cephaloceles. Other findings include blindness, seizures or developmental delay.

8.4 Diagnosis

The diagnosis is, in many cases, made on prenatal ultrasound or clinically at birth. However, some may be occult, as in many basal encephaloceles and present with complications (Fig. 8.5).

Ultrasonography is the modality of choice in foetal imaging, however, foetal magnetic resonance imaging (MRI) is increasingly being used to study foetal anomalies [33]. Given its high soft tissue resolution, MRI is able to distinguish individual foetal structures and facilitate visualisation of encephaloceles and its associated anomalies [34]. However, MRI can be limited in early gestational age due to foetal size and movement.

Postnatal neuroimaging is a combination of both CT and MRI and are both crucial to understand the defect and characterise the glial and angioarchitecture of the hernia. Computed Tomography (CT) with three-dimensional reconstruction is excellent at defining the bony anatomy and is considered the gold standard for analysis of skeletal variations and defects [35].

On the other hand, MRI is excellent in defining the extent of cerebral and vascular tissue contents within the cephaloceles. In addition, MRI is able to better characterise intracranial anomalies associated with certain cephaloceles (Fig. 8.4). For example, the relationship between basal encephalocele and agenesis of the corpus callosum. Similarly, in occipital encephalocele, when the herniation interferes with the tentorial formation and in turn disrupt venous channel development, causing a persistent falcine sinus and hypoplastic straight sinus [36]. MR-Venogram is required for the diagnosis of the venous anomalies. Arterial contents, such as the anterior cerebral artery (ACA), within the encephalocele is regularly seen, and if not studied appropriately preoperatively, territory infarcts may ensue as a surgical complication [37]. Therefore an MRA is advantageous in studying the arterial supply and contents of the encephalocele and should be acquired before surgery (Fig. 8.4).

8.5 Management

8.5.1 Sincipital and Basal Encephaloceles

In considering surgical management, unless presenting with complications of hydrocephalus, rupture and leakage or infection the repair of encephaloceles are done electively. The aim of the procedure is to remove the encephalocele, correct craniofacial defects and allow a degree of normal facial growth to be re-established (Fig. 8.6). The effect of the encephalocele is best seen as a central bony malformation, and its outcome when left untreated is analogous to the blooming of a flower [38]. As the mass occupies the central region of the midface, and the existing defect and herniated sac grow the frontal bone is displaced rostrally at the nasofrontal buttress, the nasal bones are displaced caudally, and the medial orbital walls are displaced anterolaterally (with the medial canthus being stretched in that direction).

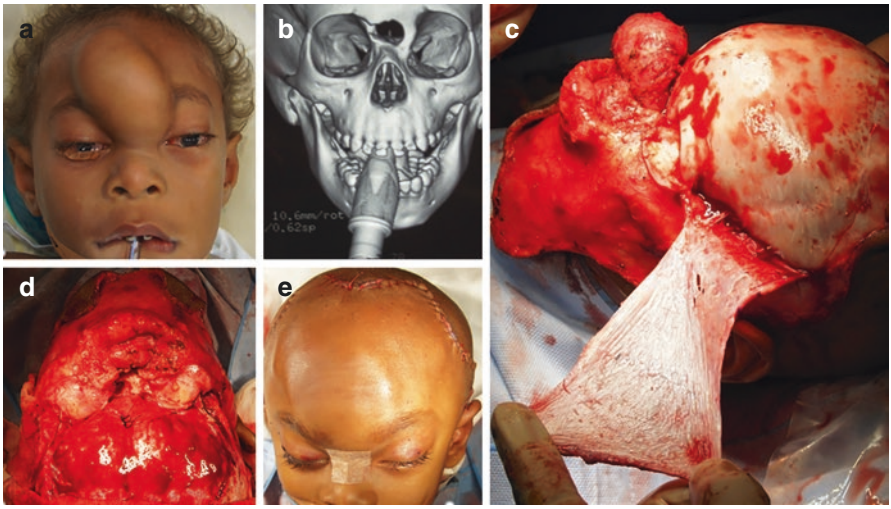

Fig. 8.6 (**a**) Intraoperative photograph of a child with sincipital encephalocele. (**b**) 3D CT reconstruction of the skull demonstrating the frontal defect and its associated medial telecanthus. (**c**) Exposed herniated sac after undergoing a bicoronal scalp flap and elevation of the periosteum. (**d**) Image taken after bifrontal craniotomy has been performed and the sac reduced into intracranial space. Sutures can be seen used to repair the dural defect. (**e**) Immediate postoperative image highlighting the reduced encephalocele

This reflects the distorting influence of the extruded intracranial contents on facial growth [39]. Therefore early correction will limit the changes driven by the forces but also avoid increased risk of damage of the overlying cutaneous layer causing CSF leak, meningitis and secondary herniation (Fig. 8.6).

Therefore the principles of repair and reconstruction consists of:

1. Removal of the herniated mass with dural repair
2. Closure of the bone defect
3. Correction of the medial hypertelorism by medial orbital translocation and canthopexy
4. Additional corrective rhinoplasty

There are at 2 common approaches to surgical correction of frontal encephalocele:

1. Transcranial (open)—*most common*
2. Transnasal (Endoscopic)

In the open approach, originally the operation was divided into two stages. The first was mainly done for closure of the bony defect and excision of the herniated mass. This was followed by the second operation to correct the telecanthus (medial hypertelorism) and facial deformity [6]. However, Mahatumarat et al., in 1991, proposed a single stage extracranial repair and reconstruction [40], later further modified to the MOCUT technique proposed by Boonvisut in 2001. This is a single-stage

repair technique, where "MOCUT" is an acronym for medial orbital composite-unit translocation. Unlike the initial method by Mahatumarat, MOCUT consists of translocation of the medial orbit *without* detaching the medial canthus [41]. More recently, in 2009, another modified single stage technique was proposed "HULA"; H = hard-tissue sealant, U = undermine and excise encephalocele, L = lowering supraorbital bar and A = augment nasal dorsum. This technique additionally addresses the correction of the inferior medial orbital deformity and lowering the radix, which improve the long nose deformity [42].

Transcranial correction of basal encephalocele is well documented [4]. Surgical summary begins with a bicoronal scalp flap, followed by a frontal craniotomy. The anterior cranial fossa is then dissected to reveal the exit hole of the encephalocele. The hernia mass was reduced and the dural defect repaired, and subsequently the bony defect closed with a small bone graft. Disadvantages of open repair include blood loss associated with the bifrontal approach, brain retraction, and disruption of growth centers, risk of injury to the supraorbital/supratrochlear neurovascular complexes associated with anterior skull base approach.

The use of endoscopic endonasal surgery (EES) for correction of anterior cephaloceles has increased in recent times [43]. The principles of the endoscopic endonasal surgical technique are:

- Harvesting a nasoseptal flap, which will later be used to close the skull defect
- Sac aspiration of CSF in order to decompress the meningoencephalocele sac
- Once sac is dissected off the walls, then the reduced sac is gently returned to the intracranial cavity—without excision
- Bony defect is then closed with various grafts but most importantly superimposed with the harvested nasoseptal flap

Some of the benefits of endoscopic correction are avoiding retraction injury to the frontal lobe, olfactory bulbs or excessive bleeding. Previously, efficacy and safety had been demonstrated on adults only, with reservations in extrapolating results to the pediatric patients. The pediatric anatomy with narrow nasal fossae, makes endoscopic procedures more challenging. Moreover, the pediatric etiologies are almost always congenital, whereas adult presentations are likely posttraumatic or iatrogenic. Finally the excessive removal of bone or cartilage from the walls of the nasal cavity might hinder nasal growth in pediatric patients [44]. However, more recently EES has been proven safe in small nasal passages and underdeveloped sinuses in children as young 1.5 months old; without interfering with craniofacial growth [45–47]. In addition, there is published literature demonstrating EES to be equally safe in children as in adults with skull defects of both congenital and acquired causes [43]. EES however, was limited by the size of the defect, when the size of the defect is larger than the middle turbinate/conchae, and therefore the nasoseptal flap could not seal it. Disadvantages of EES include postoperative palatal dehiscence, recurrence of encephalocele, CSF leak, and meningitis.

8.5.2 Occipital Encephalocele

A large number are not severe and will require a simple excision of the cephalocele and dural closure and the small underlying skull defect does not require any specific management [48]. The indication of surgery is to prevent complications of cephalocele such as progression in hernia and/or size in skull defect, CSF leak, dermal ulceration and infection. The aim of surgery is to reduce the sac into intracranial contents whilst preserving normal brain and it is achieved with the following principles of repair:

- A superficial, elliptical Incision Is made and a dissecting plane is made between skin and dura
- Cranial defect exposed and defined
- Durotomy is made In order to decompress the sac but also to explore the content
- If the contents are fibrous, gliotic, non-functional tissue then a transection across the base Is made safely
- If cerebral/cerebellar tissue is Involved then a wider duroplasty and cranioplasty may be employed to preserve neural tissue and provide coverage over the encephalocele area

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Chapter 9
Craniosynostosis

Marios Lampros, Georgios Alexiou, George Sfakianos, and Neofytos Prodromou

9.1 Introduction

Craniosynostosis is one of the most common causes of craniofacial malformations in children and is present in one per 1800 to 2500 births [1, 2]. In craniosynostosis, one or more of the cranial sutures are prematurely fused, and as a consequence, the skull architecture is significantly altered. Normally, over the first years of life, the cranial sutures are not fused, thus allowing the rapid and symmetrical growth of the brain observed during infancy. When a cranial suture is prematurely ossified ("*craniosynostosis*") the brain growth is directed to less rigid skull areas in which the sutures are still patent. As a result, the skull is developed parallel to the fused sutures instead of perpendicular (*Virchow's law*). Despite being compensatory in nature and allowing for brain development, this abnormal growth pattern leads to multiple complications including abnormal craniofacial shapes, intracranial hypertension, and neurocognitive impairments [3–5]. Two different types of craniosynostosis are recognized: the non-syndromic (or isolated), in which only the skull is affected, and the syndromic craniosynostosis which is associated with facial, limb, and truncal malformations [6, 7]. Non-syndromic craniosynostosis is the most common form of craniosynostosis accounting for 70–80% of all craniosynostosis cases. *Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, Saethre Chotzen syndrome* are some of the most common syndromes related to syndromic craniosynostosis. In

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syndromic craniosynostosis, more than one sutures are prematurely fused, while in the isolated only one suture is typically fused [8]. In this chapter, the epidemiology, types, etiology, clinical evaluation, imaging features, and management of children with nonsyndromic craniosynostosis are presented.

9.2 Epidemiology

The incidence of nonsyndromic craniosynostosis is around 1 per 2000 births [9]. In the Di Rocco et al. series concerning non-syndromic synostosis, the sagittal suture was more frequently fused (around 50%), followed by metopic (25%) and unicoronal (15%) sutures fusion (Table 9.1). Bicoronal or combined with sagittal (oxycephaly or turricephaly) account for the rest of the cases. An increase in the frequency of metopic craniosynostosis has been observed in the last years [10]. Overall, craniosynostosis is more common in males, but the sex ratio varies between the different subtypes. Sagittal and metopic (symmetric craniosynostosis) are more common in males, while coronal and lambdoidal (asymmetric craniosynostosis) in females [11]. Nonsyndromic craniosynostosis occurs sporadically in approximately 70–80% contrary to the syndromic, which is usually inherited with Mendelian patterns [12]. The rise of craniosynostosis frequency observed during recent years could be partially attributed to the alteration in the level of awareness for the condition [13]. The influence of geographical or socioeconomic predilection in the pathogenesis of the disease is still debatable [14].

9.3 Clinical Features: Definitions

Sagittal craniosynostosis is the most common form of nonsyndromic craniosynostosis, accounting for around half of the cases. In sagittal craniosynostosis, the sagittal suture is partially or entirely fused prematurely, and thus, the perpendicular growth of the calvarium is significantly restricted. To compensate, the skull grows in an anteroposterior direction. Sagittal craniosynostosis is alternatively called "*scaphocephaly*" (*boat-shaped* head) because the compensatory mechanism leads

Table 9.1 Summary of non-syndromic craniosynostosis demographic and morphological features

Type	Frequency (%)	Gender predilection	Head shape	Head symmetry
Sagittal	50	Male	Scaphocephaly	Symmetric
Metopic	25	Male	Trigonocephaly	Symmetric
Unilateral Coronal	15	Female	Anterior plagiocephaly	Asymmetric
Lambdoid	5	Female	Posterior plagiocephaly	Asymmetric

to a prominent forehead (frontal bossing) and occiput (occipital bulleting) [15]. However, in around 90% of the cases, the fusion is localized in the anterior, central, or posterior segment of the sagittal suture and only 10% have a complex form of fusion [16].

Metopic craniosynostosis is the second most common form of nonsyndromic craniosynostosis accounting for approximately 25% of all craniosynostosis cases. In this type, the metopic suture is prematurely fused resulting in a "*keel-like*" deformity at the site of fusion. The compensatory growth is guided by the coronal sutures, thus leading to a large posterior skull diameter and a short skull diameter frontally. The whole shape of the skull resembles a triangle when viewing it from above, and thus this type of craniosynostosis is called "*trigonocephaly*" (triangle-shaped head). Trigonocephaly is associated with hypotelorism due to hypoplasia of the frontal lobes and the ethmoid bone [17–19].

Coronal craniosynostosis is another common form of craniosynostosis and it is subdivided in unilateral or bilateral if the coronal suture is entirely fused. The unilateral craniosynostosis is the third most frequent type accounting for 15% of all nonsyndromic cases. Unilateral fusion results in an asymmetric compensatory growth because this suture is not placed in the midline. As a result, the head is flattened ipsilaterally due to the fusion, and in contralateral bossing. In this case, the head takes on a trapezoid shape with an anterior-lateral bulging. For this reason, the unilateral coronal craniosynostosis is alternatively called "*anterior plagiocephaly*". The compensatory growth leads to downward compression of the maxilla ipsilateral to the site of fusion and in a face rotation known as "*facial twist*" [20, 21]. Bilateral craniosynostosis is less frequent than unilateral, and contrary to the unilateral variant the entire suture is involved leading in a symmetrical compensatory growth characterized by parietal widening and occipital flattening, as predicted by Virchow's law [22].

Lambdoid craniosynostosis comprises around 5% of all nonsyndromic craniosynostosis and is a condition similar to unilateral coronal craniosynostosis. Typically, the lambdoid suture fuses unilaterally, and as a result, the head grows asymmetrically resulting in parietal bossing contralaterally ("*posterior plagiocephaly*"). Due to the pressure generated from the contralateral growth, ipsilaterally the skull base is displaced downward, the upper part of the cervical spine may be rotated, while the mastoid process is prominent and bulging [21, 23]. Posterior plagiocephaly should be differentiated from the much more frequent positional molding.

The terms "*oxycephaly*", "*turricephaly*", and "*pansynostosis*" are utilized to describe the premature closure of two or more of the cranial sutures. There exists confusion in the literature concerning the specific definition of each term, and by some authors are considered synonymous. Oxycephaly means a conoid head shape that occurs as a result of the premature fusion of a bulging bregmatic fontanel [24]. Turricephaly is an alternative term for oxycephaly, while pansynostosis is the preferred term when all the cranial sutures are prematurely fused [25]. No matter the terminology, all these types correspond to the most severe forms of craniosynostosis and are related to significant neurological complications. Fortunately, these variants are exceedingly rare, with only few cases reported in the literature (1–3% of all cases) [10, 25, 26].

9.4 Genetics and Risk Factors

To date, the etiology and genetic landscape of nonsyndromic craniosynostosis are unknown and poorly studied. The isolated form of the disease typically occurs sporadically, and a Mendelian pattern of inheritance is observed only in a minority of cases (around 5%). Recently, the pathogenesis of nonsyndromic craniosynostosis is attributed to an interplay of genetic and environmental factors. Mutations in *FGFR 1-3, TWIST 1, SMAD 6, BBS9*, and *FREM1* genes have been described in children with nonsyndromic craniosynostosis. Interestingly, mutations in *FGFR 1-3* and *TWIST* are also strongly linked with the pathogenesis of the syndromic variant (e.g. in *Muenke* ^{FGFR3P250R} syndrome). In some cases, distinction between nonsyndromic coronal craniosynostosis and Muenke syndrome can be challenging and the only way to set the diagnosis is by identifying the *FGF3 P250R* mutation that is definitive of the Muenke syndrome [27, 28]. Timberlake et al. suggested genetic screening for *SMAD6* mutations in children with sagittal or metopic nonsyndromic craniosynostosis because mutations in these genes have been linked with higher inheritance risk [12]. Finally, various environmental, maternal and other risk factors have been linked with the occurrence of nonsyndromic craniosynostosis such as increased maternal age (over 40), male sex, preterm gestation, twinning, fertility therapy of a mother with citrate clomiphene, maternal smoking, gestational diabetes, caesarian birth, and positive family history of craniosynostosis [29–32].

9.5 Clinical Evaluation

A temporal overlapping of the cranial sutures can be a normal finding in a neonate and should not be confused with craniosynostosis. Moreover, the passage of the fetus through the birth canal may cause temporal alteration in the head morphology. Therefore, confirmation of craniosynostosis's diagnosis is usually delayed until early infancy [33]. It is important to distinguish craniosynostosis from other conditions that occur on the head, such as positional plagiocephaly. Positional plagiocephaly is a condition resembling lambdoid craniosynostosis and occurs from continued pressure in the head occiput due to persistence lying in a specific position, usually during sleep. In contrast to lambdoid craniosynostosis, this condition is self-resolved and is accompanied by torticollis, while the head shape is more parallelogram than trapezoid in positional plagiocephaly [33, 34].

In the clinical suspicion of craniosynostosis, a full morphological evaluation of the skull is necessary, including the measurement of head circumference and cranial lengths. Viewing of the head from above is recommended to display any cranial asymmetries [34]. Except for the skull, the pediatrician should evaluate the child's eyes, nose, tooth, toes, spine, and organ systems for other possible anomalies as observed in the syndromic types (*Pfeiffer syndrome*, *Crouzon syndrome*, etc.).

Genetic tests are performed to evaluate the presence of syndromic variants in cases of diagnostic doubts. Full evaluation and further management are completed in reference centers for craniosynostosis [35].

Except for the aesthetic problems, craniosynostosis is related to multiple serious complications such as intracranial hypertension, ophthalmological problems, neurocognitive impairments, and breathing problems such as obstructive sleep apnea. Although, these complications usually occur in children with syndromic craniosynostosis, they can also be observed in a milder form in nonsyndromic craniosynostosis. Most complications occur as a result of intracranial hypertension (ICH), while the frequency of intracranial hypertension is directly related to the number of sutures prematurely fused. Increased intracranial pressure is observed in approximately 20% of the children with nonsyndromic craniosynostosis until normalized in approximately 5–8 years of life. The patients usually experience episodes of headaches or nausea in the most severe cases. Periodic fundoscopy for papilledema evaluation to prevent optic nerve atrophy and permanent blindness is necessary [36]. Neurocognitive impairments have been linked with ICH. However, a study found that approximately half of the children with corrected craniosynostosis in infancy developed neurocognitive regression later in childhood [37]. Obstructive sleep apnea is uncommon in children in the nonsyndromic type and usually occurs as a part of craniofacial syndromes due to midface hypoplasia. Finally, other severe manifestations such as epilepsy and cranial nerve compression are observed in cases of premature fusion in multiple sutures, accompanied by significant increase of intracranial pressure [3, 36].

9.6 Imaging

Despite clinical evaluation being the cornerstone of craniosynostosis diagnosis, the application of imaging procedures is a common practice to confirm the diagnosis and set a therapeutic plan. In the pre-Computed Tomography (CT) era, the plain X-ray was the imaging procedure of choice for the evaluation of craniosynostosis. Lately, a combination of imaging procedures is utilized for the full assessment of patients with craniosynostosis, including three-dimensional (3D) CT scan, ultrasounds (U/S), and Magnetic Resonance Imaging (MRI) [38]. Novel imaging techniques such as “black-bone” MRI are expected to be introduced in the assessment of children with craniosynostosis aiming at the reduction of the infant’s expose to ionizing radiation, thus reducing the risk of future malignancies [38, 39].

Plain X-ray of the skull is an examination of high specificity, but low sensitivity in the diagnosis of craniosynostosis. Thus, the exclusion of craniosynostosis’s diagnosis cannot be solely based on the plain X-rays. Both anteroposterior and lateral views are obtained. In plain X-rays, fused sutures are straightened, sclerotic and with loss of clarity, contrary to the patent sutures that are non-linear and lucent [1, 38]. The diagnostic value of plain X-rays in the first three months of life is probably limited due to low thickness and calcification of the skull [40].

Fig. 9.1 (**a**) Computed tomography of a child with trigonocephaly. (**b**) Sagittal craniosynostosis repair surgery. Removal of the sagittal suture and parasagittal osteotomies. (**c**) Postoperative

U/S is considered an effective imaging technique to assess children with craniosynostosis. Recent studies support that both the sensitivity and specificity of U/S in the evaluation of suture's patency are approximately 95–100%. Lately, in some institutions, plain X-rays have been replaced with U/S as an initial imaging procedure due to the high efficacy of the latter technique. Additionally, the U/S does not involve radiation exposure, and is thus a safe technique for application in children. The patent sutures display a hypoechoic gap between the hyperechoic skull bones. The absence of this gap is compatible with the diagnosis of craniosynostosis [38]. However, the diagnostic accuracy of the technique decreases as the infant grows due to dynamic changes in the pediatric skull, such as closure of the sutures. [38, 41, 42]. Finally, another potential role of U/S is in the prenatal diagnosis of craniosynostosis. Nevertheless, the efficacy of prenatal U/S in the diagnosis of single suture craniosynostosis is probably limited and primarily used in the diagnosis of the syndromic forms that are accompanied by other extracranial manifestations. Skull deformities are usually detected in the prenatal U/S during the second or third trimester of pregnancy [43].

The 3D-CT scan is considered the "*gold-standard*" imaging technique in the diagnosis of craniosynostosis and for surgical decision making (Fig. 9.1a). It is the method with the highest accuracy for the assessment of the suture's patency and skull base. Additionally, it allows an evaluation of the ventricular system for signs of hydrocephalus as well as of other congenital anomalies such as Chiari-malformation or holoprosencephaly. However, due to the high level of radiation exposure it is mainly preferred in cases of syndromic or multi-suture craniosynostosis, or cases of diagnostic doubt [44].

The potential diagnostic role of MRI in children with craniosynostosis has gone beyond the depiction of intracranial structures for any co-existing congenital malformations. Introduction of "black bone" MRI allows direct visualization of the cranial sutures by minimizing the contrast of the surrounding soft tissues. This technique applies the 3D low flip angle gradient-echo MRI sequence, also known as the "black bone" sequence, to evaluate a variety of cranial vault pathologies [45]. A

recent study performed by Tan [46] suggested that "black-bone" MRI has the potential to replace 3D-CT scan in the near future due to its high efficacy and the absence of ionizing radiation.

9.7 Management

The management of children with craniosynostosis is multidisciplinary, requiring a comprehensive evaluation from physicians of different specialties, including pediatricians, neurosurgeons, neurologists, maxillofacial surgeons/dentists, radiologists, and ophthalmologists for the setting of a therapeutic plan. Additionally, psychologists, speech and language pathologists and social workers are also involved in the therapeutic team, providing the appropriate support to the affected children and their families [47]. Craniosynostosis treatment is surgical either with open or via endoscopic approaches in some cases. The vast majority of craniosynostosis cases have an indication for surgical management, except for some mild cases in which a molding helmet can be used as an initial treatment. The latter is performed in children with only limited aesthetic dysmorphy that are not complicated by other intracranial pathologies [48, 49].

Operative goals of craniosynostosis include suturectomy with linear strip craniectomies, followed by correction of the compensatory anomalies with skull remodeling techniques (Fig. 9.1b and c). Thus, it is recommended that craniosynostosis surgery should be performed in early infancy (around 4–9 months) and before the first year of life to prevent the compensatory mechanisms [36]. Multiple skull bone remodeling techniques exist to correct the different types of craniosynostosis. In general, convexity anomalies are corrected with radial osteotomies, while flat anomalies are corrected with radial wedge resections. The surgery carries a relatively low risk, with scalp hemorrhage being the most common complication. The use of epinephrine scalp injections and the application of common hemostatic procedures can limit blood loss. In cases of unusual blood loss, tear of venous sinuses should be suspected [50].

Concerning open procedures, the correction of sagittal synostosis in children younger than 1 year is performed with suturectomy and cranial vault remodeling aiming to reduce the anteroposterior length of the skull and to extend the lateral width. Bilateral frontal, occiput, and parietal craniotomies are performed, followed by radial osteotomies in the frontal and occipital grafts to correct the convexity, while correction of the flattening is performed in the parietal grafts. Width correction is additionally achieved with vertical osteotomies (*Barrel-Stave* osteotomies) in the temporal bone. In older children (over 3 years), the correction of deformities with typical remodeling is not feasible, and thus an entirely different procedure is performed which includes reshaping of multiple frontal, parietal, and occipital grafts [50]. In metopic craniosynostosis, the typical procedure includes a combination of cranial vault remodeling and fronto-orbital advancement to increase the anterior fossa volume and to correct the "*keel-like*" deformity. The correction of the

"*keel-like*" deformity is achieved with radial graft osteotomies of the frontal bone, while the lateral expansion of the head is achieved with parallel parietal osteotomies. However, many modified or alternative techniques have been proposed. A popular alternative method for the treatment of metopic craniosynostosis includes the removal of the frontal bandeau through "C-shaped" osteotomies. After removal, the bandeau is split medially. Then the two segments are placed back, with a wide bone or absorbable plate graft placed between them, thus achieving the widening of the narrow frontal bandeau [4, 50]. A modified anterior cranial vault reconstruction is performed for the treatment of anterior plagiocephaly. The procedure includes anterior advancement of the divided orbital bandeau ipsilaterally and an attempt to make both orbits symmetrical. Additionally, a bone graft is placed between the divided bandeau segments to cover the width difference [3, 4]. Alternatively, the asymmetry between supraorbital rims or of the orbit's dimensions can be corrected with a drill, while a vault remodeling technique can be used for the correction of plagiocephaly [51].

In the 1990s an alternative, minimally invasive approach to the treatment of craniosynostosis via endoscopy was introduced by Vicari [52], Barone, and Jimenez [53]. In the endoscopic treatment of craniosynostosis, a strip craniectomy is typically performed in the fused sutures with the assistance of an endoscope. The procedure has substantial differences in the mechanism of correction compared to the classic remodeling techniques as per Proktor's suggestion [54]. In the endoscopic approaches, the aim is to restore normal anatomy, contrary to the open remodeling techniques in which the skull anatomy is altered to allow a symmetrical head growth. One week after the operation, an orthotic helmet is placed in the child's head for around a year to direct skull development. Additionally, the family should be informed that the aesthetic improvement will be delayed and will not be immediate as in open approaches. The ideal age for endoscopic operation is around 3 months during the period of fast brain growth. The correction of asymmetries is induced through skull expansion, and thus the operation should be performed as early as possible following the diagnosis. It is easily understood that the efficacy of the technique is limited in children over 7 months, in which cases open surgery is the preferable option. Despite that, the introduction of vault expansion devices such as springs and retractors allowed the endoscopic option in older infants. However, these devices should be removed, and thus, a second surgery for their removal is unavoidable. The advantages of endoscopic treatment are similar to those observed in other endoscopic operations, including lower bleeding, risk of infections, and fewer days of hospitalization [36, 54, 55]. To date, only a few studies comparing the efficacy and safety of open vs endoscopic approaches exist in the literature. In general, the open approach is considered the "*standard of care*" by many authors [36]. Recently, a meta-analysis comparing the perioperative outcomes of these approaches found that the endoscopic approach is related to significantly lower blood loss, complications, and reoperation. However, the authors reported very low evidence

grade, thus necessitating further research to clarify either method's superiority over the other [56].

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Chapter 10
Craniofacial Syndromes

I. N. Mavridis, W. S. B. Wimalachandra, and D. Rodrigues

Abbreviations

CSF	Cerebrospinal fluid
CT	Computed tomography
FGFR	Fibroblast growth factor receptor
MRI	Magnetic resonance imaging

10.1 Introduction

The study of abnormal skull growth related to craniosynostosis has its scientific origin in the late 1700s [1]. Craniosynostosis is the premature fusion (ossification) of one or more cranial (calvarial) sutures [2–6]. Cranial sutures are fibrous joints consisting of nonossified mesenchymal cells that play an important role in the development of healthy craniofacial skeletons [6]. Once the suture ossifies, normal growth of the skull perpendicular to the suture terminates and tends to progress parallel to the suture [4]. Early fusion of the sutures results in incomplete brain development that may lead to severe complications including seizures, brain damage, mental delay, complex deformities, strabismus, visual and breathing problems [6].

Craniosynostosis is classified as nonsyndromic or syndromic based on phenotypic descriptions [2, 6]. Children with syndromic disorders are more likely to have multiple sutures fused prematurely, harbor other skeletal anomalies, and have a strong family history [2]. Syndromic craniosynostosis, a clinically and genetically

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heterogeneous congenital anomaly [5], appears to be a generalized disorder of mesenchymal development [1]. Cranial deformity and brain compression are obvious problems. Additional facial involvement in craniosynostosis patients raises functional (e.g. breathing difficulties) and morphologic problems, such as ocular malposition [7]. Syndromic craniosynostosis's presentation varies from mild sutural involvement to severe pansynostoses, with a spectrum of extracraniofacial dysmorphic manifestations [8]. It causes characteristic craniofacial growth restrictions, deformities, and other associated abnormalities, such as joint anomalies and cognitive function impairment [9].

To date, approximately 200 syndromes have been linked to craniosynostosis and more than 50 genes that relate to craniosynostosis have been identified [6]. The commonest forms of syndromic craniosynostosis are Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, Saethre-Chotzen syndrome, and Muenke syndrome (Table 10.1) [2, 8]. Other craniosynostosis syndromes include Carpenter syndrome, Jackson-Weiss syndrome, Boston-type craniosynostosis, craniofrontonasal syndrome, Shprintzen-Goldberg syndrome, Antley-Bixler syndrome, Baller-Gerold syndrome, and Beare-Stevenson cutis gyrate syndrome [2].

10.2 Epidemiology

Craniosynostosis occurs in 0.4–0.6/1,000 live births [1, 2, 4, 5]. Syndromic craniosynostosis is much less common [1] affecting up to 1/25,000–30,000 live births [7, 9]. In approximately 25–30% of patients, craniosynostosis presents as a feature of a genetic syndrome due to chromosomal defects or mutations in genes within interconnected signaling pathways [5]. Of the craniosynostosis patients, 8% have familial forms of synostosis, and in the remainder it occurs as a spontaneous isolated defect [3]. Crouzon syndrome occurs in 1/25,000 live births [1, 7] and the frequency of familial cases varies between 26–75% [4, 7], with the rest being sporadic [4]. Apert syndrome occurs in 1/100,000–160,000 live births [1, 7]. Most cases are sporadic (95%) [4, 7] and few affected patients have children because of the disease's severity [7]. Saethre-Chotzen syndrome has an estimated prevalence of 1/50,000 people [12]. An incidence of 1/30,000 births has been reported for Muenke syndrome [10] whereas Pfeiffer syndrome affects 1/100,000 neonates [13, 14].

Table 10.1 Common craniosynostosis syndromes and the involved mutated genes [2, 8, 10, 11]

	Syndrome	Gene(s)
►	Crouzon	*FGFR2*
►	Apert	*FGFR2*
►	Pfeiffer	*FGFR1, FGFR2*
►	Muenke	*FGFR3*
►	Saethre-Chotzen	*TWIST*

FGFR, Fibroblast growth factor receptor

Although rare in general population, these syndromes are not infrequent in pediatric neurosurgical practice.

10.3 Etiology-Genetics

There are similarities in the genetic basis of craniofacial syndromes because certain genes are able to broadly affect the processes of bone growth and development. This explains common features often seen in some of these syndromes, such as bony anomalies of the midface, skull base, and digits [2]. Craniosynostosis can be caused by mutations in multiple genes. Those for fibroblast growth factor receptor (*FGFR*) and *TWIST*, which encodes a transcription factor, are responsible for the vast majority of syndromic craniosynostosis [2] (Table 10.1).

The two major genetic mechanisms are loss-of-function mutations and gain-of-function mutations. *TWIST* is an example of the first category. It normally inhibits the process of suture formation, and a loss-of-function mutation in this gene leads to bone formation and sutural fusion. In contrast, *FGFRs* are downstream of *TWIST*, and their overexpression leads to gain-of-function and fusion of sutures. Different genes at different chromosome locations may be responsible for the same syndromic disorder and mutations in the same gene can lead to different disorders [2].

Autosomal dominant inheritance patterns are the general rule in these syndromes [1–3], usually with variable penetrance [2]. Autosomal recessive disorders, such as Carpenter's syndrome, do not commonly occur [1, 15, 16]. Although many of the syndromic conditions follow a familial inheritance, spontaneous mutations are possible. Advanced paternal age has been associated with sporadic cases [2].

Regarding specific syndromes, Crouzon's transmission is autosomal dominant with greatly variable expression but sporadic cases occur as well [7]. Genetics play an important role in the etiology of Crouzon's considerable phenotypic heterogeneity [17]. On the contrary, although most cases of Apert syndrome are sporadic, dominant transmission with complete penetrance can occur [7]. Although Pfeiffer syndrome has autosomal dominant inheritance with complete penetrance and variable expression, most cases seem to be sporadic [7], especially in types II and III of the syndrome [2]. Furthermore, Saethre-Chotzen syndrome also has autosomal dominant transmission with incomplete penetrance and variable expression [7]. Finally, Muenke syndrome is an autosomal dominant disorder with reduced penetrance and variable expressivity which contribute to the wide spectrum of its clinical findings [10].

10.4 Pathological and Imaging Findings

Pathological findings determine clinical manifestations and macroscopic pathological findings can often be seen as imaging findings. Imaging modalities are used to aid diagnosis especially of concurrent problems like raised intracranial pressure

(ICP) or cerebral malformations, as well as for monitoring and of course for surgical treatment planning [18, 19].

10.4.1 Crouzon Syndrome

A classic triad of coronal synostosis, maxillary hypoplasia, and exorbitism characterizes this entity. Synostosis is commonly bicoronal or even multisuture, including skull base [2, 4, 20–23]. In almost all cases the coronal and sagittal, and frequently the lambdoid, sutures are involved. There is backward horizontal displacement of the entire frontofacial skeleton [7]. Hypoplasia of the facial skeleton may be severe and accompanied by receding malar bones, abnormalities of the sphenoid and orbital bones. Shallow orbits can cause proptosis; airway malformations may coexist [2, 4, 7, 20–23]. Intracranial hypertension may occur in 62.5% of patients, papilledema in 35%, and optic atrophy in 10%. Associated brain malformations include Chiari I malformation (tonsillar herniation), hydrocephalus, non-progressive ventricular dilation, and syringomyelia [7]. Finally, extracranial maldevelopment can cause cervical vertebral or elbow joint fusion [24].

10.4.2 Apert Syndrome

There is a wide range of severity [2] and findings in this disorder include (bi)coronal, skull base or pan-synostosis (which is complete by the age of two years), syndactyly, maxillary hypoplasia, shallow orbits, and proptosis [2, 4, 7, 25–27] (Fig. 10.1). Intracranial hypertension may occur in 45% of patients. Associated brain malformations include non-progressive ventricular dilation, corpus callosum hypoplasia or aplasia, aplasia of the septum pellucidum, septal cyst, Chiari I malformation [7], and hydrocephalus [4, 7]. Palatal clefts are commonly seen and viscerocutaneous malformations are also present [2, 28]. Syndactyly (fused digits) is always severe and affects almost all digits [7] (Fig. 10.1). Radiohumeral fusion is another potential finding [2].

10.4.3 Pfeiffer Syndrome

It is an association of faciocraniosynostosis and anomalies of the extremities [7]. Again in this entity, synostosis' severity ranges from (bi)coronal to pan-synostosis. Limb malformations include radiohumeral synostosis and soft tissue (partial) syndactyly [2, 7, 29, 30]. Characteristic findings of the facial skeleton include maxillary hypoplasia, shallow orbits, and proptosis [2, 7]. Three different types have been described based on the severity of the maldevelopment [2, 31]. Cloverleaf skull (Kleeblatschädel) deformity, i.e. trilobular skull [4], is characteristic in type II. Raised ICP and hydrocephalus are more common in this group [32, 33].

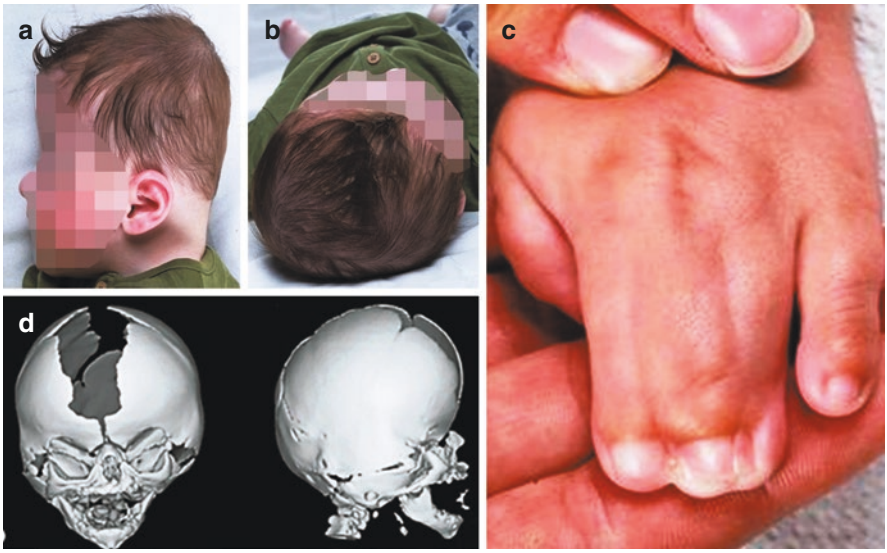

Fig. 10.1 Apert syndrome. (**a**) lateral view of the head of an affected child; (**b**) superior view of the same patient's head; (**c**) hand digits' syndactyly; (**d**) 3D computed tomography (CT) reconstruction of the patient's skull (anterior and lateral view)

10.4.4 Saethre-Chotzen Syndrome

Features are highly variable and include (bi)coronal synostosis with characteristic limb and facial abnormalities, such as partial syndactyly, maxillary hypoplasia, and proptosis [2, 7, 34, 35] (Fig. 10.2).

10.4.5 Muenke Syndrome

(Bi)coronal synostosis is typical in this syndrome as well [2, 10, 32]. Other pathological or imaging findings include coned epiphyses and carpal, tarsal, and calcaneal fusions [2, 10].

10.5 Clinical Features

Underlying pathological abnormalities are responsible for the clinical picture of the affected children. In cases of complex craniofacial maldevelopment, beside morphological findings, airway and feeding issues are also commonly observed [36].

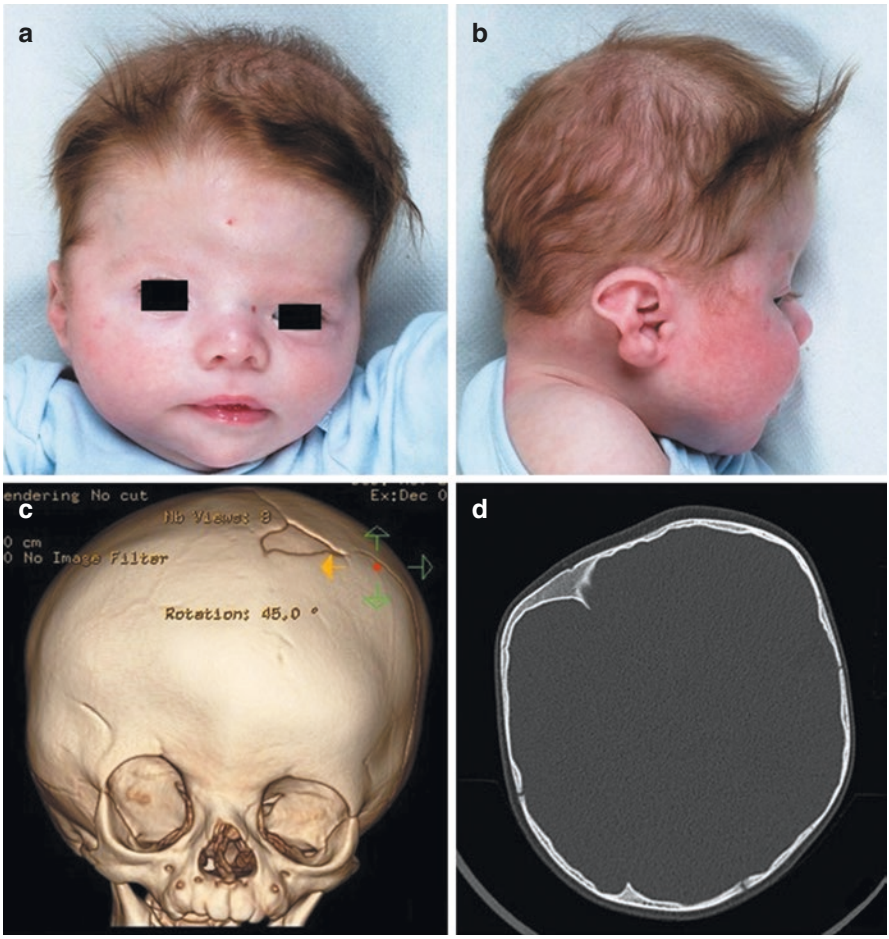

Fig. 10.2 Saethre-Chotzen syndrome. (**a**) face of affected child; (**b**) lateral view of the same patient; (**c**) 3D computed tomography (CT) reconstruction of the patient's skull (anterior view); (**d**) computed tomography (CT) of the same skull (transverse section at the level of midbrain)

10.5.1 Crouzon Syndrome

The common clinical features are brachycephaly, exophthalmos (prominent eyes), hypertelorism, midfacial hypoplasia with class 3 jaw malocclusion, and "beaked" nose (Fig. 10.3) [2, 20–23]. Occasionally scaphocephaly or a cloverleaf skull may be observed [7]. Symptoms and signs of intracranial hypertension, Chiari I malformation, hydrocephalus, syringomyelia [2, 7], and respiratory disturbances [21] may also be detected. Despite these malformations, affected children have usually normal intelligence, but the ones with severe craniofacial maldevelopment are more likely to have learning difficulties [24] or even mental retardation [2]. Extracranial manifestations include orthopedic problems and acanthosis nigricans [24].

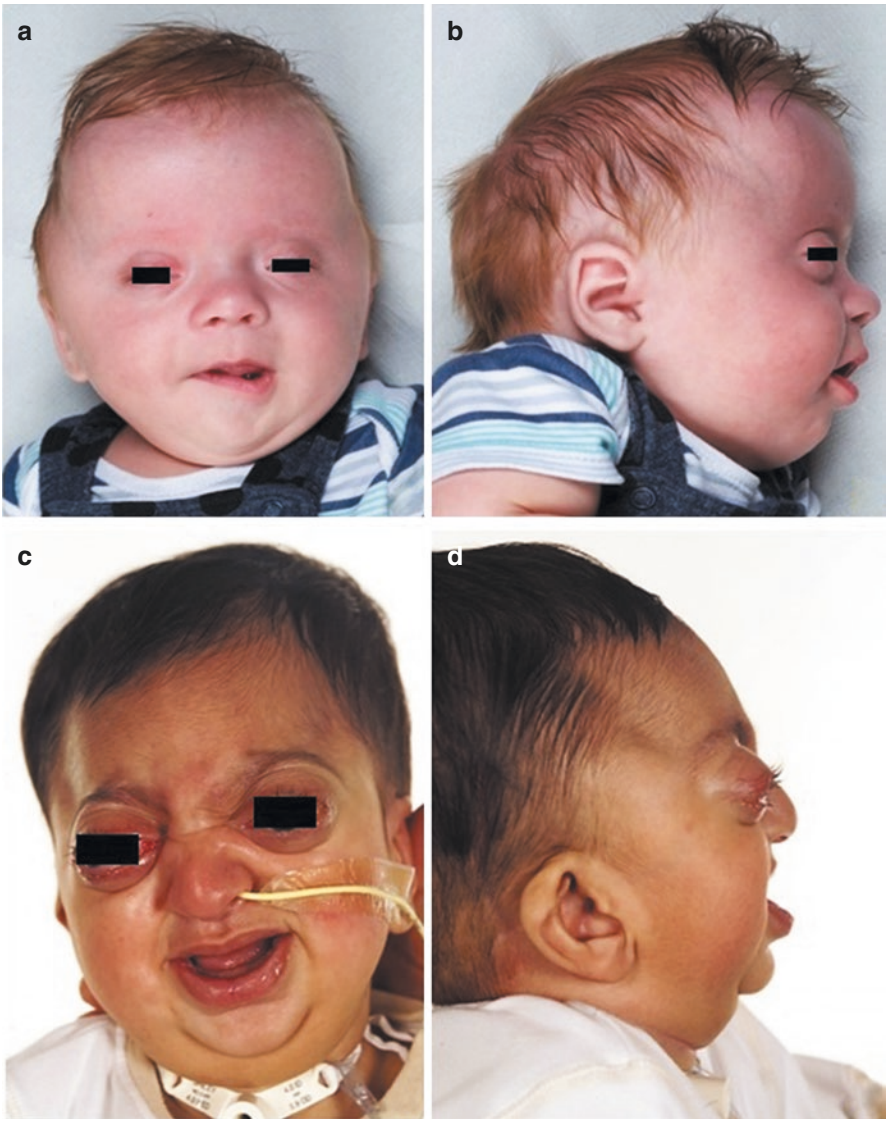

Fig. 10.3 Crouzon syndrome. (**a**) affected infant (anterior facial view); (**b**) same patient (lateral facial view); (**c**) severely affected child (anterior facial view; right eye strabismus exists as well); (**d**) same patient (lateral facial view)

10.5.2 Apert Syndrome

Tall and shortened from front to back (turribrachycephaly) is the characteristic head shape of these patients (Fig. 10.1). Brachycephaly is common and the anterior fontanelle is widely open in affected neonates [7]. Severe syndactyly characteristically coexists with craniofacial features (Fig. 10.1). Similarly to Crouzon syndrome, these children have also midface hypoplasia, proptosis, and hypertelorism [2, 7, 25–27]. Other facial features are short nose, depressed nasal bridge [2], variable facial retrusion, and abnormally wide face [7]. In contrast to Crouzon syndrome, children with Apert syndrome have significant developmental and learning difficulties [28]. Poor cognitive development is the usual and, as already mentioned, hydrocephalus and/or intracranial hypertension may occur [7]. Orthopedic problems include shortened upper extremities [4] and dermatologic manifestations include severe acne [2].

10.5.3 Pfeiffer Syndrome

Although less dramatic than Apert syndrome, this condition can commonly cause digital abnormalities such as short thumbs, large thumbs and great toes with varus deformity, and partial syndactyly [2, 7, 29, 30]. The face of these patients may have small nose with a low nasal bridge, hypertelorism, proptosis, and strabismus [2] (Fig. 10.4). Regarding the severity and prognosis of different types, Type I (classic) is milder whereas types II and III are more severe with early death [2].

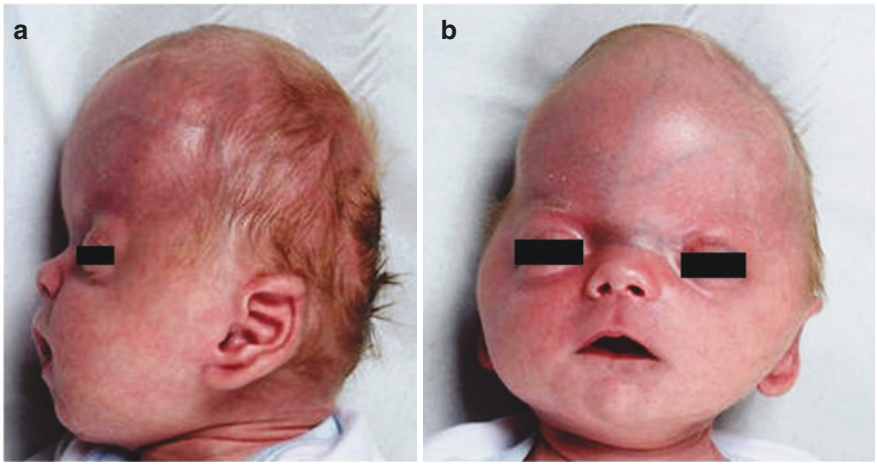

Fig. 10.4 Pfeiffer syndrome. (**a**) affected neonate (lateral facial view); (**b**) same patient (anterior facial view)

10.5.4 Saethre-Chotzen Syndrome

The head is usually brachycephalic but occasionally plagiocephaly or oxycephaly may be present [7]. This syndrome contrasts with the ones discussed so far in that midfacial anomalies and airway complications, as well as raised ICP, are uncommon [32]. Clinical features include low frontal hairline, prominent nose [34, 35], small ears, facial asymmetry [2], mild midface retrusion [7], short digits, and partial syndactyly (Fig. 10.2) [2, 34, 35].

10.5.5 Muenke Syndrome

This syndrome has striking phenotypic variability [2] and is characterized by sensorineural hearing loss, developmental delay, joint problems, brachydactyly, and behavioral issues [2, 10]. Shallow supraorbital regions and prominent forehead are commonly seen. It is less known to cause raised ICP and learning difficulties compared to other common craniofacial syndromes [32].

10.6 Diagnosis

Obtaining a thorough history and a complete physical examination is obviously of paramount importance [9] as clinical features form the basis of diagnosis [19]. Most of the time, the diagnosis is suspected at birth and clinical findings point towards the abnormality. Presence of syndactyly, for example, makes the diagnosis of Apert syndrome together with other craniofacial features [25–27]. In some cases the full effect of synostosis may not be apparent until about 2 years of age. Considering the paradigm of Crouzon syndrome, clinical diagnosis is usually difficult to be established during the first year of life because midface is affected later in life [7]. Familiarity with the characteristic head shapes resulting from craniosynostosis allows bedside diagnosis and differentiation from non-syndromic conditions such as (the commoner) positional plagiocephaly [3]. Moreover, the high variability in phenotype and the association of coronal synostosis with numerous craniosynostosis syndromes, make genetic testing often necessary to establish the diagnosis, such as in Muenke syndrome [2].

Finally, imaging investigations are aimed at establishing the full extent of the synostosis and possible other malformations [19]. Computed tomography (CT) is a quick but detailed way of assessing skull and brain [37]. A 3D CT scan is particularly useful in visualizing the extent of suture involvement and facial abnormalities. An MRI of the brain is indicated when an underlying brain malformation is suspected.

10.7 Management

Syndromic craniosynostosis presents a management challenge [38]. Understanding the multifaceted syndromic presentations while appreciating the panoply of variable presentations is central to delivering necessary individualized care [8]. The complexity and plethora of maldevelopment dictates a multidisciplinary approach, which involves multiple medical and allied health professionals and is best delivered by dedicated craniofacial services [23, 36, 39–42]. A vital component of the provided care is assessment of co-morbidities such as airway, feeding (Fig. 10.3), and nutrition issues, cardiorespiratory abnormalities, orthopedic issues, learning and development, hearing, and vision.

Because of the risks associated with untreated craniosynostosis, surgical treatment is usually undertaken soon after diagnosis [3]. Multidisciplinary teams can provide optimal care for complex reconstructive approaches [8]. Current surgical methods include open calvarial reconstruction (Fig. 10.5), minimally invasive strip craniectomy with use of postoperative molding helmet, minimally invasive strip

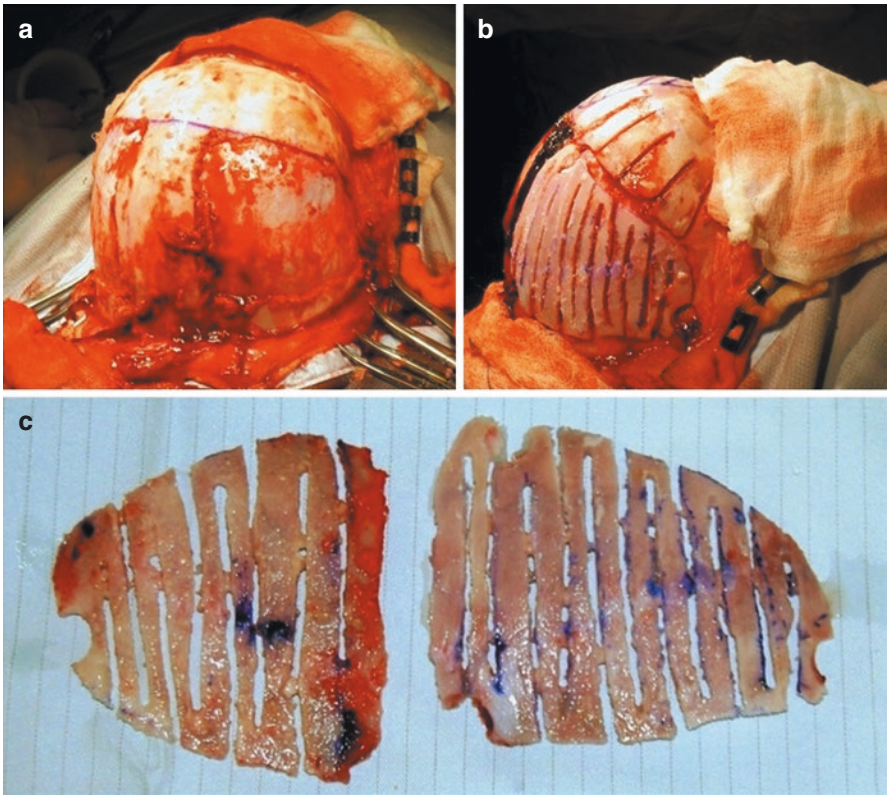

Fig. 10.5 Total calvarial remodeling (intraoperative photos). (**a**) craniotomy sites of the procedure; (**b**) remodeled calvarial bones; (**c**) remodeled skull grafts prior to repositioning

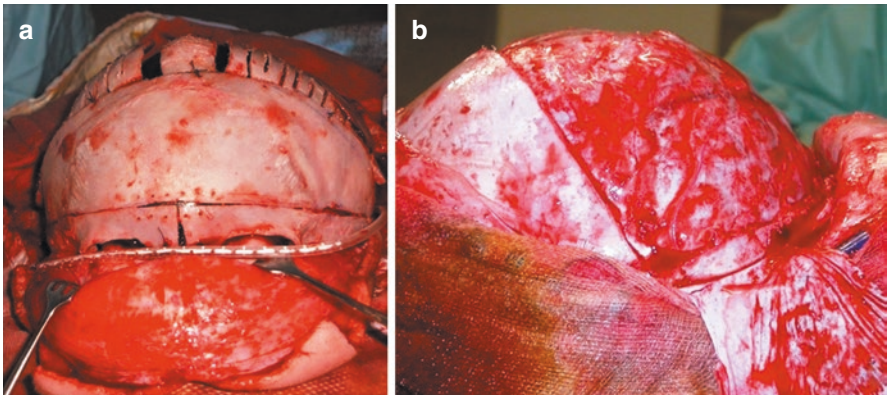

Fig. 10.6 Fronto-orbital advancement reconstruction (intraoperative photos). (**a**) reconstructed bones of the frontal and orbital areas; (**b**) frontal craniotomy site

craniectomy with spring implantation, and cranial distraction. Early referral to a pediatric craniofacial center allows all treatment options to be explored [3].

Health services have to work in a coordinated fashion to deliver treatment and rehabilitation to these children. Surgical treatment is aimed at cranial, orbital, and maxillofacial remodeling and shows the extent of surgical subspecialist involvement as well as the complexity of the procedures. Open surgical correction is probably the standard of care and involves excision of fused sutures with cranial vault expansion (Fig. 10.5) or fronto-orbital advancement reconstruction (Fig. 10.6), where panels of bone are removed, reshaped and reapplied to achieve enhanced intracranial volume and a desired skull shape [43, 44]. Cranial vault remodeling aims to relieve restriction of cranial development and elevated ICP and restore normal morphology [8]. Application of springs and distractors is used as a dynamic cranial vault expansion technique (Fig. 10.7). Complex craniofacial deformities require extended procedures like monobloc frontofacial advancement and facial bipartition [43, 44]. Complications include intraoperative blood loss [45, 46], and, infrequently, cerebrospinal fluid (CSF) leak, infection, surgical wound failure, and neurological sequelae [38, 47, 48].

Management surrounds not only craniofacial deformities but also other associated range of abnormalities which can be challenging. From a craniofacial surgical point, it is important to identify the drivers of surgical correction. Particularly in syndromic craniosynostosis, raised ICP is an established complication [28, 49–51] and it can cause visual and cognitive impairment [28, 52]. Presence of ventriculomegaly with Chiari I malformation does not usually require surgical management as they are relatively stable findings and respond to calvarial remodeling [53]. It is important to identify clinical (bulging fontanelle, papilledema) and imaging (copper beaten appearance of skull on X-ray) findings of intracranial hypertension and, when indicated, invasive measurement of ICP should be considered [54]. Important contributors for raised ICP are airway obstruction during sleep which causes cerebral hypo-oxygenation [55], intracranial venous hypertension [53, 56, 57] due to

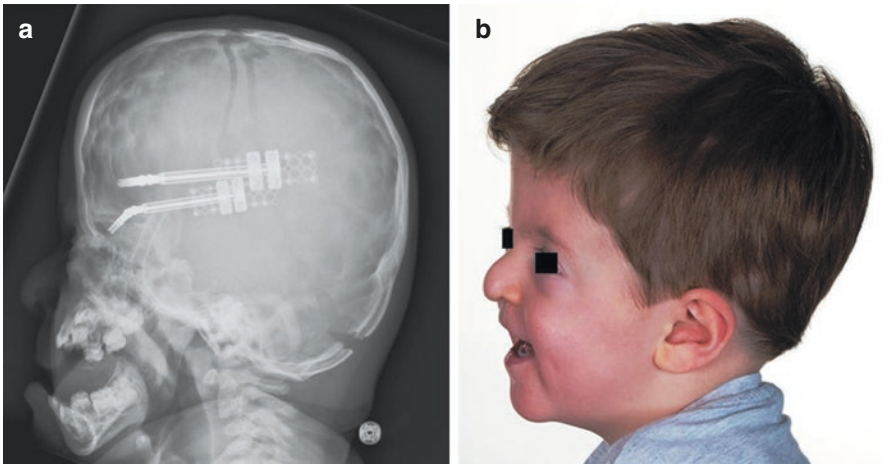

Fig. 10.7 (**a**) Lateral skull X-ray showing bilaterally implanted distractors for dynamic cranial vault expansion. (**b**) Clinical outcome of the same patient at two years postoperatively

narrowed venous spaces, and hydrocephalus [19], but not craniocerebral disproportion [58]. Complications like obstructed airway and corneal exposure need specific interventions. Cosmesis is of course an important aspect of the patient's psychosocial development.

10.8 Conclusion

Syndromic craniosynostosis is a clinically and genetically heterogeneous congenital anomaly. Similarities in the genetic basis of craniofacial syndromes explain common features seen in many of these syndromes, such as bony anomalies of the skull and digits. Autosomal dominant inheritance is the general rule. Pathological findings determine clinical manifestations and macroscopic pathological findings can often be seen as imaging findings. Cranial deformity is obvious and facial involvement causes functional and morphologic problems. Presentation varies from mild sutural involvement to severe pansynostosis, with characteristic craniofacial growth restrictions and a spectrum of extracranial dysmorphic manifestations. Clinical features are the basis of diagnosis, which can be aided with imaging studies and genetic testing. Syndromic craniosynostosis constitutes a management challenge and necessitates a multidisciplinary approach from multiple health professionals, usually in the context of dedicated pediatric craniofacial services. Surgical treatment is usually undertaken soon after diagnosis and assessment of co-morbidities is a vital component of the provided care.

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Part III
Congenital and Developmental Spinal Anomalies

Chapter 11
Myelomeningocele-Lipomyelomeningocele

Dimitrios Pachatouridis

11.1 Introduction

Spinal dysraphism is an umbrella term that describes a number of conditions present at birth in which the midline structures of the spine fail to fuse. The spinal dysraphism result in the third week of embryonic development. The top of the neural tube forms the brain and the rest of the neuronal tube develops into the spine and spinal cord. The neural plate folds up to form the neural tube that will become the spine and spinal cord.

There are two types of spinal dysraphism:

(1) Spina bifida cystica (spina bifida aperta, open spina bifida). In this term was included the myelomeningocele in which the spinal cord and its membranes are not contained and is obvious at the birth the herniation of elements through the bony defect and the skin.
(2) Spina bifida occulta. A condition in which a congenital defect of one or more spinous processes and variable amounts of lamina results in a non visible exposure of meninges or neural tissue. In this term were included the lipomyelomeningocele (spinal cord lipoma), dermal sinus tract, tight filum terminale and tethered spinal cord. In a person with spinal dysraphism is possible to coexist more than one type of lesions.

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11.2 Myelomeningocele

Myelomeningocele is the most common significant birth defect involving the spine and results in devastating, lifelong disability. The prevalence of myelomeningocele is approximately 0.8 to 1 per 1000 live births worldwide, whereas, in the United States, the incidence is estimated to be 0.2 to 0.4 per 1000 live births [1]. The spinal abnormality is only a part of a more wide spectrum of central nervous system abnormalities in which hydrocephalus, Chiari malformation and gyral anomalies are included. Myelomeningoceles are commonly located in sacral or lumbosacral are, however, thoracic and cervical myelomeningoceles exist (Fig. 11.1). A recent study showed that approximately 70% of myelomeningocele cases have ultra-rare deleterious variants in 302 genes that have been previously showed to cause neural tube defects phenotypes in both animal models and humans [2]. These genes are involved among others in cell migration, remodeling of extracellular matrix and cytoskeleton, SHH and WNT signaling [2].

Over the last decades developments in prenatal diagnosis of fetal anomalies have made the recognition of myelomeningocele commonplace. The diagnosis of myelomeningocele is possible in the first trimester of pregnancy. Amniocentesis is helpful and usually favored for high-risk pregnancies. However, ultrasonography is noninvasive, safe, effective, and often used for second-trimester anomaly scanning [3]. Fetal karyotyping and magnetic resonance imaging (MRI) could also be an option if the tests were not sufficient for the diagnosis [4].

The cornerstone of management of myelomeningocele is the initial evaluation by a coordinated multidisciplinary team that will provide sophisticated counseling for parents and future continuity of care [5]. The first step in managing the newborn is

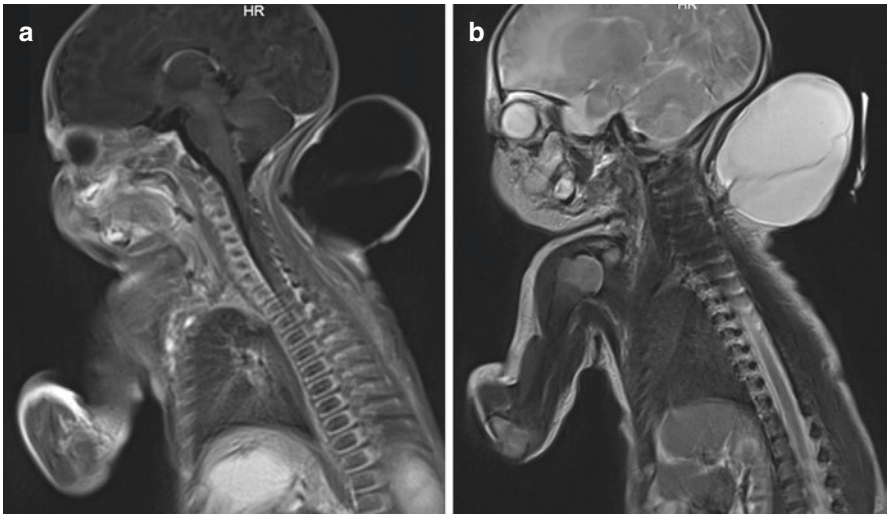

Fig. 11.1 (**a**) T1-weighted and T2-weighted (**b**) MRI of an infant with a cervical meningocele

the physical examination by a pediatrician. It is important to have in mind that a detailed examination of the newborn should be done after delivery avoiding the use of latex gloves. Most of the children with spina bifida experience latex allergy, which makes them prone to severe problems such as anaphylaxis [6]. A thorough evaluation may reveal renal, respiratory and cardiac complications which are common causes of mortality in patients with spina bifida and might contraindicate surgical closure of the defect [7]. The presence of coexisting disorders such as Chiari II malformation, and hydrocephalus, can complicate the condition of the patient and lower the survival rate (Fig. 11.2) [8]. While only 10% of neonates have clinically apparent hydrocephalus at birth, within the first week of life this incidence increases in up to 85% of cases and require placement of a ventriculoperitoneal shunt to prevent neurological and intellectual impairment secondary to hydrocephalus [9]. Several other cerebral abnormalities in infants with myelomeningocele have been reported such as total or partial agenesis of the corpus callosum, wide interhemispheric fissure, missing septum pellucidum and colpocephaly. In the posterior fossa apart from Chiari II, hypoplasia of the cerebellum and of the brain stem (mainly pontine hypoplasia) can be observed [8].

The clinical manifestation of spina bifida depends on the affected spinal cord level. Neurologic manifestations include pain, motor or sensory changes, altered gait, bowel and bladder changes. Orthopaedic findings such as scoliosis, limb length discrepancies, unequal feet size, varus and equinus deformities and clawing of the toes are all suggestive of a neural tube defect [10]. Myelomeningoceles presentation is commonly a midline anomaly in the lumbosacral region where the skin is deficient and on initial inspection the area simply appears red, ulcerated and moist with an exposed granular neural placode surrounded by the primitive neuronal epithelium [1].

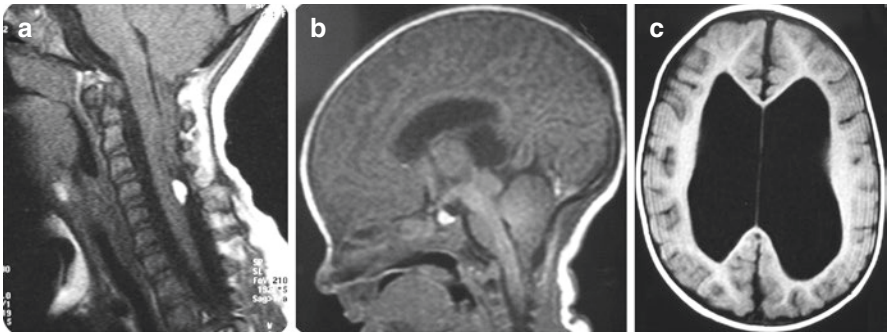

Fig. 11.2 (**a**) Sagittal cervical T1-weighted MRI of an infant with myelomeningocele revealing the presence of Chiari II malformation and of an intradural lipoma. (**b**) Sagittal brain T1-weighted MRI in an infant with myelomeningocele, demonstrating displacement of the brainstem and lower cerebellum into the cervical spinal canal and the presence of a small posterior fossa, findings consisted with Chiari II malformation. (**c**) Axial brain MRI in an infant with myelomeningocele revealing hydrocephalus

Once the diagnosis has made, early surgical repair (in the first 24 hours) of the spinal lesion is essential not to improve neurological function but to prevent further deficits and neurological damage as well as to lower infection rate with early closure. Prenatal surgery was proven to be more effective than postnatal surgery in lowering the occurrence of future complications [7, 11–13]. Intrauterine repair reduced hydrocephalus and hindbrain herniation and improved motor function in children that persisted into school age [14]. Other long-term benefits of prenatal surgery were fewer operations for shunt placement and revision, however no strong evidence of improved cognitive functioning were found [15].

11.3 Lipomyelomeningocele

Lipomeningocele constitute 14.4% of spina bifida cases. Interestingly, cases of spina bifida have not been reduced after folic acid supplementation contrary to all other types of spinal dysraphism. It is usually located in the lumbar and sacral region and is characterized by the lipomatous tissue which inserts into the neural structures and extends through a bony dysraphic defect into the subcutaneous tissues, and merges with an abnormally low tethered cord [1]. The lipoma is usually covered by skin but may have pigmentation, hair or cutaneous dimples on it. Lipomeningoceles may be associated with other developmental anomalies such as syringomyelia, Chiari malformation and hydrocephalus. The MRI scan and neurophysiological testing are useful for identifying the spinal cord pathology and assisting with surgical planning to remove the mass and its relationships with the neural elements [13]. A patient with lipomyelomeningocele at first may be asymptomatic, however neurological sequelae may become apparent later in life. The majority of neurosurgeons advocate that surgical treatment should be performed when diagnosed, even prophylactic [16–19] when the patient is over 3 months of age. The goal of early surgical intervention is to avoid the risk of worsening neurological and urological function secondary to a tethered spinal cord. The targets of the surgery are to remove as much of the lipomatous mass as possible without any damage of the neural tissue releasing the spinal cord. The reconstruction of the dura to avoid leakage of CSF and discourage retethering is the final step [20]. Early surgical intervention has a positive effect in reversing neurological deficits. On MRI presence of syrinx and partial resection of the lipoma were identified as independent risk factors for delayed deterioration [21].

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Chapter 12
Split Cord Malformations

Anastasios Nasios, Georgios Alexiou, George Sfakianos, and Neofytos Prodromou

12.1 Introduction

Split cord malformations (SCM) represent a subgroup of congenital abnormalities related to spinal dysraphism, in which the spinal cord is split into two hemicords along a portion of its length. They are relatively rare accounting for 3.8–5% of all spinal dysraphisms and are often associated with other forms of spinal dysraphism, mainly tethered spinal cord syndrome [1, 2]. Diagnosis is usually established during early childhood and only scattered cases are encountered during adulthood [3]. Due to the risk of neurologic impairment of patients suffering from split cord malformations, early diagnosis and proper management are mandatory.

12.2 Embryology

Gastrulation is the embryonic developmental process of gestation, through which all three germ layers are produced—ectoderm, mesoderm, endoderm. Ectodermal germ cells form the neural tube and neural crests from which the central and peripheral nervous systems are formed respectively in a process called neurulation.

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Mesoderm is responsible for the formation of the notochord, which gives rise to the nucleus pulposus, and the somites, thus ultimately forming the spinal column. Failure at different points during these developmental stages, results in various congenital abnormalities of the nervous system. Split cord malformation pathogenesis is thought to be initiated by the presence of an ecto-endodermal adhesion, which will eventually form two hemineural plates and two heminotochords, during neurulation [4].

12.3 Classification

Over the years, split cord malformation nomenclature underwent changes. Terms such as diastematomyelia, diplomyelia and dimyelia have been used in the past. Diastematomyelia describes a single cord, which is split caudally by a septum with two distinct dural sacs. Diplomyelia refers to an accessory spinal cord dorsal or ventral to the original one, encased in a single dural sac. Dimyelia describes the presence of two separated spinal cords with two distinct dural sacs. Pang et al. in 1992 proposed a classification system that described two distinct types of split cord malformations, split cord malformation type I and type II [5]. Split cord malformation type I consists of two distinct hemicords, each one encased in its own dural sac, which are separated from an anteroposterior bony or fibrocartilaginous spur. This type of malformation is usually located in the lumbar and lower thoracic spine. Spilt cord malformation type II refers to the presence of two hemicords contained into a single dural sac and separated intradural by fibrous bands [6]. This type of malformation can also be found in the cervical region. In 2005 Mahapatra and Gupta proposed a new classification system for type I SCM, based on the location of the bony septum that produces the split. The proposed classification includes four categories: Ia in which there is a bone spur in the center with an equally duplicated cord above and below the septum, Ib the bone spur is located at the superior pole with no space above it and a large duplicated cord lower down; Ic, the bone spur is found at the lower pole with a large duplicated cord above; and Id, a bone spur straddling the bifurcation with no space above or below the spur [7].

12.4 Relation to Other Abnormalities

Split cord malformations are often associated with several congenital abnormalities. These abnormalities arise from anomalies related to all three germ layers. Most of them represent complex craniospinal congenital malformations produced by ectodermal-endodermal abnormal adhesions. Common findings include myelomeningoceles, intramedullary lipomas, dermal sinuses, neurenteric cysts, hemivertebrae, Klippel-Feil syndrome and Chiari malformation [8]. Extra-craniospinal

abnormalities have also been reported, such as intestinal duplications and diverticula.

12.5 Clinical Presentation

The clinical features of split cord malformation include a wide range of manifestations. Some patients can be asymptomatic, but in most cases various symptoms can be seen. Both SCM types are tethering lesions. The majority of children may be asymptomatic at birth and neurological deterioration usually begins within the first 2 to 3 years of life [7]. Symptoms involve several neurologic deficits, deformities of the spinal column or the extremities and various cutaneous markers. Patients usually complain of lower extremities pain and persistent back pain. Neurologic deficits most commonly involve the lower limbs. Motor and sensory deficits such as weakness, atrophy of the lower limbs, gait disturbances, radicular pain, hypoesthesia or paresthesia represent common manifestations. Bladder and bowel disturbances can also be seen in about 20–40% of patients and should raise clinical suspicion [2, 7]. Skeletal deformity can also be present, usually in the form of scoliosis or kyphoscoliosis and are more common in SCM type I. Thus, all patients with congenital and progressive scoliosis should be investigated with MRI. Congenital talipes equinovarus is commonly encountered in these patients and should be carefully evaluated when present. Cutaneous markers can be seen in the form of capillary hemangiomas, subcutaneous lipomas, hyperpigmented patches, though hypertrichosis is the most common skin anomaly encountered [9]. SCM type I has more severe symptomatology, whereas in type II presenting symptoms might be subtle or can be incidentally detected [8].

12.6 Imaging

Diagnosis of spilt cord malformations is obtained through careful clinical evaluation and proper imaging techniques. X-rays of the spine have been traditionally used in the initial investigation of patients. Their usefulness relies in depicting several skeletal anomalies associated with split cord malformations, such as kyphoscoliosis, vertebral or rib anomalies, but lack sensitivity in diagnosing split cord malformations. Computed tomography can provide more detailed information related to skeletal pathology of the spine and can also demonstrate the presence of a bony or fibrocartilaginous septum, which is indicative of split cord malformation [Fig. 12.1]. The gold standard imaging modality is magnetic resonance imaging (MRI). Due to its superiority in demonstrating the neural elements, it can establish the diagnosis of split cord malformation by depicting the presence of hemicords and the dural sac or sacs containing them, depending on the type of malformation

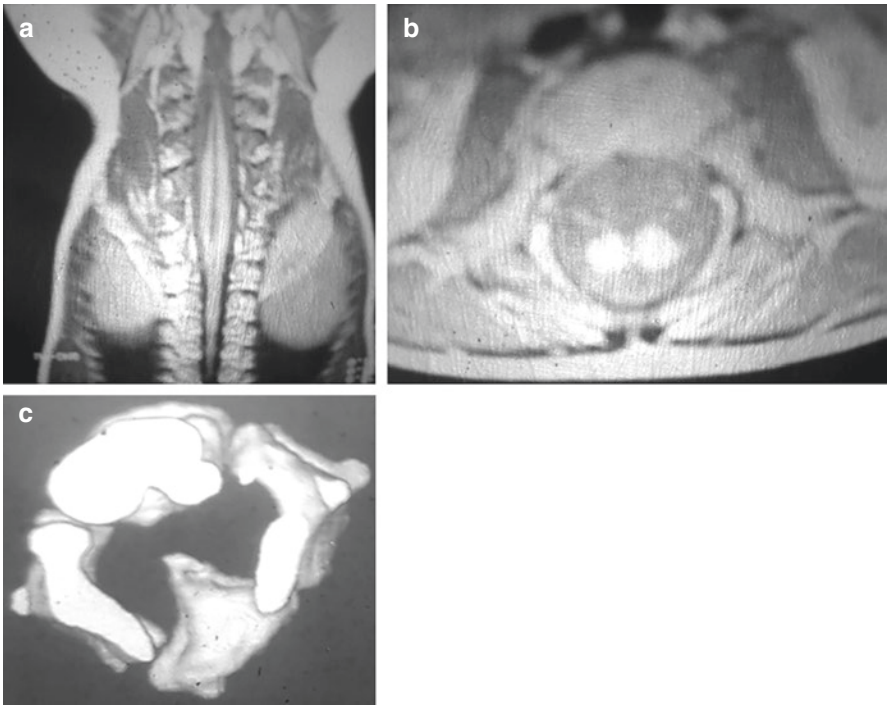

Fig. 12.1 Type I split cord malformation. (**a**) Coronal and axial (**b**) MRI revealing the two hemicords. (**c**) 3D Computed Tomography (CT) reconstruction scan revealing the bony spur. The patient was operated via a laminotomy. The bony spur was dissected extradurally between the two dural sacs and removed piecemeal

encountered, as well as by demonstrating other anomalies related to split cord malformation, such as tethered spinal cord [10].

12.7 Management

The treatment of split cord malformation is mainly surgical. Patients with split cord malformations who remain untreated show increased rates of neurologic deterioration and have a low chance of complete recovery postoperatively. There is an association between increased age and the risk and severity of neurological deficits, due to tethering of the spinal cord. Thus, surgery is indicated in all patients with symptomatic split cord malformations and is also suggested in most asymptomatic patients at the time of diagnosis. The goal of surgery is spinal cord detethering and includes resection of the bony or fibrocartilaginous spur, removal of any other tethering attachments of the spinal cord, such as thick filum terminale, as well as management of any other coexisting craniospinal abnormalities. Type Ia is easier to treat with

surgery, whereas type Id is the most difficult to address surgically. In approximately 10% of type I SCMs cases, the bony spur may be diagonal, separating the canal into a large and a small compartment. Late symptomatic retethering is relative uncommon in adults but common in children. Reoperation should be proposed and provides years of relief [8, 11]. Severe scoliosis in type I SCM is among the most complex conditions in all types of spine deformities because the presence of the bony spur increase the risk of neurological deterioration during deformity correction surgery [12]. These patients are usually treated by two stage surgery. First, bony spur removal can be performed followed by scoliosis correction after 3–6 months. Recently, single-stage bony septum resection followed by spinal deformity correction, as well as, single-stage spine-shortening posterior vertebral column resection without prophylactic resection of bony spur have been performed with good results [12, 13].

12.8 Conclusion

Split cord malformations are rare congenital anomalies traditionally classified in two types. These malformations are often associated with other congenital abnormalities, that cause cord tethering and neurologic impairment. Careful clinical examination, early definitive diagnosis and timely surgical treatment are of paramount importance.

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Chapter 13
Myeloschisis

Sandip Chatterjee and Arjun Dasgupta

13.1 Definition

Open neural tube defects (NTD) are malformations of the spinal cord and brain where during embryonic development the neural tube fails to close completely. By definition, these defects may be considered to be of two types: those where there is a CSF filled sac or meningeal layer covering the neural tissue (called spina bifida cystica) or those where the neural tube is exposed to the surface called myeloschisis. Myeloschisis therefore essentially refers to a meningocele without a CSF filled meningeal covering.

13.2 Epidemiology

The prevalence of all open neural tube defects has declined over the years with better available antenatal diagnosis leading to termination of pregnancy, and availability of folic acid supplementation. There was a reported 19% fall in prevalence of neural tube defects after folic acid supplementation [1]. Across the planet the prevalence of spina bifida is reported as varying between 0.1 per 1000 live births among native Africans to 12.5 per 1000 live births among Celts [2].

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13.3 Embryology

On Post ovulatory day (POD) 4, the human embryo forms a 32 cell mass called the blastocyst which contains an eccentrically located inner cell mass, the embryonic cell itself, and a thin surrounding ring of cells called the trophoblast. The inner cell mass forms two layers the dorsal epiblast and the ventral hypoblast. The primitive streak develops at the caudal end of the blastocyst on POD 13 and reaches its full length on POD16. This primitive streak ends cranially as Hensen's node, and a midline primitive groove along the length of the primitive streak ends at the Hensen's node as the primitive pit. Prospective mesodermal cells ingress between the epiblast and the endoderm which develops from the hypoblasts. This transformation of a two-layered embryo into a three layered embryo is called gastrulation.

The notochordal process is formed from cells in the Hensen'snode arranged around a central lumen called the notochordal canal. By POD 17, the neural groove develops as a trough above the midline notochord [3]. Shortly afterwards the edges of the neural plate elevate laterally forming the neural folds. Paired dorsolateral hinge points (DLHP) develop in the cranial neural tube and in the future lumbar spinal cord and cause the neural folds to converge towards the midline, thus ensuring that the converging neural folds meet and fuse to form a closed neural tube between POD 21 and 23. As the neural tube closes it separates from the cutaneous ectoderm by a process called dysjunction.

Failure of closure of the neural tube produces an open NTD, and the exact location of the non-closure determines the type of defect [4]. The "overdistension" theory [5] which proposed that the neural tube closes but overdistends and ruptures producing the neural tube defect is no longer considered as valid.

13.4 Folate and NTD

When women with a NTD-affected pregnancy were given a trial of folic acid supplementation, recurrence of NTD was observed in 4% of unsupplemented versus 0.5% of supplemented pregnancies [6]. Subsequent trials established beyond doubt the role of folate so much so that now current guidelines recommend all women planning pregnancy should take 0.4 mg to 0.8 mg of folic acid daily beginning 1 month prior to conception [7]. The mechanism by which folic acid promotes neural tube closure is still a subject of investigation. One hypothesis is that folate deficiency produces inadequate nucleotides as a result of which development of the neural folds is slowed. The role of folic acid in methylation may also cause NTDs.

13.5 Prenatal Diagnosis

Maternal serum alpha-foetoprotein (MSAFP) is ideally measured in maternal serum between 16 and 18 weeks of gestation, and has a diagnostic accuracy of 75–90% [8]. Ultrasonography has improved both the detection sensitivity and the cost

efficiency. Serial transverse section of each vertebral segment are taken, to detect the bifid spine and the spinal cord defect beneath it. The "lemon sign" refers to scalloping of frontal bones and concavity of parietal bones on transverse section, and the "banana sign" refers to the abnormal shape of the midbrain and cerebellum. Both signs are seen in 97% of fetuses with spina bifida [8].

In patients with raised MSAFP and abnormal ultrasound findings, amniotic fluid sampling may be done. Karyotyping, checking of AFP and acetylcholinesterase may be done. Fetal MR with 1.5 Tesla magnets are considered safe today for more detailed imaging of the spinal defect. Prenatal counselling may be done by the pediatric neurosurgeon after taking into consideration all the prenatal investigative tools.

13.6 Prenatal Repair

The Management of Myelomeningocele Study (MOMS [9]), a randomized trial of prenatal versus postnatal repair for myelomeningocele, found that prenatal surgery resulted in reduced hindbrain herniation and need for shunt diversion at 12 months of age and better motor function at 30 months. Following this a number of centres worldwide began prenatal repair of myeloschisis. This fetal surgery is performed by a multidisciplinary team and can be an open procedure or an endoscopic procedure where the uterus is opened and the myeloschisis repaired and the uterus closed thereafter. Despite the presence of favorable outcomes for the children, prenatal surgery was associated with a higher maternal morbidity, evidenced by the rates of PPROM (46%), preterm labor (38%), complete or partial dehiscence of the hysterotomy site (30%), chorioamniotic separation (26%), need for maternal blood transfusion at delivery [10].

13.7 Clinical Features

Myeloschisis is readily diagnosed at birth by a midline defect in the spine where the neural tissue is exposed at the surface without any membranes as covering (Fig. 13.1). This is in contradistinction with the meningoceles where there is a layer of membrane or abnormal "skin" over the defect, and in the limited dorsal myeloschisis where the swelling in the midline is covered by normal skin.

There may of course be associated neurological deficits, and associated hydrocephalus. Examination for other congenital anomalies including urogenital abnormalities is of course necessary.

13.8 Investigations

In our practice MRscan of whole spine with screening of the brain is done routinely in the neonates although this is by no means the standard practice everywhere. The MR scan not only gives detailed information about the anatomy of the myeloschisis,

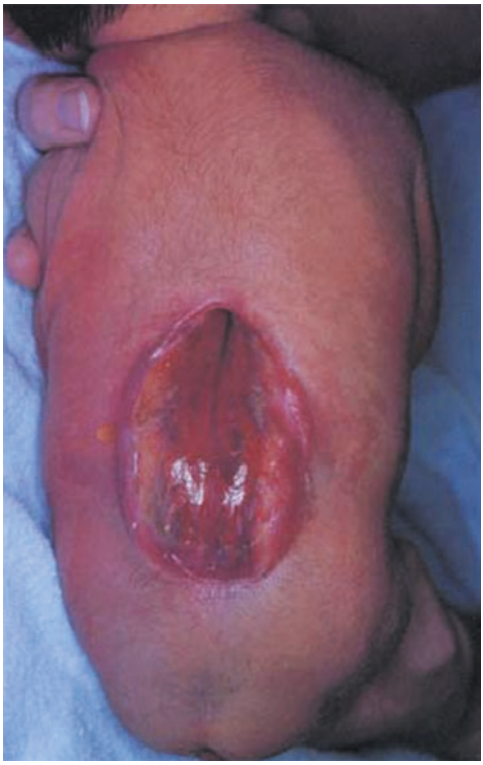

Fig. 13.1 Appearance of myeloschisis

but also demonstrates the presence of Chiari 2 malformation if it exists. Ultrasound examination of the urological system and the brain if necessary are also done, the latter when brain MR is not available. Chest radiography is also routine in our practice, as is echocardiography in cases where congenital cardiac problems are suspected.

It would not be out of place to point out that given the increased incidence of latex allergy amongst this population, latex free gloves should be used routinely when handling these neonates [11].

13.9 Postnatal Management

Once the neonate is stable, the defect should be examined and cleaned with sterile saline. The defect should be thereafter covered with sterile saline soaked dressing. The infant is then placed prone or in lateral position, while a thorough examination is done.

The timing of surgery should be as soon as possible after birth. It has been proposed that the defect be closed within 72 hours of birth, as failure to do so increases risks of meningitis and ventriculitis [12, 13].

13.10 Technique of Surgical Repair

After induction and endotracheal intubation, the infant is positioned prone with bolsters or even rolled up skin towels under the chest and pelvis. The back is prepared with povidone iodeine solution, and then a dose of antibiotic is administered intravenously. We tend to perform the entire operation under an operating microscope. The skin is incised at the junction of normal and abnormal skin and the incision is deepened till dura or fascia is encountered. The placode is separated from the surrounding skin and dura working circumferentially from cranial to caudal.

The separated placode is then sutured to form the new neural tube by approximating the pia on one side to the other side. The everted dura is then sutured as a separate layer as is the fascia. (Fig. 13.2).

The skin is then sutured, and in our practice we always leave a suction drain under minimum suction.

13.11 Postoperatve Care

It is our practice to continue antibiotics for 72 hours postrepair. We usually nurse the neonates prone with waterproof dressing to prevent soiling of the wound. At all times the neonate is monitored for increase in head circumference or for brainstem signs caused by the Chiari 2 malformation.

In cases of hydrocephalus associated with myeloschisis it is our practice to perform CSF diversion at the same time as the repair, and the diversion is first

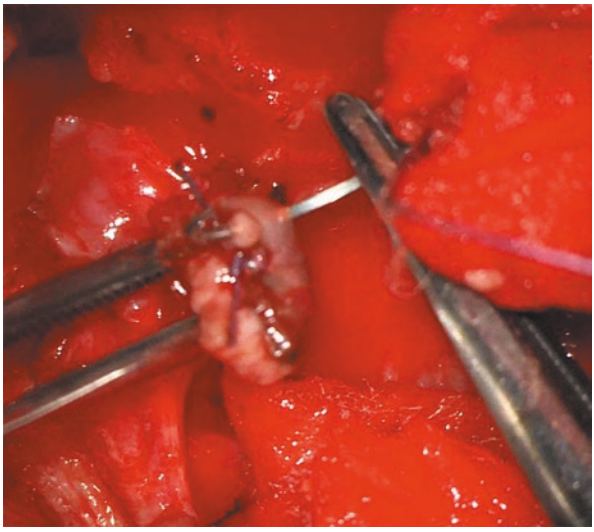

Fig. 13.2 Intra operative picture demonstrating neurilation via pial suturing. Forceps holding the neural placode and pia to pia suturing is done

performed before turning the baby prone. Regarding the mode of diversion, we prefer to do a ventriculosubgaleal shunt.

13.12 Complications

Wound dehiscence and infections are the two commonest complications. Myelomeningocele closure, when delayed more than 1 day after birth, is associated with an increased rate of infection and length ofstay [14]. CSF leakage if it occurs may be the sign of hydrocephalus which requires attention. Neurological deficits are rare after this surgery [15].

There is no doubt that management of neonates with myeloschisis requires proper training and multidisciplinary care [16].

13.13 The Future

The main area where work needs to be done is to make the practice of folate supplementation more widespread in our communities [17]. It will still need to be acknowledged that our knowledge of the causative factors for open neural tube defects still remain unclear, our knowledge being based on the molecular and genetic basis of neural tube closure in mice and lower vertebrates only [18]. Meanwhile the physiological [19] and economic impact of foetal surgery will continue to be popularised [20].

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Chapter 14
Non-Dysraphic Spinal Lipomas

Chandrashekhar Deopujari, Mayur Mhatre, and Harshal Agrawal

14.1 Introduction

The non-dysraphic spinal lipomas (NDSL) are characterised by the absence of skin or bony abnormality (spinal dysraphism) and presence of intact dura over the lesion with often normally placed conus. It is a rare congenital entity, contributing only about 1% of all spinal tumors in earlier reports when only sub-pial (intramedullary) variety was considered [1]. Frequent finding of filar lipomas (7–46%) in many asymptomatic children may revise this concept [2, 3]. Lipomas are not neoplasms as they are histologically identical to normal adipose tissue and do not usually grow except during periods of rapid weight gain and may be called hamartomas.

Several classifications of spinal lipomas are described in the literature. Chapman first classified them in pre-MRI era (1982) based on anatomical and morphological considerations into dorsal, transitional, and caudal types [4]. Though most of the lumbosacral lipomas are associated with spinal dysraphism, subpial lipomas with intact dura were described by McLone and Naidich as a small group (4%) in their surgical experience in 1985 [5]. Subsequent classifications have further subdivided the lumbosacral lipomas into dorsal, transitional, lipomyelomeningocele, caudal and filar based on MRI findings (Arai et al. [6]). In 1995, Pang et al. added embryological perspective to the classification and divided them into dorsal, transitional and terminal, subsequently adding the chaotic variety [7, 8]. Based on new insight

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in embryological development due to the recognition of the phase of junctional neurulation, Morota et al. recently reclassified spinal lipomas into 4 types [9].

The most clinically relevant classification is probably a simple division into 3 broad categories: Conus, filar and subpial types (Finn and Walker [10]). Though subpial and filar varieties will have intact dura, some conus lipomas may rarely be without dysraphism and covered with normal dura. This includes the terminal variety of Pang's classification as well as the subtype of conal lipomas (type 3) as described in the new classification by Morota et al. [9].

Non-dysraphic spinal lipomas therefore may be described as of 3 types:

1. Filar lipomas (the most common variety)
2. Conal lipomas and
3. Dorsal (cervical or thoracic sub-pial and intramedullary type, the rarest variety)

14.2 Embryology of Non-Dysraphic Spinal Lipomas (NDSL)

A variety of theories to explain the fat in dorsal aspect of spinal cord have been proposed including observation of adipocytes in adjacent leptomeningeal tissue by Virchow [11] and Chiari [12, 13], fatty degeneration of glial cells in the meninges by Taubner [14] and mesenchymal cells from the blood vessels of the spinal cord with metaplasia by Ehni and Love [15].The most relevant theories for NDSL have been described as follows:

1. Premature Dysjunction Phenomenon during Primary Neurulation for Dorsal Lipomas

   The most accepted theory for formation of dorsal lipomas is aberrant primary neurulation due to premature separation of the cutaneous ectoderm from the neuroepithelium prior to neural fold fusion. The theory of separation of neuroectoderm from ipsilateral surface ectoderm allowing mesenchymal tissue to invade into the central canal is called premature dysjunction as first described by Naidich et al. in 1983 [16]. As elaborated further by Pang et al. [17], the primary neurulation process starts with formation of neural pore followed by formation of neural plate and ultimately followed by formation of the neural tube. The paraxial mesodermal cells infiltrate in the infolding of neural tube formation. These cells undergo a process of metaplasia into adipocytes and formation of a dorsal spinal lipoma which prevents closure of neural tube [16]. The premature dysjunction could be bilateral or unilateral producing a midline dorsal lipoma or an eccentric lipoma with rotation of the cord respectively. This theory is well supported by a study using chick embryo models to determine the pathogenesis of lumbosacral lipoma. (Fig. 14.1) [18]. Usually, the dysraphic anomalies with wide canal and lack of posterior elements including dura are commonly associated and this may allow the lesion to extend outside the canal. However, during the premature dysjunction, when the anomalous mesenchyme gets embedded in the central canal with formation of fat, the mesenchyme adjacent to the outer

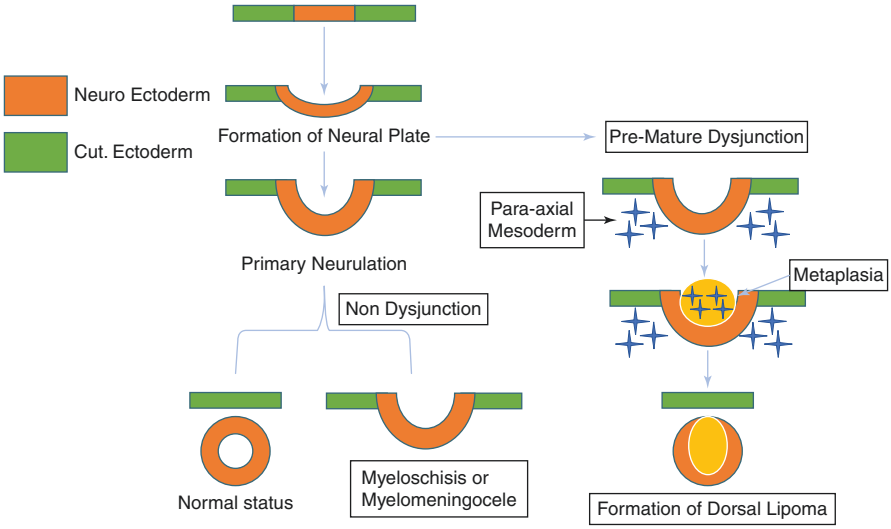

Fig. 14.1 Embryology of dorsal or intramedullary lipoma. Diagrammatic representation of premature dysjunction theory in the formation of dorsal lipoma

basal surface of the neural tube can be normally induced to form dura explaining an intact dura in cases of non dysraphic subpial or intramedullary lipomas [16].

2. Defect in Secondary Neurulation causing Conus and Filar Lipomas

Secondary neurulation begins on post-ovulatory day 26–27 and consists of a process where mesenchymal cells undergo epithelization and tubulogenesis. During the early phase of the secondary neurulation, as the fusion process starts, the caudal eminence develops (at about 20–22 days of gestation). The caudal eminence gives rise to the digestive tract, blood vessels, and the somites of S1 & S 2. Cavitation in the caudal neuropore starts by day 26 and forms a secondary tube that joins the primary neural tube. The distal end of the secondary tube undergoes retrogressive differentiation and gets transformed into the filum terminale.

Using chick embryo models, Dady et al. in 2014 elucidated a complex process that ensures continuity between the primary and secondary neural tubes. This process was termed as "junctional neurulation" by them and an error in this process was hypothesized to be one of the reasons for development of neural tube defects in the thoracolumbar region [19]. The concept of junctional neural tube defect was further put forward by Eibach et al. in 2017 wherein they found that the connection between the primary and secondary neural tubes was deficient leading to formation of functional conus separate from the spinal cord leading to a closed defect [20, 21]. This phenomenon was subsequently used by Morota et al. to explain the formation of type 2 lipoma and differentiate them from type 3 lipomas, which they attributed to failure in early phase of secondary neurulation [9].

According to this new theory and classification proposed by Morota and colleagues, the aberrant primary neurulation results in type 1 lipomas, junctional

neurulation failure probably leads to formation of dysraphic conal lipoma (type 2), while the non dysraphic conal (or type 3) lipomas develop early during secondary neurulation and involve the conus medullaris to which they are directly connected [9]. Tethering of the cord often occurs followed by the formation of a proximal syrinx. Occasionally this fat is connected to the subcutaneous fat through a sacral hiatus, though they are not associated with anatomical dysraphism (no dural or bony defect). They represent the caudal type of lipomas in the older classification and the terminal type of lipoma in the Pang's classification. During this period of growth, cloacal and genital organogenesis also starts and this helps to understand the frequent association of type 3 lipomas with anorectal and urogenital anomalies.

The most common variety of nondysraphic lipomas, the lipomas of the filum terminale have been classified as type 4 lipomas in this new classification of Morota et al. and they develop during the late stages of secondary neurulation. [9] During the retrogressive differentiation phenomenon leading to filum formation, these lipomas are situated within the filum terminale. These too are not associated with anatomical dysraphism (no dural, fascial, or bony defect). They have been variously described as fatty filum or tight filum in earlier reports with a criterion for thickness to be over 2 mm [22]. In filar lipomas, conus may be normal or positioned low and may cause neurological deficits due to the tethering phenomenon during the ascent of the cord at the time of growth spurts [23]. These lipomas are usually not associated with anorectal anomalies. (Fig. 14.2(a)).

14.3 Clinical Presentation

This depends on the age of presentation and consists of local, urogenital, anorectal as well as neurological manifestation including sphincter involvement and differs in various subtypes.

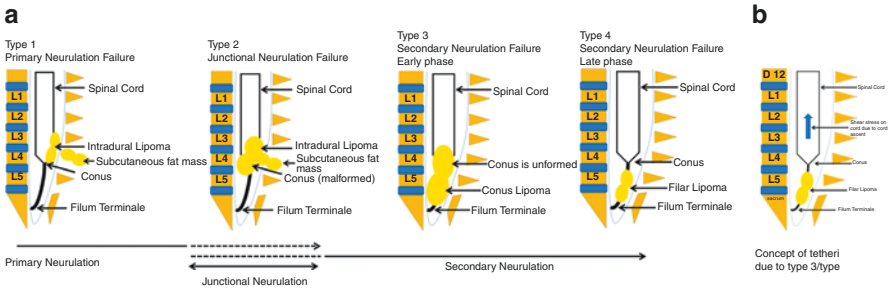

Fig. 14.2 (**a**) Types of spinal lipomas. (**b**) Concept of tethering due to conal/filar lipoma. Diagrammatic representation of development of various types of spinal lipomas due to primary, secondary or junctional neurulation failure. Failure of secondary neurulation results in conal and filar lipomas. These lipomas can cause tethering of cord with low lying conus

Dorsal spinal lipomas: These lipomas are commonly situated on the dorsal surface of cervical or thoracic region of the spinal cord. The common age of presentation is in young adults and rarely at a much later age [24]. These are the least common variety of spinal lipomas forming about 4% of all spinal lipomas [25]. These lipomas are present mostly in the dorsal subpial-intramedullary plane, with frequently an exophytic component and dural impingement. (Fig. 14.3). Rare cases

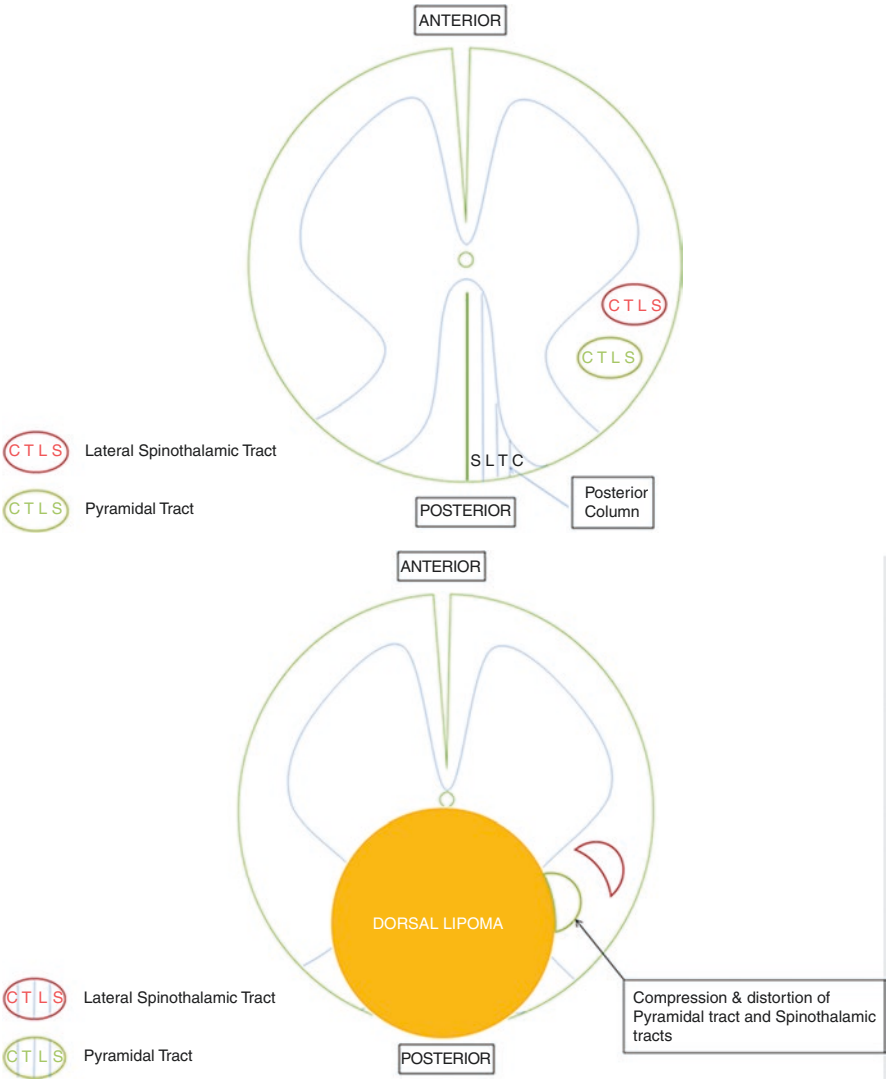

Fig. 14.3 Axial sections of spinal cord with anatomic location of dorsal lipoma. Diagrammatic representation of axial cut sections of the spinal cord showing relationship of dorsal lipomas with the compression of long tracts resulting in characteristic clinical presentation

of cervical lipoma extending intracranially causing obstruction of the fourth ventricle have also been described [26].

Patients usually complain of pain in the region of the lipoma which increases in intensity while lying down, especially at night (funicular type). This type of pain is the most common feature followed by paraesthesia and bilateral upper motor neuron (UMN) signs while bladder and bowel complaints occur later. In later stages, they may present with stiff and spastic gait with proximal and distal muscle weakness. This usually manifests as a history of loosening of footwear, difficulty in walking upstairs, difficulty in squatting, difficulty in writing, buttoning, and placing things overhead etc. Patients may complain of imbalance while walking especially at night, wash-basin sign (imbalance while splashing water over the face) and Lhermitte's phenomenon (sudden flexion of the neck produces painful paraesthesias in all the limbs) due to posterior column involvement. Irritative symptoms such as urgency, precipitancy, and increased frequency for urination suggest upper motor neuron type bladder dysfunction. Local examination in these cases shows absence of cutaneous stigmata of dysraphism. On neurological examination, these children will exhibit UMN signs like hypertonia (spasticity), hyperreflexia, extensor plantar response, absent superficial reflexes with impaired joint position and vibration sense (due to posterior column involvement). Perianal sensations are usually normal and there is bladder involvement in form of detrusor sphincter dyssynergia.

Conal and filar lipomas: Amongst these lipomas (the type 3 and type 4 lipomas as per Morota's classification), filar type are more common as compared to conal [9]. These lipomas do not have signs of anatomical dysraphism. While the filar lipomas usually present in infancy or early in life, the conal lipomas may present much later, in toddlers or older children. Filar lipomas may remain asymptomatic during life in a large number of cases. These lipomas may be associated with sacral dimple, usually present with UMN signs due to tethering of cord; bowel and bladder involvement is usually late and is of LMN type. They are not associated with urogenital or anorectal anomalies. On the other hand, the conal lipomas may present with lower motor neuron (LMN) type lower limb weakness with foot deformity. They may have early bowel and bladder involvement of LMN type (perianal anaesthesia with reduced anal tone, dribbling incontinence and absent bulbocavernosus reflex. They may be associated with anorectal or urogenital anomalies or sacral agenesis.

14.4 The Concept of Tethering of the Spinal Cord Due to Lipoma

While dorsal lipomas present only with pain or mass effect and have subtle neurological signs and symptoms, the non dysraphic lumbosacral lipomas manifest clinically because of tethering. When the child is born, the conus (the terminal end of the spinal cord) normally ends at the L3 and ascends to L1 level by adulthood. As the height of the child grows, due to disproportionate growth of the spinal canal and the

cord, during this ascent, spinal cord damage may occur due to shear stress of stretching due to tethering effect of a conus or filar lipoma, which is much exaggerated with spinal flexion. This manifests as upper motor neuron (UMN) type of clinical symptoms and signs in bilateral lower limbs with upper or lower motor type of bladder. This phenomenon can be more pronounced during growth spurts (Fig. 14.2(b)). Patients who undergo meningomyelocele repair in infancy along with the process of detethering may present with late onset deterioration of neurological function due to retethering of cord to scar tissue.

In addition to the mechanical tethering, the development of characteristic symptoms in tethered cord have been attributed to reduced cord perfusion due to tethering resulting in hypoxic-ischemic injury to the conus [27, 28] which has been shown by Yamada et al. in human and animal models [29]. Other probable cause of neurological deterioration in tethering could be due to reduced compliance of a distally fixed cord to the changes in CSF pressure [27].

14.5 Investigations and Diagnosis

1. **X ray of Lumbosacral or Cervicothoracic spine (anteroposterior (AP) and lateral views)**

   Usually, no bony abnormality is seen maybe except for lumbosacral scoliosis.

2. **MRI of Cervicothoracic spine or of lumbosacral spine with whole spine screening** (Fig. 14.4I)

   MR imaging is the most important diagnostic tool [30, 31]. MRI of the cervical, dorsal or lumbosacral region will be the primary area of interest depending on clinical signs and symptoms and is supplemented by whole spine screening to check the end of conus and fat in the filum as well as for possible Chiari malformation. Though rare, it should also be accompanied by one sequence of the brain to see for the ventricular size and/or any other associated anomaly as well. Contrast study may rarely be required, as occasionally an associated dermoid/epidermoid may be present. One should not miss association of other defects (urogenital or gastrointestinal) in the gastrulation process.

(a) *The intramedullary or dorsal subpial lipoma* is a circumscribed intradural intramedullary lesion causing compression of the cord. These lesions are usually hyperintense on T1WI and hypointense on T2WI hypointense. Hypointense signal on fat suppressed image and no contrast enhancement is characteristic [31]. Axial images are important to understand the relation of lipoma with the cord structure (Fig. 14.5).

(b) *Conal lipoma* usually shows low lying conus with classical T1WI hyperintense signal, T2WI hypointense signal with fat suppression. Lipomas are attached to the dorsal surface of the conus and extend into the cauda equina region. The lipoma is frequently associated with proximal syringomyelia. The lipoma can be seen extending into the subcutaneous fat through sacral hiatus with no obvi-

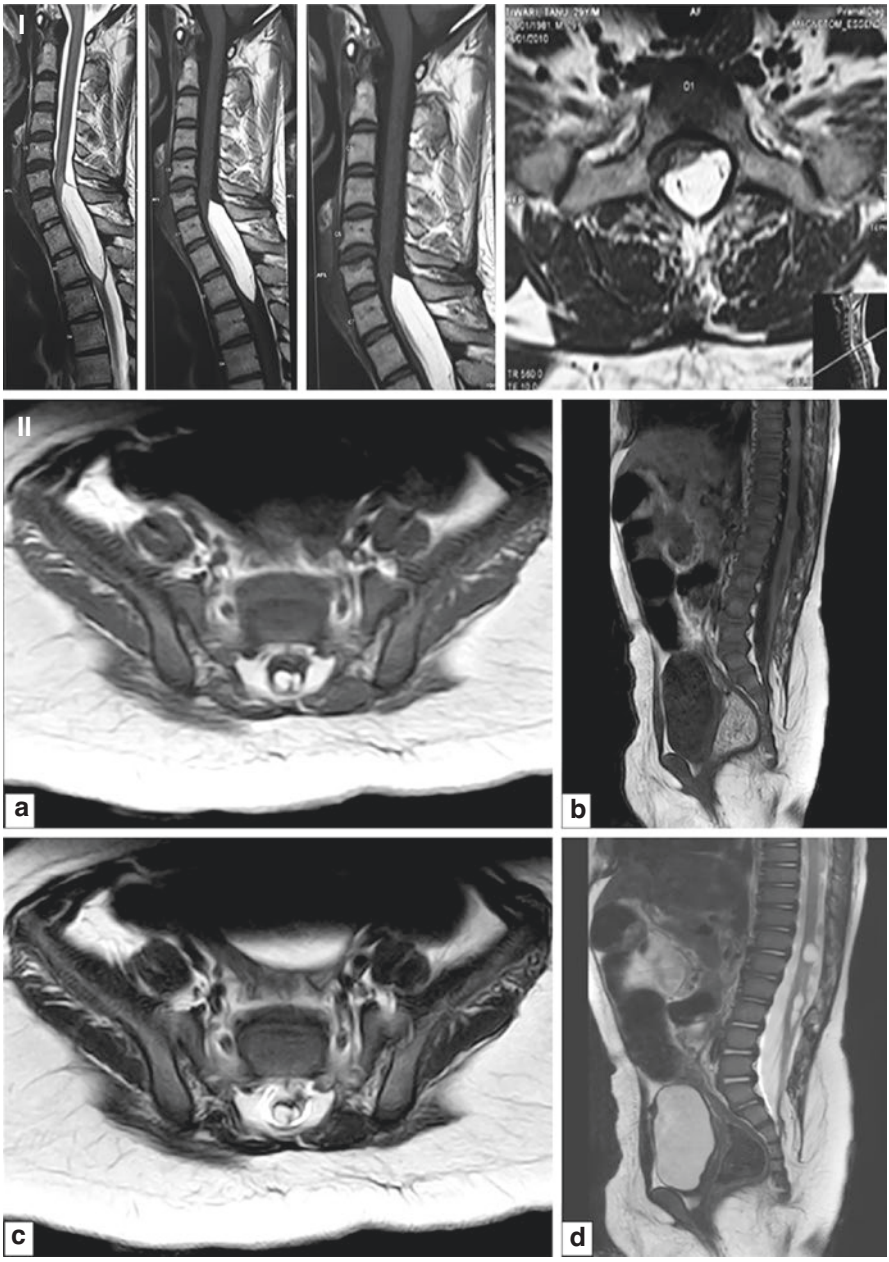

Fig. 14.4 MR images of a case: **I**: Cervicothoracic Subpial Lipoma **II**: Conal Lipoma **III**: Filar Lipoma. **I**: MRI of cervicothoracic spine (sagittal and axial views) showing cervicothoracic intramedullary lipoma located dorsolaterally and extending from C6–C7 disc space to D2–D3 disc space level. **II**: (**a**, **b**) T1WI & **c**, **d**) T2WI axial and sagittal imaging of lumbosacral spine showing an unformed conus with an intradural lipoma with low lying cord and proximal syringomyelia. **III**: (**a**) Sagittal image with conus at level (within normal range) and thick filum. (**b**) Axial image showing fat within filum

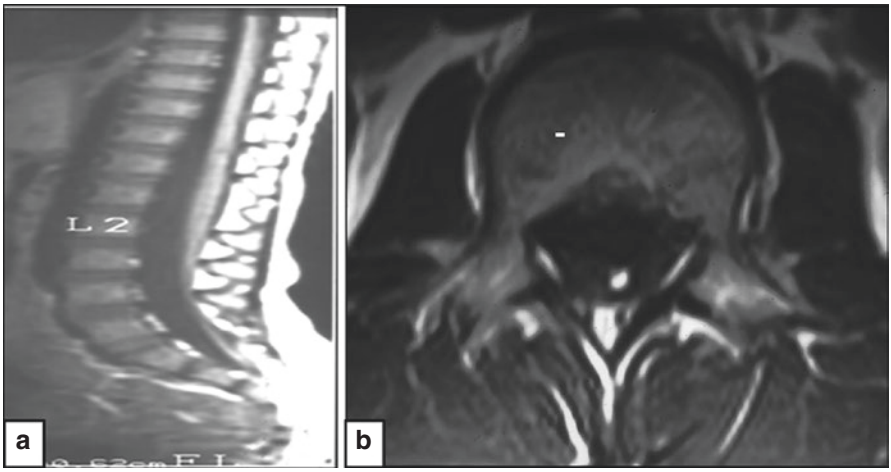

Fig. 14.4 (continued)

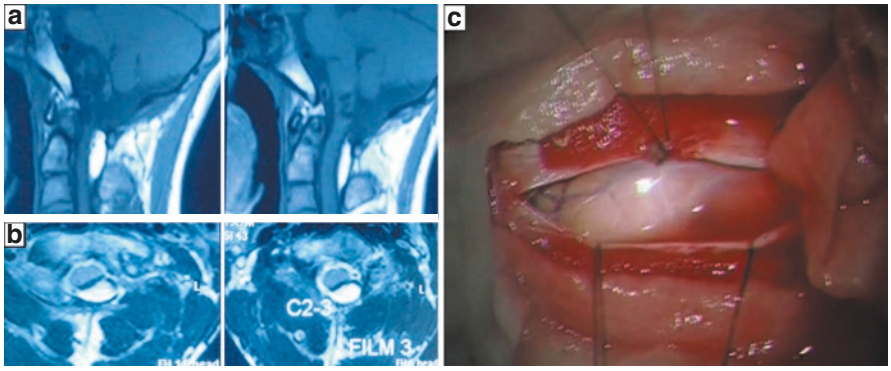

Fig. 14.5 MRI images of a subpial lipoma with morphology after opening of dura at surgery. (**a**, **b**): MRI images in sagittal and axial views showing a cervical dorsal subpial lipoma. (**c**): Morphology of a subpial lipoma after opening the dura

ous dural defect (Fig. 14.4II). 3D CT spine with bony window reconstructed images help in identifying sacral agenesis or hypoplasia. Type 3 lipomas can be associated with type 1 Chiari malformation and other defects viz. congenital abnormalities of gastrulation. An USG or CT scan of the abdomen and pelvis should be performed to see the presence of any other congenital malformation depending upon the clinical examination.

(c) *Filar lipoma* usually presents with a thick filum and a streak of fat within. This may be associated with low lying conus and descent of the filum, best seen on T1 sagittal images and confirmed on axial T1 sections. There is no evidence of extradural component in these lesions (Fig. 14.4III). Type 4 lipomas can be rarely associated with syringomyelia.

3. *USG (Ultrasonography) of KUB (Kidney, Ureter, Bladder)* should be done to look for hydronephrosis with hydroureter and post void residual urine. Post void residue (PVR) which is 1/third or more of the pre void urinary volume is considered significant. Significant PVR informs us about the lower motor neuron type of bladder. An urodynamic study is important to understand bladder dynamics to differentiate types of the bladder and to compare post-operative status. An urodynamic study is difficult to perform in infants. Urinary infections are quite common in these children and a routine urine and culture / sensitivity examination should be performed.
4. *Electrophysiological studies as EMG (Electromyography) with NCV (Nerve Conduction Study) with SSEP (Somatosensory Evoked Potential) studies* are needed to evaluate the degree of neural dysfunction, which helps to prognosticate and evaluate post-operative recovery.
5. *Post-natal USG of the spine* in suspected cases may be done to evaluate intraspinal lipoma but confirmation of any abnormality should be done by MR Imaging.

14.6 Management of Non-Dysraphic Lipomas

(A) *Dorsal spinal lipoma*: The goal of surgery here is to decompress the long tracts in the spinal cord for neurological improvement [19]. This is usually done with the help of intraoperative electrophysiological monitoring (IONM). Complete excision is often difficult in these cases due to ill-defined margins and counselling about the neurological outcome and the prognosis is of significant importance.

Surgery with Neuromonitoring and Anaesthesia planning: The anaesthesia team have an added responsibility to co-ordinate between the neurosurgeon and the monitoring electrophysiologist. Special steps to be followed include:

1. Maintaining a MAP of 70–80 mm of Hg, Normothermia, MAC (Minimum Alveolar concentration) about 0.4–03, BIS (Bi-Spectral Index) around 60.
2. The type of anaesthesia will be TIVA (Total Intravenous Anaesthesia) mostly with agents like propofol, dexmedetomidine, remifentanil with an inhalational gas agent like Desflurane, etc. No muscle relaxant is used during the procedure during monitoring.
3. During surgery initial trauma dose of steroid (Methylprednisolone) is given in our unit.

The electrophysiologist performs this monitoring which includes motor evoked potentials (MEP) for limb muscles and sphincter muscle control and somatosensory evoked potentials (SSEP). Intraoperative stimulation with monopolar and bipolar probes and D wave monitoring may be used during surgery. IONM plays a major role in preventing and predicting irreversible neurological deficit by calculating MEP amplitude, latencies, and waveforms or complete absence of waves so that further surgical steps can be modulated (Fig. 14.6).

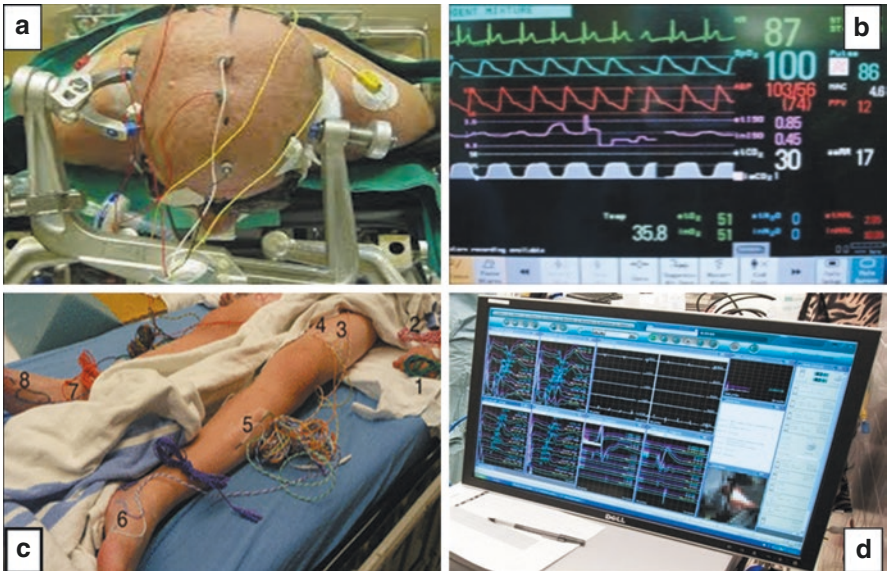

Fig. 14.6 Intraoperative Neuromonitoring (IONM) during surgery. (**a**) application of cork screw to cranium for MEP and SEP, (**b**) anaesthesia monitor, (**c**) Electrophysiological monitoring (position of electrode in lower limbs for MEP and (**d**) MEP wave pattern on monitor

Steps of Surgery for Dorsal Subpial or Intramedullary Lipoma (Fig. 14.7)

1. The patient is placed in prone position with hands-on side. Care should be taken of pressure points to prevent nerve compression.
2. Prior to positioning the patient, baseline neuromonitoring readings are taken.
3. C-arm is used to confirm the level of surgery with mainly AP images.
4. Opening of midline and removing posterior elements of the vertebra (laminotomy is preferred) is then performed; intraoperative ultrasonography helps for confirming the location and extent of the intradural lesion [32].
5. After achieving haemostasis, the dura is opened with tagging sutures.
6. Before dissection on arachnoid, neuromonitoring readings are repeated.
7. Posterior column tracts may have to be dissected occasionally when the tumor is not subpial and not coming up to the surface. Lipoma removal is then done with sharp dissection and coagulation if a proper plane can be found and till monitoring is maintained. Removal of lipoma can be done either by bipolar coagulation and micro scissors or CUSA (Cavitron Ultrasonic Surgical Aspirator) and CO_2 LASER can be used. During the removal of lipoma electrophysiological study should not show drop in amplitude below 50% to prevent neurodeficit. It is needed to generate less heat by using low power coagulation and continuous irrigation. A thin rim of lipoma may be kept over the dorsal surface of the cord in the absence of a proper plane. Pial sutures to neurulate the cord are particularly important. Before closing the surgical wound, monitoring parameters are rechecked.

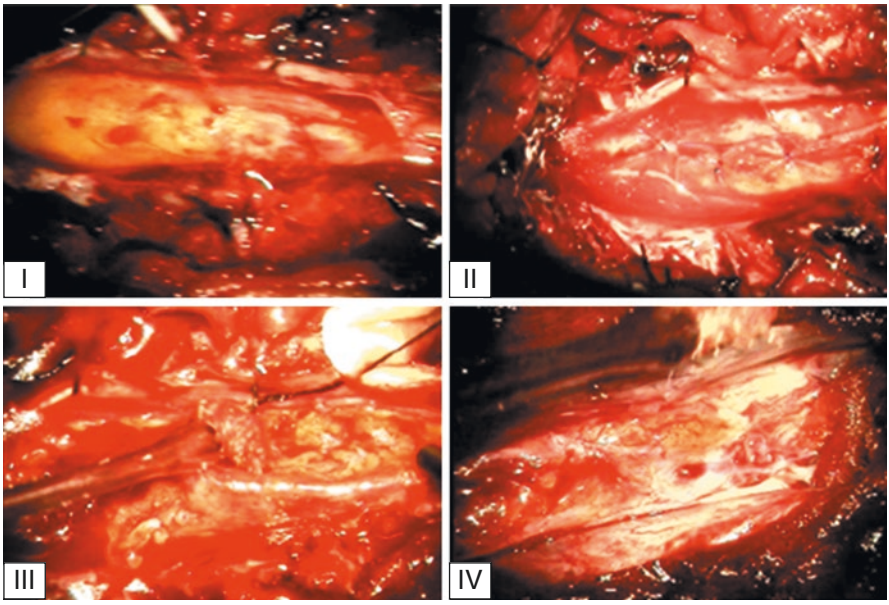

Fig. 14.7 Surgical steps for a dorsal (subpial) lipoma in cervico thoracic region. Operative steps for intradural-subpial lipoma. (**I**) Opening of the dura, (**II**) Excision of the lipoma with help of CUSA, note the sub-pial location of the lesion. (**III**) Towards the end of excision, (**IV**) Achieving proper neurulation. (For MRI images, refer to Fig. 14.4I)

8. Dura is closed with monofilament sutures (PDS is our preference) and tissue glue can be used to reinforce watertight closure.

   Pre-operative and post-operative neurological examination and comparison between them should be documented. Blood pressure and oxygenation should be well maintained for the next 24 hours.

The goal of excision in this type of lesion is to decompress the spinal cord (tracts) while preserving the neurological function. Therefore, excision is less likely to be complete. We can grade the excision as partial, subtotal, and complete. Bhatoe et al. have described 14 cases of intradural lipomas predominantly in the cervicothoracic region and impressed upon the fact that they have ill-defined margins and the goal of surgery is decompression and have reported a good recovery in all their cases with this strategy [33] The clinical outcome does not match the aggressive removal in another study which reported on experience of 5 patients with these rare lesions [34] and their proposed guidelines also suggest a less aggressive removal. Though Pang in his recent article on spinal lipomas recommends a radical resection for most lipomas except the chaotic variety [35] the subpial or intradural non dysraphic lipomas would also be an exception for radical excision.

(B) Surgery for Conal Lipoma

The goals of surgery in conal (type 3) lipomas are to detether and to excise the lipoma. The conus is tethered by lipoma and the filum terminale. Detethering

can be achieved by cutting the filum terminale and decompression of conus and nerve roots by debulking of lipomatous tissue. Either complete or enough lipoma should be removed so that neurulation with monofilament Prolene or PDS sutures to reform neural tube can be done which helps to prevent retethering in future. (Fig. 14.8).

The complete procedure requires neuromonitoring as an adjunct. Identifying filum terminale is important before cutting it. Watertight dural closure is also an important step in surgery followed by laminoplasty. Postoperative CSF leak and wound complications depend on proper closure of dura and optimum preservation of subcutaneous fat. Delayed tethering should be watched for. An associated congenital anorectal lesion should be managed with the pediatric surgery team.

(C) Surgery for Filar Lipomas

Blount and Elton broadly classified lipomas of filum terminale into 4 types based on position of conus and presence of clinical signs or symptoms. As the operative morbidity for this lesion is very low, they strongly advised surgery for Grade 1 lipomas (symptomatic patient with low lying conus with fatty filum)

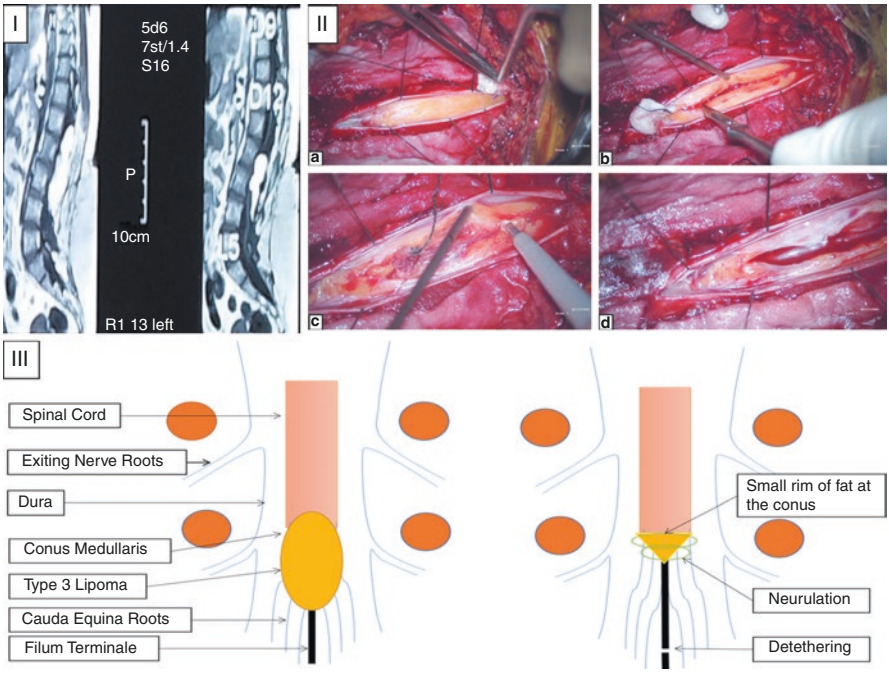

Fig. 14.8 Surgical steps for Conus lipoma. (**I**) T1WI of LS spine showing a type 3 lipoma involving the conus. (**II**) Intraoperative picture of conal Lipoma demonstrating the surgical Steps: (**a**). Exposure of conal lipoma, (**b**). Incision through middle of lipoma (**c**). Debulking with help of CUSA (**d**). Small remnant at the conus at the end of excision (Pictures 14.8 I and II courtesy of Dr. N. Venkataramana). (**III**) Diagrammatic representation of location of type 3 lipoma and diagrammatic representation of partial excision of type 3 lipoma with a small residual lesion at the conus followed by neurulation with pial sutures and detethering of cord

and emphasized on using discretion in and Grade 3 lipomas (symptomatic patient with normal position of conus with fatty filum). However, the role of surgery in asymptomatic patients (Grade 2 with low lying conus and Grade 4 with normal position of conus associated with fatty filum) remains ill-defined as many of them remain asymptomatic and stable through life [27].

In filar lipoma, detethering is the goal of surgery as there is no compressive mass lesion. Usually, the conus is low lying and at first identifying and then cutting of filum terminale achieves this goal effectively. We identify the filum by its typical morphology, as it usually contains some fat and is accompanied by a corkscrew vein, unlike the neighbouring roots. Further confirmation can be done by stimulation with the monitoring probe. Filum is cut with Liga clips applied at two places a centimetre apart and dividing it in between the clips to avoid bleeding and coagulation (Fig. 14.9).

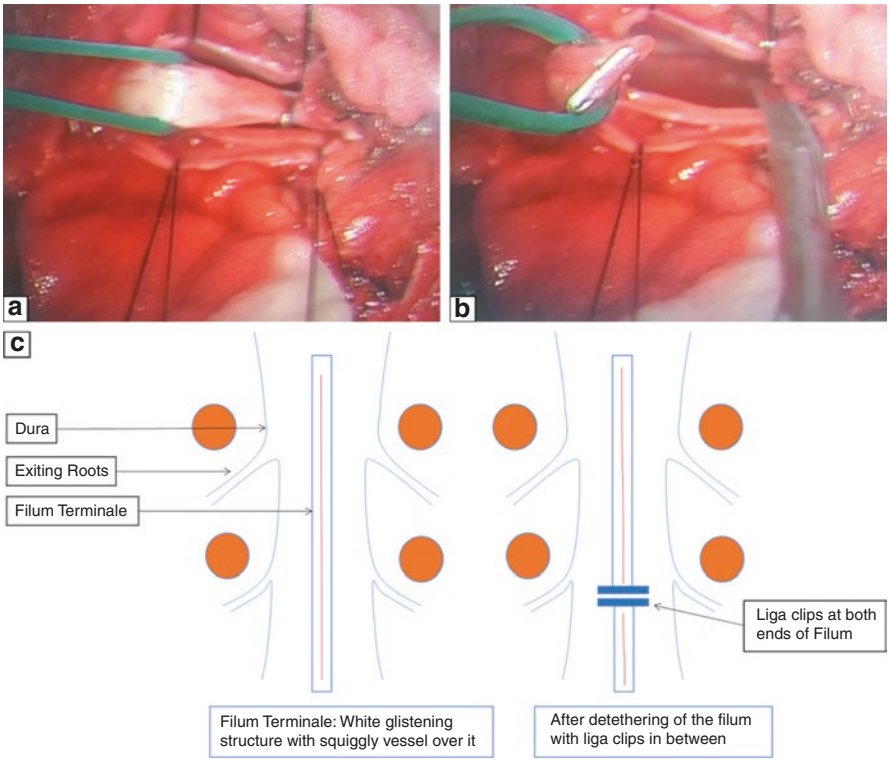

Fig. 14.9 Surgical steps for Filar lipoma. Intraoperative images of excision of a filar lipoma. (**a**) filar lipoma with taut filum terminale and fat within (**b**) Following detethering of cord by cutting (in between the liga clips applied on the edges) the filum (**c**) Diagrammatic representation of detethering of filar lipoma

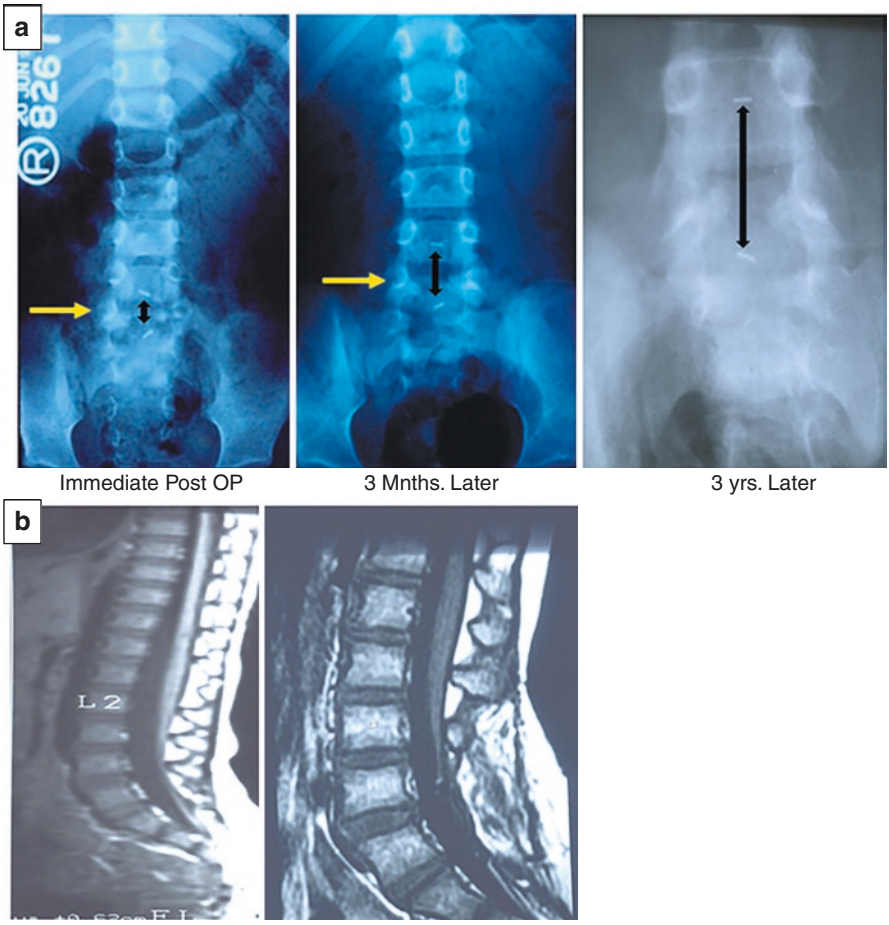

Fig. 14.10 (**a**) Post-operative X Rays of the LS spine after cutting a filar lipoma. (**b**) Pre & Post-operative MRI–LS spine of same case. (**a**) Post-operative X rays of LS spine (AP view) showing the relative increase in the distance between the two liga clips over a period of time indicating adequate cord ascent. (**b**) Pre-operative & post-operative MRI LS spine (sagittal sections) showing complete division of the filar lipoma with relaxed end of filum which is unattached to the posterior dura

A post-operative X-ray is done to see the separation of Liga clips and this distance may increase on further follow-up (Fig. 14.10(a)). After closing the dura, a layer of fat and fibrin glue can be used to reinforce the suture line. Proper closure of thoracolumbar fascia is also important to prevent CSF leak and formation of pseudomeningocele. Follow-up MRI usually shows a relaxed end of the filum without posterior attachment (Fig. 14.10(b)). No postoperative worsening or retethering is reported in follow up of this type of lipoma in large series of cases [36]. A detailed intraoperative electrophysiological monitoring is not required except occasionally to identify the filum.

14.7 Post-Operative Management

The patient is not mobilized for first 24–48 hours but can be turned in bed from one side to another. A sequential compression device (SCD) may be used to prevent deep venous thrombosis. Low molecular weight heparin can be started after 48–72 hours of surgery if patient is unable to walk. With the help of a physiotherapist, the patient is then mobilized out of bed. The postoperative dressing is checked after 48–72 hours. Suture removal is done on or after 14 days. Patients who have LMN type of bladder are kept on a silicone catheter for 4–6 weeks. In other patients, the urinary catheter is removed once the patient is mobilized. An ultrasound study to determine the post void residual (PVR) urine volume may be done. If PVR is significant then clean intermittent self-catheterization (CISC) procedure is advised. Follow-up MR imaging is done after 3 months.

Overall aim of the surgery is stabilization of the neurological deficit and control of the disease. Neurological improvement may be seen in patients with effective decompression and detethering, even in those with late presentation. [37] Rehabilitation forms an important aspect of post-operative management and includes physiotherapy for the neurological deficit, bladder care, and counselling of parents.

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Part IV
Tumors

Chapter 15
Predisposing Syndromes

Kalliopi Stefanaki

15.1 Introduction

Central Nervous System (CNS) neoplasms are the most common solid tumors in children and constitute the second most frequent malignancy, second only to leukemias. Although the majority of nervous system tumors occur sporadically, possible genetic susceptibility exists in a substantial number [1]. The latest advances in genetics and molecular biology have shed light to several inherited conditions that are associated with increased risk for developing CNS neoplasms. The majority of tumor predisposition syndromes have autosomal dominant inheritance pattern, such as Neurofibromatosis type 1 and 2 and Li-Fraumeni syndrome [1]. In a recent analysis of genetic alterations in a cohort of childhood cancers, 7.6% of samples found to be associated with a pathogenic germline variant. Most germline variants were associated with DNA repair genes from mismatch and double-stranded break repair. An important finding was that 52% of primary pediatric neoplasms harbor a potentially targetable genetic event [2]. The most common CNS familial tumor predisposition syndromes are Neurofibromatosis type 1 and 2. Tuberous sclerosis complex, Turcot syndrome, Li-Fraumeni syndrome, Cowden disease, Rhabdoid Tumor Predisposition Syndrome and DICER1 [1, 2]. Herewith, we provide a review on the characteristics of CNS tumors that are associated with the above mentioned genetic syndromes.

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15.2 Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) was delineated as a distinct nosological entity by von Recklinghausen in 1882. NF1 is an autosomal dominant disorder affecting approximately 1/3000 individuals and characterized by mutations of the *NF1* gene located on chromosome 17q11.2 [3]. The gene spans approximately 350 kb and contains 60 exons. The *NF1* genes codes for neurofibrin, a protein located in the cytoplasm, that belongs to GTPase-activating protein group. Inactivation of *NF1* in turn activates RAS signaling cascade and leads to activation of mitogenic mediators like cAmp, AKT, ERK1/2, RAF, PI3K and mTOR [4].

NF1 is the most frequent among the neurocutaneous disorders. Approximately half of all cases are spontaneous mutations. The diagnosis can be made clinically requiring at least 2 from the following: more than 6 café-au-lait spots or hyperpigmented macules, optic nerve glioma, skinfold freckling, more than 2 typical neurofibromas or one plexiform neurofibroma, Lisch nodules, sphenoid dysplasia or long-bone abnormalities such as pseudarthrosis and first-degree relative with NF1 [5]. Neurofibromas are among the most frequent manifestations in these patients, however cases without NF1 can also be found (Fig. 15.1) [6]. The tumors of CNS

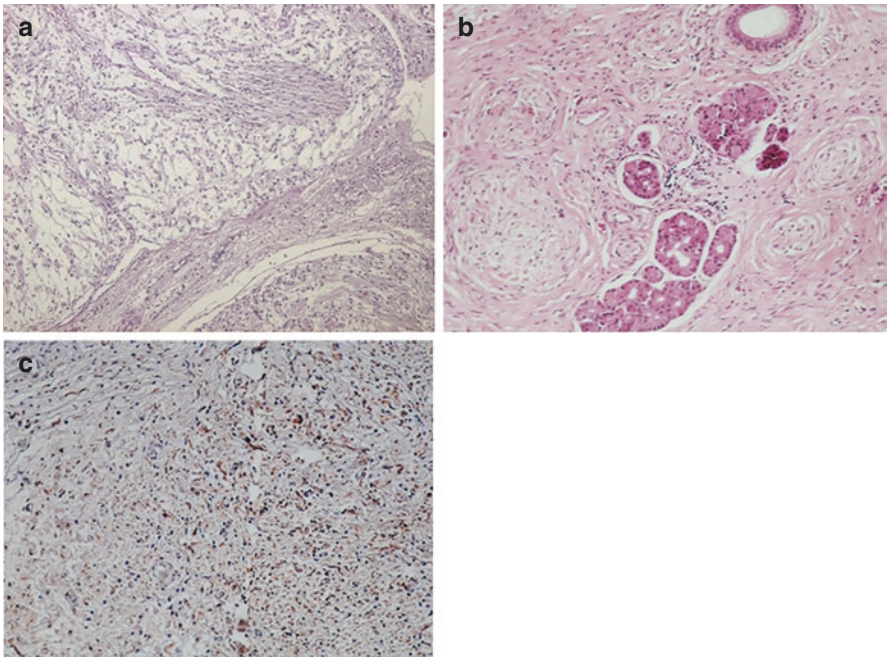

Fig. 15.1 (**a**) Histopathological findings of plexiform neurofibromas. Schwann cells and fibroblasts in a variable matrix of collagen fibers and myxoid material are the major cellular components. (**b**) Entrapment of salivary gland acini in the nerve bundles of a plexiform neurofibroma. (**c**) Heterogenous S-100 expression.in the Schwann cells

more frequent observed in NF1 are pilocytic astrocytoma, diffuse astrocytomas and high-grade gliomas and from the peripheral nervous system the malignant peripheral nerve sheath tumors (MPNST) which is highly malignant and Triton tumors or Gastrointestinal stromal tumors (GIST) [7]. Furthermore, in patients with NF1 there might be non-neoplastic disorders such as macrocephaly, cerebrovascular disorders, epilepsy or neurocognitive deficits [3].

15.2.1 Tumors of the Central Nervous System

Among the CNS tumors, pilocytic astrocytoma is the most common neoplasm associated with NF1, whereas optic pathway gliomas affect 15–20% of children. Furthermore, approximately 1/3 of patients diagnosed with a pilocytic astrocytoma have NF1. Optic pathway gliomas usually do not require pretreatment pathological confirmation of the diagnosis and remain stable or grow slowly and may even regress. However, half of the patients have visual impairment. Girls may exhibit five times more frequent visual loss and require treatment [8]. Chemotherapy usually involves carboplatin with vincristine, whereas selumetinib, a selective inhibitor of MAPK kinase (MEK) 1 and 2 that can be administered *per os*, showed confirmed partial responses after long-term dose-adjusted treatment. Selumetinib administration was not associated with excess toxic effects [9].

NF1 and sporadic pilocytic asrocytomas are similar tumors of low to moderate cellularity, well-circumscribed and exhibit a biphasic histologic pattern of loose textured multipolar cells and compact bipolar cells with Rosenthal fibers (Fig. 15.2). Immunohistochemistry shows heterogenous expression of glial fibrillary acid protein (GFAP) mainly in the compact bipolar cells and of oligodendrocyte transcription factor 2 (OLIG2) predominantly in the loose textured multipolar cells. The Ki-67/MIB-1 index is low ranging from 0–3.9% (mean 1.1%). On the contrary, optic pathway pilocytic astrocytomas are diffuse in the nerve and difficult to stage. Diffuse astrocytomas, mainly of low-grade and usually in children over 10 years of age may be observed. High-grade gliomas and glioblastomas are not so frequent [3]. In a study of 4 glioblastomas in NF1 patients all tumors were well-circumscribed. None of these tumors had *IDH1*, *BRAF* gene mutation or *TERT* gene promoter mutation. The patients exhibited a relative favorable prognosis [10].

15.3 Neurofibromatosis Type 2

Wishart in 1822 first described a syndrome consistent with Neurofibromatosis type 2 (NF2). NF2 has an autosomal dominant mode of transmission with an incidence estimated to be 1 per 40.000 newborns. The syndrome is due to inactivation of the *NF2* gene **located on chromosome** 22q12. The gene spans approximately 110 kb and encodes the protein Merlin which belongs to ezrin, radixin, moesin superfamily

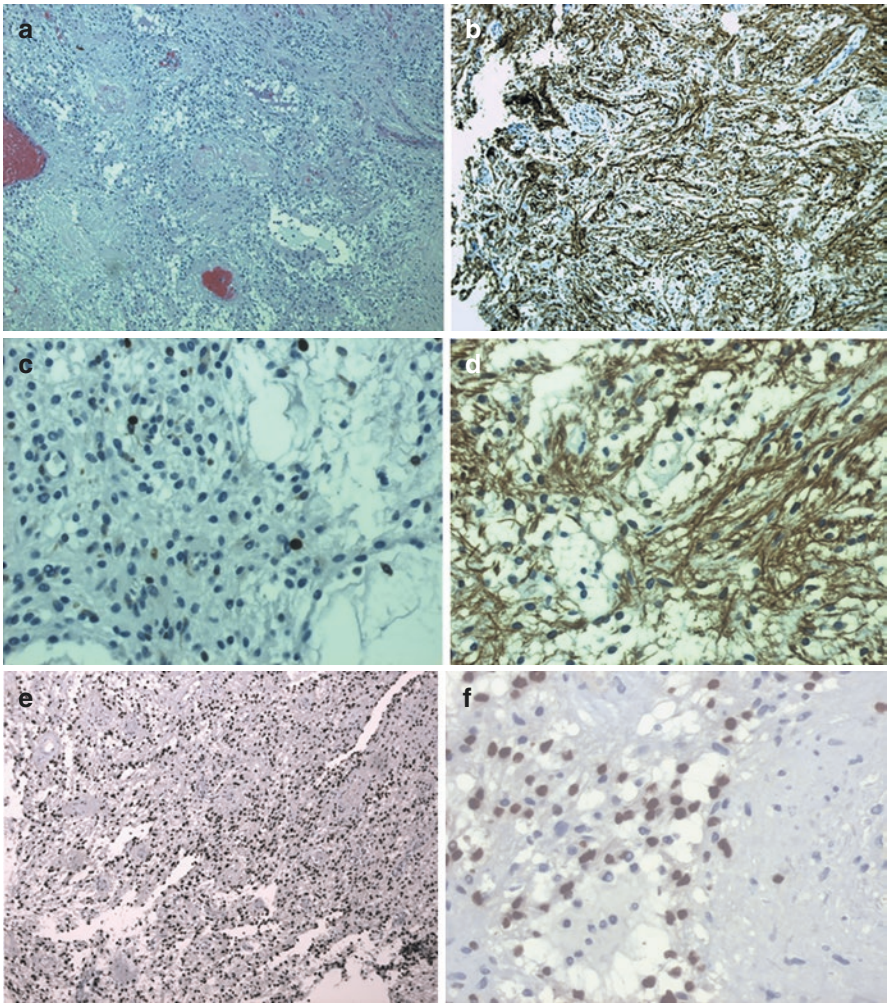

Fig. 15.2 (**a**) A NF1-associated pilocytic astrocytoma exhibiting similar findings to the sporadic form with a biphasic pattern. There are compact bipolar cells alternating with small cystic spaces. (**b**) Immunohistochemical expression of GFAP mainly in the bipolar piloid cells. (**c**) Low Ki-67/MIB-1 immunohistochemical expression. (**d**) Higher magnification of GFAP expression. (**e**) Immunohistochemical expression of OLIG-2 mainly in the nuclei of multipolar cells. (**f**) Higher magnification of OLIG-2 expression

of cytoskeleton associated proteins. Merlin downregulates mTOR complex 1 which in turn is implicated in the growth of schwannomas and meningiomas [11]. Several other signaling pathways, such as Wnt/β-catenin, PI3K-Akt, Ras, Rac/Rho and Hippo have been implicated [12]. Several germline and somatic mutations of *NF2* gene have been reported supporting its tumor suppressor function. Inactivating *NF2*

mutations have been reported in 60% of sporadic meningiomas and schwannomas. The Manchester diagnostic criteria for NF2 are widely used and describe additional diagnostic criteria apart from bilateral vestibular schwannomas or family history of NF2. Recently, even the presence of bilateral vestibular schwannomas, was reported to occur by chance. Presence of ependymoma showed 100% positive predictive value in a database of 2.777 individuals with molecular testing [13].

15.3.1 Schwannomas (WHO, Grade I)

The vast majority of schwannomas (90%) are solitary and sporadic and approximately 4% arise in the context of NF2. However, schwannoma is the most common tumor in patients with NF2. When located intracranially they exhibit a strong predilection for the eighth cranial nerve and only rarely for the trigeminal nerve or oculomotor nerve. These tumors are composed of neoplastic schwann cells with Antoni A areas of elongated cells with nuclear palisading, whorling patterns, and Verocay bodies (Fig. 15.3). There is also Antoni B regions with textured cells with indistinct processes and variable lipidization. Immunohistochemistry reveals diffuse strong staining of S-100 protein and basement membrane markers. There is also variable expression of GFAP, CD57/Leu-7 and calretinin. VEGF was expressed in 100% of vestibular schwannomas and VEGFR-2 in 32% of tumor vessels on immunohistochemical analysis. Using bevacizumab, to block VEGF, there was hearing improvement in some NF2 patients. Bevacizumab was administered based on an immunohistochemical analysis that showed 100% VEGF expression in vestibular schwannomas and 32% of VEGFR-2 in tumor vessels [14].

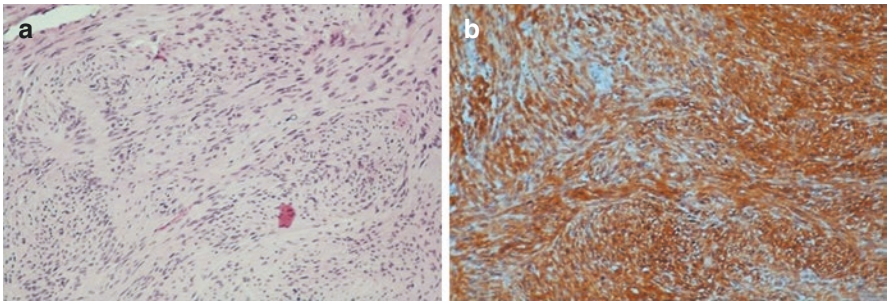

Fig. 15.3 (**a**) In the cellular Antoni A areas the tumour nuclei may show a tendency to align in alternating parallel rows, forming nuclear palisades. When marked, nuclear palisades are referred to as Verocay bodies shown in this Fig. (**b**) Diffuse strong S-100 expression in the neoplastic cells [cytoplasmic and nuclear]

15.3.2 Meningioma

Meningiomas are the most frequent primary brain tumor in adults. In NF2, meningioma is the second most frequently identified tumor and occurs intracranially in approximately 50% of these patients while spinal meningioma is observed in 20% of patients. Presence of multiple meningiomas is a hallmark of the syndrome and contrary to sporadic, meningiomas related to NF2 occur at an earlier age. Histologically, all benign subtypes can be found, however fibrous variant is the most common [15]. Atypical histology and peritumoral edema have also been reported frequently and have been significantly associated with preoperative seizures (Fig. 15.4) [16].

15.3.3 Ependymoma

Ependymomas can be found in nearly 1/3 to 1/2 of patients with NF2 and are usually of grade II. Spinal ependymomas are usually multiple, they can be intramedullary or located in the cauda equina. Histologically, perivascular pseudorosettes and ependymal rosettes are the main diagnostic features (Fig. 15.5). Pilocytic and

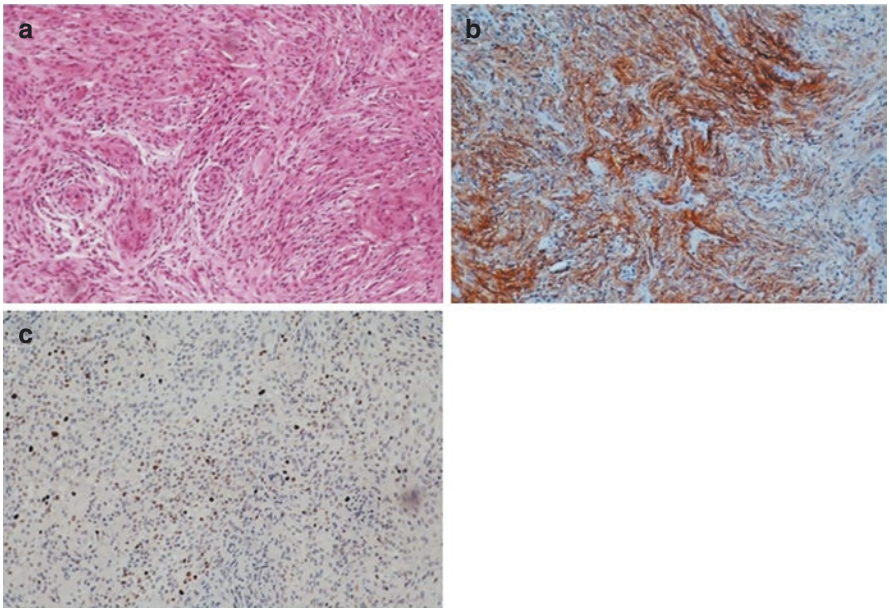

Fig. 15.4 (**a**) A case of NF-2 related meningioma. (**b**) Immunohistochemical expression of EMA. (**c**) Moderate expression of Ki-67/MIB1 in the nuclei of the neoplastic cells

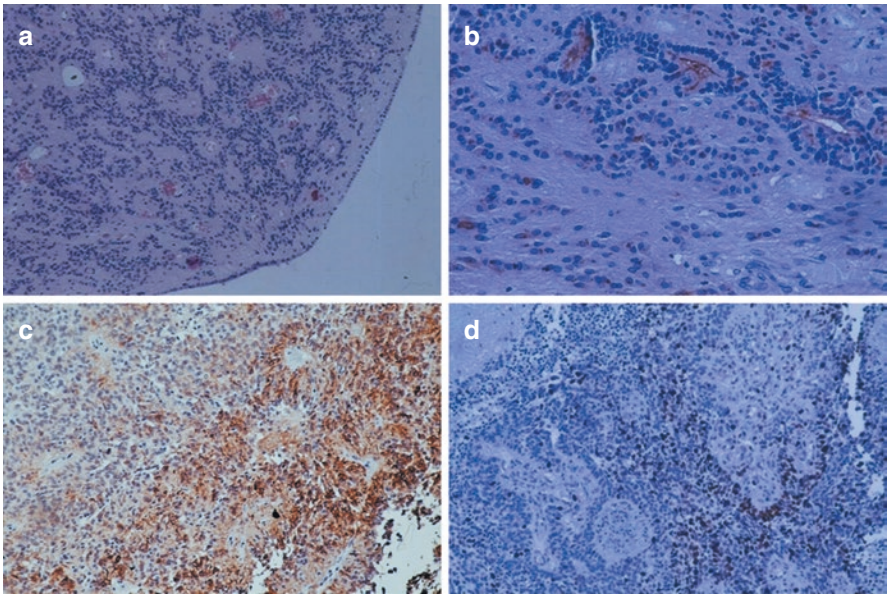

Fig. 15.5 (**a**) A case of classical ependymoma. Characteristic perivascular pseudorosettes and ependymal rosettes. (**b**) Classical ependymoma Immunohistochemical expression of EMA in ependymal rosettes [membranous] and dot-like cytoplasmic expression in the adjacent neoplastic cells. (**c**) Immunohistochemical expression of GFAP in an anaplastic ependymoma. (**d**) Ki-67/MIB-1 expression in an anaplastic ependymoma

diffuse astrocytomas are not so common. Bevacizumab treatment has been shown to improve symptomatology in NF2-related spinal ependymoma in selected cases, however half of the patients experienced radiographic response 3 to 6 months post-treatment [17].

15.3.4 Other Tumors

Other less frequent nervous system manifestations associated with NF2 are: A) Schwannosis, which is a proliferation of Schwann cells not forming a tumor. B) Meningioangiomatosis is a cortical plaque-like proliferation of meningothelial and fibroblast-like cells surrounding small vessels. NF2-associated cases of meningiomatosis are usually multiple and asymptomatic, whereas sporadic cases are associated with epilepsy and should be considered in cases of intractable epilepsy. Gross total excision is usually associated with favorable outcome [18]. C) Glial microhamartomas is another rare manifestation composed of clusters of small stellate cells with atypical pleomorphic nuclei, immunopositive for S-100 and Merlin with low GFAP expression [1].

15.4 Tuberous Sclerosis Complex and Subependymal Giant Cell Astrocytoma

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder due to mutations in *TSC1* gene located on chromosome 9q. *TSC1* gene encodes the protein hamartin and *TSC2* gene on chromosome 16p encodes the protein tuberin. Both genes are tumor suppressors and are involved mainly in the mTOR regulatory pathway [19]. The prevalence of TSC is approximately 1:6000 newborns and the diagnosis is based on the clinical criteria revised in 1998 [1]. The criteria have been revised by the 2012 International Tuberous Sclerosis Complex Consensus Group and included genetic testing and reduced possible, probable and definite diagnostic classes to only possible and definite [20]. Hamartomas are benign neoplastic lesions and the hallmark of TSC affecting central nervous system and several non-neural tissues. Main CNS findings are cortical hamartomas (tubers), subcortical glioneuronal hamartomas, subependymal glial nodules and subependymal giant cell astrocytomas (SEGA) (Fig. 15.6) [1, 19]. Extraneural manifestations of NF2 comprise cutaneous angiofibromas, visceral cysts, peau chagrin, subungual fibromas, cardiac

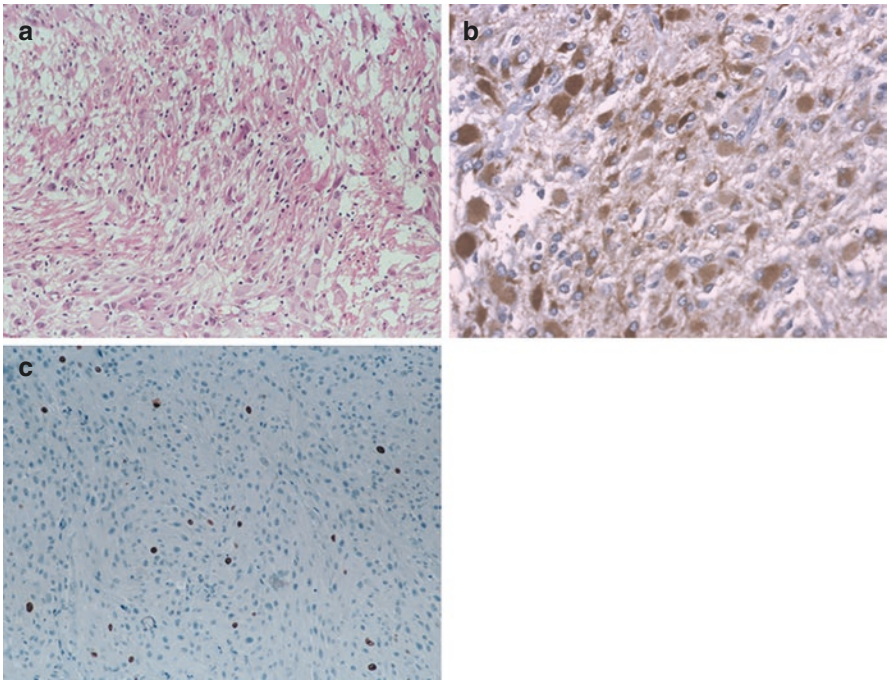

Fig. 15.6 (**a**) A case of a SEGA. Large astrocyte-like cells and spindle cells in a fibrillary matrix. (**b**) Heterogenous expression of GFAP in the neoplastic cells. (**c**) Low Ki-67/MIB-1 expression in the nuclei of the neoplastic cells

rabdomyoma, intestinal polyps, lymphangioleiomyomatosis, and renal angiomyolipoma.

Subependymal nodules are a major diagnostic criterion for TSC and can be found in lateral ventricles. Pathologically they are similar to SEGA. SEGA is a slowly growing neoplasm, grade I according to WHO Classification 2016 typically arising from the caudothalamic groove wall of the lateral ventricles in 5–15% of TSC patients. Sybependymal nodules are considered to be precursor lesions of SEGA. SEGA more frequently is observed in the first two decades of life, although infantile and congenital cases have been reported as well. These lesions may cause hydrocephalus due to obstruction of the foramen of Monro and epilepsy. Rarely massive hemorrhage can be observed. Histologically SEGA is composed of clusters of large astrocyte-like cells with variable astroglial phenotypes, spindle cells and ganglioid cells in a variable fibrillary matrix. Characteristic features are: a) the presence of large gemistocytic-like glial cells with glassy eosinophilic cytoplasm b) the perivascular arrangement of neoplastic cells and variable calcifications.

Giant cells, pleomorphism and mitoses are occasionally observed, whereas necrosis or microvascular proliferation, when present, are not definite signs of malignancy. Immunohistochemically neoplastic cells show a mixed glioneuronal phenotype, with variable expression of S-100 protein, glial markers such as GFAP, neuronal markers like, Neurofilaments, b-Tubilin-III and rarely Synaptophysin (Fig. 15.5). Apart from surgical excision, everolimus, an inhibitor of the mammalian target of rapamycin, has been shown to produce a clinically meaningful reduction in volume of these tumors and in seizure frequency [21].

15.5 Cowden Disease

Cowden disease (CD) is an autosomal dominant disorder caused by germline mutations of the *PTEN* tumor suppressor gene located on chromosome 10 (10q23.3). *PTEN* encodes a dual phosphatase protein and is the only central negative regulator of PI3K signaling [22]. Cowden disease is estimated to affect about 1:250.000 individuals, while the incidence of Lhermitte-Duclos disease is unknown [23]. The cardinal findings are multiple hamartomas, involving tissues from the three germ layers, oral mucosal papillomas, gastrointestinal polyps and an increase risk of breast, endometrial, non-medullary thyroid cancer and other cancers. The criteria for the diagnosis of CD have been established by the International Cowden Syndrome Consortium and include both major and minor criteria [23]. Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease) is a benign tumor composed of multiple gangliocytes with distinct nucleoli corresponding to a grade I lesion according to WHO.Classification,2016 An important diagnostic finding is the preservation of cerebellar architecture without obliteration of the folia. Microcalcifications and ecstatic vessels are frequently found. Immunohistochemistry reveals expression of Synaptophysin in the band-like tumor and expression of

Purkinje cells markers (leu4, L7, PEP19). There is loss of PTEN nuclear expression in the dysplastic neurons. Since CS is associated with activation of the PI3K-Akt-mTOR pathway due to *PTEN* inactivation, mTOR inhibitors as therapeutic agents have been investigated. Sirolimus proved to be well tolerated in 18 patients with CD and showed some evidence of clinical improvement, skin and gastrointestinal lesions, cerebellar function as assessed by the modified Scale for the Assessment and Rating of Ataxia, and down-regulation of mTOR signaling [24].

15.6 Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is an autosomal dominant disorder caused by germline mutation in the *TP53* gene located on chromosome 17p13.1. Checkpoint kinase 2 gene (*CHEK2*) at 22q12.1 has been considered as a second susceptibility locus. The *P53* is a tumor suppressor gene and has a pivotal role in apoptosis, genomic stability, and angiogenesis [1, 25]. Several criteria for diagnosis of LFS have been proposed. Among them, Chompret criteria are used to define patients requiring germline *TP53* testing [26]. Neoplasms that usually occur in LFS are sarcomas, osteosarcomas, breast cancer, brain tumors and adrenocortical carcinomas in children and young adults. An analysis of 475 tumors in 91 families reported that brain tumors occur in 12% of patients [27]. In infants the most common brain tumor is choroid plexus carcinoma, in children medulloblastomas (Fig. 15.7), usually of the SHH and WNT molecular subgroups, and in adults infiltrative astrocytomas. Pediatric astrocytomas are usually IDH-wildtype. Histologically, brain tumors found in LFS patients are similar to their sporadic counterparts. In patient with high index of suspicion and clinical criteria for LFS, germline TP53 testing should be performed. LFS patients require close surveillance by means of annual brain MRI according to National Comprehensive Cancer Network.

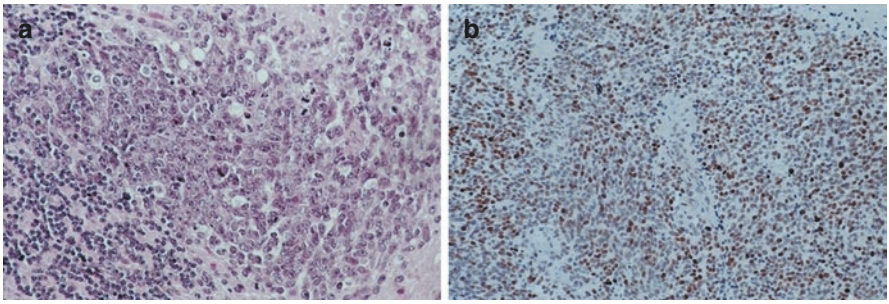

Fig. 15.7 (**a**) A large cell medulloblastoma associated with Li-Fraumeni syndrome. (**b**) Immunohistochemical expression of p53 protein in the nuclei of the neoplastic cells

15.7 Turcot Syndrome

Turcot syndrome (TS) can be classified in TS type 1 and type 2. In type I there is no familial adenomatous polyposis (FAP) and there are germline mutations in DNA mismatch repair genes (*MMR, PMS2, MHL1, MSH2*) [1, 27]. In TS1 there is hereditary non–polyposis-related colorectal cancer and regarding brain tumors, glioblastoma may occur usually before the age of 30 and is usually characterized by better prognosis. The TS type 2 can be found in patients with FAP, which has an autosomal dominant inheritance and there is *APC* gene mutation (5q21). The *APC* gene encodes a protein that interacts with b-catenin and mediates its degradation [1]. Medulloblastomas occurring in these patients, usually after the age of 10, are usually of the WNT molecular subtype. Histologically, CNS tumors are similar to their sporadic counterparts and are treated accordingly.

15.8 Atypical Teratoid Rhabdoid Tumour / Rhabdoid Tumour Predisposition Syndrome [RTPS 1 and 2]

Atypical Teratoid Rhabdoid tumour (AT/RT), grade IV, can occur sporadically or as a part of Rhabdoid Tumour predisposition syndrome (RTPS) [28–30]. AT/RT represents 1–2% of pediatric brain tumours and 10% of CNS tumours in infants, showing aggressive biological behaviour. AT/RT can be supratentorial or infratentorial, whereas spinal localization is rare. RTPS is a disorder characterized by an increased risk to develop malignant rhabdoid tumours (AT/RT, renal, extrarenal extracranial rhabdoid tumours) generally due to constitutional loss or inactivation of one allele of *INI1/hSNF5/SMARCB1*, tumor suppressor gene on chromosome 22q11.2. Mutation or loss of the *INI1/SMARCB1* gene locus at 22q11.2 is the genetic hallmark of AT/RT. INI1 protein is a component of the mammalian SWI/SNF complex, controlling chromatin remodelling and is recruited to promoters of genes regulating growth, cell cycle and differentiation. Loss of the INI1 protein is seen in almost all AT/RT cases and 75% of them have deletions or mutations of the *INI1* gene. Mutations of *SMARCA4/BRG1*, an alternate locus of the SWI/SNF complex can cause RTPS 2. Although AT/RT is genetically simple, recent molecular studies revealed that AT/RT is comprised of 3 distinct epigenetic subgroups: AT/RT-TYR, AT/RT-SHH, ATR/RT–MYC. AT/RT-TYR are mostly infratentorial, with broad *SMARCB1* deletions and overexpression of melanosomal antigens [28–30]. AT/RT-SHH are supra and infratentorial with focal *SMARCB1* aberrations and overexpression of the SHH pathway. AT/RT–MYC are mostly supratentorial, with focal *SMARCB1* deletions and overexpression of MYC and HOX cluster.

Histologically the hallmark of AT/RT is heterogeneity. Rhabdoid cells are the characteristic features in many cases. In 2/3 of the cases AT/RT, a small cell component predominates, while mesenchymal differentiation and epithelial differentiation

are less common. Abundant mitoses and geographic necrosis are common features. Immunohistochemistry reveals expression of various markers reflecting the polyphenotypic differentiation of AT/RT. Vimentin, EMA, less frequently Smooth muscle actin are consistently detected in rhabdoid cells, while GFAP, Neurofilaments, Keratins especially Keratin 8, Synaptophysin are commonly seen. Glypican 3, SALL-4 and Osteopontin have also been reported in AT/RT. Immunohistochemical staining for expression of the INI1 protein is a sensitive and specific marker for AT/RT, since biallelic inactivation of the INI1 gene results in loss of nuclear expression in the tumors, while normal cells and the other embryonal neoplasms retain nuclear staining.

15.9 DICER1 Syndrome

DICER1 syndrome is a recently described cancer predisposing syndrome and is an autosomal dominant disorder caused by genetic alterations of *DICER1* gene located on chromosome 14 [31]. The gene encodes a RNase III enzyme that is involved in micro-RNA (miRNA) processing. A study on the prevalence of pathogenic DICER1 variants showed a range between 1:310–1:10.600 [32]. Tumors associated with DICER1 are pleuropulmonary blastoma (PPB), usually in children under the age of 7, cystic nephroma and Ovarian Sertoli-Leydig cell tumor. Regarding CNS manifestations, metastasis of PPB to the brain is the most frequent followed by pituitary blastoma, pineoblastoma and ciliary body medulloepithelioma. Moreover, recently DICER-1 associated CNS sarcomas and ETMR [embryonal tumor with multilayered rosettes]-like infantile cerebellar tumors have been described in DICER1 patients [31].

15.10 Conclusion

Diagnosis of a familial tumor predisposition syndrome is important for both patients and their families. Certain surveillance and screening recommendations exist for several syndromes. Furthermore, many familial tumor predisposition syndromes affect the nervous system. Over the last years new syndromes have been identified, whereas hole-genome and transcriptome analysis will certainly provide more data to better characterize these syndromes and to provide potential new therapeutic targets.

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Chapter 16
Scalp and Skull Tumors

Georgios Alexiou, Georgios Kafritsas, and Neofytos Prodromou

16.1 Introduction

Scalp and skull lesions in children are relatively frequent, and they often constitute a diagnostic challenge. The age of the child narrows the differential diagnosis, with congenital and benign lesions being more commonly diagnosed in neonates and infants, while in older children, inflammatory and, in particular, neoplastic lesions need to be identified [1, 2]. For lesions that require biopsy, and enlarging masses, complete excision should be performed, with careful attention to the risk of disfigurement. In some cases, resection may require immediate reconstruction. Patients suspected of having Langerhans cell histiocytosis (LCH) should be evaluated for systemic disease.

16.2 Diagnostic Procedures

Even in the era of ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) plain X-rays continue to be of great value for the differential diagnosis of scalp and skull tumors, in combination with the clinical data. CT is useful in evaluating the degree of bone destruction. MRI provides evidence of the nature of the tissue of the lesion, and its extension and infiltration (e.g., of the diploë), and of the vascularity [2]. Nuclear medicine techniques may be useful to investigate

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possible underlying multifocal disease. For example, in the case of eosinophilic granuloma (EG), technetium-99 m-methylene diphosphonate scintigraphy may provide necessary information, since focal EG has a more favorable prognosis [3].

16.3 Lesions of the Scalp

A variety of scalp lesions of diverse pathology are encountered in children, ranging from congenital and vascular lesions and benign tumors to malignant tumors and, rarely, metastasis. Among congenital lesions, encephaloceles are most commonly encountered, most frequently in the occipital region, followed by the frontoethmoidal and basal regions. Occipital encephaloceles may be associated with hydrocephalus [4]. Aplasia cutis congenita is an exceedingly rare disorder in which there is an absence of skin. In the more severe cases the skull and meninges are affected, and in the case of large defects, skin grafts are utilized [5]. Nevus sebaceous of Jadassohn (NSJ) is a cutaneous hamartoma often found in children, presenting as a yellow-orange hairless patch. Less frequent are melanocytic nevus, which needs close monitoring to rule out malignant transformation, and juvenile xanthogranuloma [6]. Vascular anomalies are hemangiomas and vascular malformations. Propranolol, a beta-blocker, has changed the treatment of infantile hemangiomas; it is currently the treatment of choice, reducing the need for a surgical procedure in up to 90% of cases [7].

Lipoma is an accumulation of fat tissue in the subcutaneous tissue. It is a well-defined mobile, non-painful benign lesion, that may require surgical removal, mainly for esthetic reasons. If the capsule is not completely excised there is a risk of recurrence. Myofibroma is a benign mesenchymal lesion, usually observed in children under the age of two years as a painless purple to pink subcutaneous mass. Complete excision is curative. Cranial fasciitis is an uncommon benign fibroproliferative lesion of infants or young children, usually located in the temporoparietal region. It may show local invasion, and may erode the outer table of the skull, but timely diagnosis and excision is usually curative [8]. Congenital infantile fibrosarcoma of the scalp is exceedingly rare, but should be included in the differential diagnosis. This tumor is associated with a specific genotype, namely fusion of the *ETV6* gene from 12p13 with the 15q25 *NTRK3* gene. The mass usually grows rapidly and bone erosion may be detected. Complete excision is associated with a favorable prognosis [9].

16.4 Lesions of the Skull

16.4.1 Epidermoid and Dermoid Cysts

Epidermoid and dermoid cysts are among the most common lesions of the skull in children. They may be congenital, originating entirely from the ectoderm and involving embryologic closure lines, or they may be a result of trauma, following

which epidermal or dermal elements are included within the diploë [2]. They are usually located near sutures or the anterior fontanel. Epidermoids and dermoids are diagnosed most frequently in children aged younger than 3 years, presenting as a painless subcutaneous mass. They tend to enlarge and to erode bone, with epidural extension (Fig. 16.1). Dermoid cysts can be associated with a dermal tract, infection of which may cause bacterial meningitis or abscess formation. Total removal of the

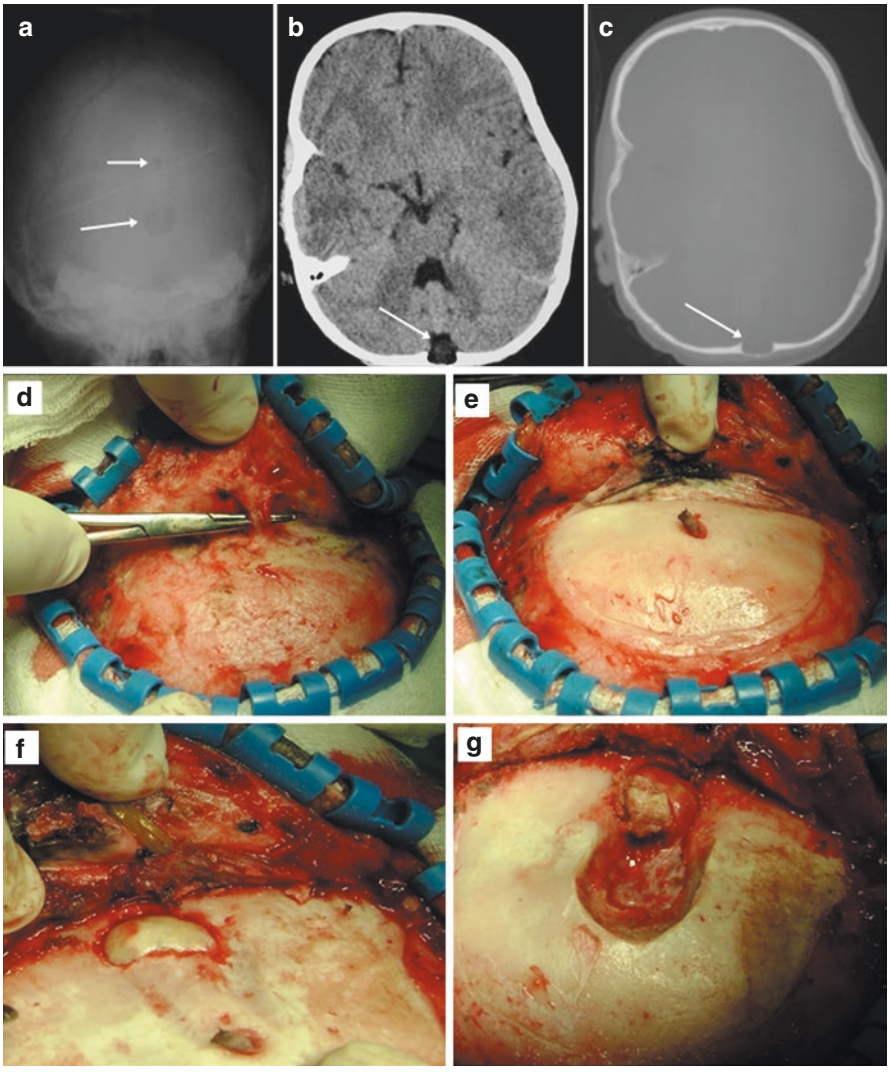

Fig. 16.1 (**a**) Dermoid cyst. Anteroposterior X-ray (Towne view) showing two osteolytic regions (arrows) of a dermoid cyst with a dermal sinus. (**b**) and (**c**) Computed tomography (CT) showing a midline suboccipital lesion eroding the bone. (**d**) and (**e**) Dermoid cyst. Intraoperative images showing the sinus tract (**f**) Dermoid cyst capsule. (**g**) Total resection of the dermoid cyst

dermal sinus and the tumor is preferred, in order to minimize the risk of recurrence or malignant transformation (Fig. 16.1) [10]. In the posterior fossa, a connection between a dermoid cyst, the dermal sinus and a cranial venous confluence is possible, and unanticipated penetration may result in rapid and fatal exsanguinations [11]. For dermoid cysts in the nasal region, dual intracranial and extracranial approaches should be always planned, in order to ensure complete excision [12].

16.4.2 Aneurysmal Bone Cyst

Aneurysmal bone cyst (ABC) was first described in 1942 by Jaffe and Lichtenstein [13]. It is a rare benign bone lesion that usually involves long tubular bones, and location in the skull is exceedingly rare, accounting for about 1% of all cases of ABC. ABCs are diagnosed mainly in childhood and are primary in the majority of cases. They may also be secondary to an underlying lesion, such as chondroblastoma, osteoblastoma, fibrous dysplasia or even osteosarcoma. The pathogenesis is unclear, and they have been associated with head trauma or are congenital abnormalities and chromosomal translocation involving 16q22 and 17p13 has been implicated [14, 15]. ABCs are composed of several blood-filled channels of variable size, separated by septal proliferations of fibroblasts covered with thin cortical bone. On MRI the lesion is well defined, showing prominent enhancement of the wall and septa, and fluid levels. The symptoms include local pain and swelling, but ABC may grow asymptomatically and cause hydrocephalus, cranial nerve palsy or epilepsy from local pressure [16]. Surgical excision alone is the mainstay of treatment and there is no underlying dural penetration. In the case of residual or recurrent ABC, radiotherapy can be used. Skull base lesions are difficult to treat. Gamma knife stereotactic radiosurgery has shown promise in the treatment of these lesions, resulting in possible obliteration of the ABC and long-term stability [16].

16.4.3 Langerhans Cell Histiocytosis

LCH includes a range of diseases involving clonal proliferation of histiocytes. EG, the most common form of LCH, is a benign local disease of bone that affects children and young adults. EG most frequently occurs as a solitary lesion in the skull, mandible, spine, ribs and long bones. In the skull, EG usually presents as a gradually enlarging, painless skull mass. On X-ray, these lesions show a destructive punched-out appearance in the bone (Fig. 16.2). On CT the lesion appears as a soft tissue mass with bone erosion, and on MRI it has intermediate signal intensity on T1-weighted images and is hyperintense on T2-weighted images. Bone scan should always be performed in LCH, to rule out systemic disease [3]. Microscopically the lesion is characterized by large mononuclear giant cells with indented nuclei and

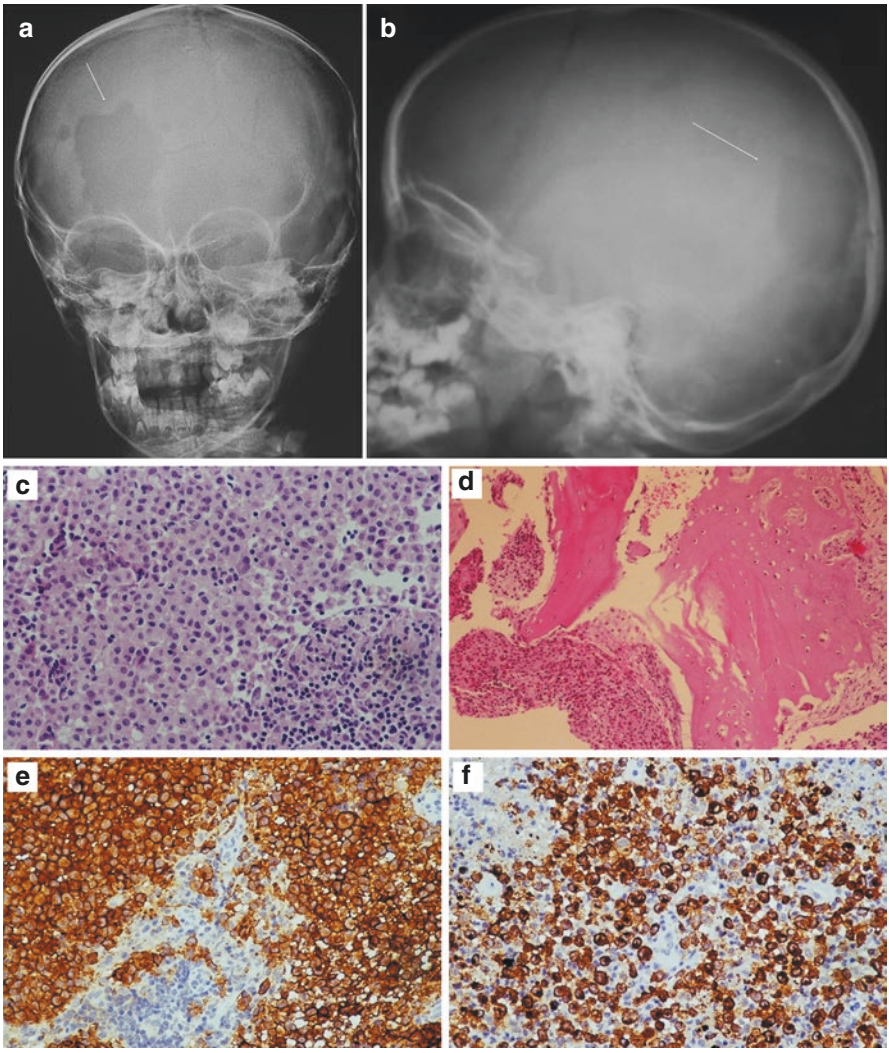

Fig. 16.2 Langerhans cell histiocytosis. Anteroposterior (**a**) and lateral (**b**) X-rays of the skull show a well-defined lytic lesion (arrow) with beveled edges. The lesion involves both the inner and outer table. Histological examination verified the diagnosis of eosinophilic granuloma. (**c**) and (**d**). Langerhans cell histiocytosis. Histological examination. The classic histopathological features of eosinophilic granuloma are mononuclear histiocyte-like oval cells, with a prominent nuclear groove and eosinophilic cytoplasm. The tumor shows strong immunopositivity for CD1a (**e**) and langerin (**f**)

pale cytoplasm (Langerhans cells). On immunohistochemical staining, Langerin and CD1a serve as specific diagnostic markers in the diagnosis of LCH (Fig. 16.2). Surgical excision is the treatment of choice; rarely, there is extension into the dura, and reconstruction of the defect can be performed, even with autologous skull bone.

Injection into the lesion of corticosteroid, and administration of sulfamethoxazole, trimethoprim and indomethacin have also shown therapeutic promise [17].

16.4.4 Osteoma

Osteoma is a rare, slowly growing, benign neoplasm composed of mature compact or medullary bone. Osteoma may present as a painless lesion in a child's skull. It is usually asymptomatic and is often an incidental finding, and monitoring usually suffices, although cosmetic disfigurement may require prompt treatment. In the case of multiple osteomas, Gardner syndrome should be ruled out.

Osteoblastomas are more aggressive than osteomas, and have a diameter greater than 15 mm. Cranial osteoblastoma is rare, accounting for 2–4% of all cases, and there is no gender prevalence [18]. The frontal bone is most commonly affected. Osteoblastomas and may extend into soft tissue, they tend to recur after excision, and they are associated with sarcomatous dedifferentiation and metastasis [19]. For these reasons, complete resection should be performed. The surgical approach is guided by tumor location, with the objective of not producing a cosmetic defect. In one series, gross total excision was possible in 64% of cases and surgery was curative in 82.8% of the patients. Close post-operative monitoring is required. In the case of recurrence, re-operation should be undertaken, and is usually associated with favorable results [20]. The role of chemotherapy or radiotherapy in partially resected lesions is unclear.

16.4.5 Fibrous Dysplasia

Fibrous dysplasia (FD) is a benign condition in which normal bone is replaced by fibrous-type tissue. FD may be solitary or it can be widespread, affecting several bones. FD tin association with café-au-lait spots and precocious puberty is a hallmark of the McCune-Albright syndrome [21]. This syndrome is associated with activating mutations of the *GNAS1* gene. On bone scintigraphy, FD shows dense accumulation of the radiotracer, and bone scan is used to investigate the extent of the bone disease. Presentation in the skull is observed in one in four cases, and the history is that of painless increasing deformity, continuing into adulthood. If the orbit is involved, FD may produce facial asymmetry, and the most severe complication is blindness. FD may also cause skull base deformities, such as the Chiari I malformation in 6.3% of cases, and secondary basilar invagination in 7.6% [22], and screening for cranial base abnormalities should always be performed in patients with craniofacial FD. Malignant transformation occurs in 0.4–4% of cases [23]. Gross total excision is the goal, when possible, followed by primary reconstruction. Bisphosphonates have been used to treat FD since they inhibit bone resorption and may relieve pain, but the response is variable. An increase in the level of

interleukin-6 (IL-6) has been detected in FD, which leads to normal osteoclast congregation and increased bone resorption. Treatment with tocilizumaba, a humanized anti-IL-6 receptor antibody, has shown efficacy in FD with pain refractory to bisphosphonates [24].

16.4.6 Osteosarcoma and Ewing Sarcoma

Osteosarcoma is of primitive mesenchymal cell origin, and in children it usually arises in the extremities. Skull osteosarcoma accounts for 10% of all osteosarcomas. The clinical picture is that of a painful expanding skull mass. Tumors localized in the orbit may cause exophthalmos and diplopia, and in the nasal cavity, nasal bleeding. On CT the lesion appears mainly osteoblastic, with or without an osteolytic component, and with irregular margins. On MRI, osteosarcoma has no specific imaging findings on T1 and T2-weighted images, and there is usually contrast enhancement [25]. Complete surgical resection, when possible, is associated with a favorable prognosis, but in the case of local and distant disease recurrence the prognosis is poor.

Ewing's sarcoma was first described by James Ewing in 1921. Ewing's sarcoma usually occurs in the pelvis or long bones, and skull involvement is rare, accounting for 1–6% of all Ewing's sarcomas. The temporal bone is most commonly affected. These tumors are associated with a typical chromosomal translocation, *t*(11; 22) (q24; q12), and fusion between exon 7 EWS and exon 5 of FLI. Plain X-ray shows a lytic bone lesion with soft tissue extension, periosteal reaction and no calcifications. Typical CT findings are those of an extra-axial lytic skull vault lesion. On MRI the lesion appears iso- or hypointense on T1-weighted images and hypo- to hyperintense on T2-weighted images, enhancing after gadolinium administration. Both osteosarcoma and Ewing's sarcoma have been reported to occur after radiation therapy [26, 27], with a median latency period after radiation of 2.5–14 years. Radical surgical excision is the mainstay of treatment for Ewing's sarcoma. Proton therapy is another therapeutic option for Ewing's sarcoma of the cranium and skull base, with 4-year local control, disease-free survival, and overall survival rates of 96%, 86%, and 92%, respectively. Hearing loss, intracranial vasculopathy and neuroendocrine deficits have been reported following this treatment [27].

16.4.7 Metastatic Neuroblastoma

Neuroblastoma (NB) is the third most common malignancy in children and the most common extracranial solid tumor of childhood. NB is usually diagnosed in children aged younger than 5 years, and 40% of patients are diagnosed before one year of age. NB most frequently arises in one of the adrenal glands, and it has a tendency to metastasize, mainly to lymph nodes, liver and bone marrow. Metastatic spread to

the skull is rare. Metastasis to the orbit is the most common site, and results in periorbital ecchymoses and proptosis. The treatment usually entails chemotherapy, radiotherapy, autologous hematopoietic stem cell transplantation, and surgery, when possible. The prognosis depends on the age of the patient, and the stage and histological grade of the tumor [28, 29].

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Chapter 17
Astrocytomas

Matheus F. M. Ballestero, Luciano Furlanetti, Guilherme G. Podolsky, and Ricardo S. de Oliveira

17.1 Background

Astrocytomas are tumors of glial origin that the neurosurgeon, especially the pediatric neurosurgeon, must be used to. The World Health Organization (WHO) classification of tumors of the central nervous system (CNS) has been the standard diagnostic system for the classification of brain tumors for almost 50 years, since its first edition back in the 70s. Originally organized according to the morphological appearance of tumor cells, similarities and presumed level of differentiation in relation to the cells of origin, with a grading system based on the clinical outcome of tumors if left untreated, it has been recently restructured in order to meet current clinical needs [1]. A major advance of the latest *Revised fourth Edition* was the inclusion of molecular features, for the first time, in addition to histology to define tumor entities. The aim of the new classification is to add objectivity with more biologically homogeneous and well defined diagnostic entities, than in prior classifications, improving diagnosis, patient management, response to treatment and counselling [1]. According to the 2007 WHO classification of brain tumors,

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low-grade glioma (LGG) comprised of several types of tumor, i.e. astrocytoma, oligodendroglioma and oligoastrocytoma, however molecular abnormalities were not routinely taken into consideration as diagnostic criteria.

On the other hand, malignant astrocytomas are the most common primary brain tumor in adults, and can appear de novo or degenerate from an anaplastic or diffuse glioma [2]. As previously discussed, the criteria for establishing the diagnosis of CNS tumors, including astrocytomas, was classically based on morphologic findings, such as mitotic activity and the presence of anaplastic nuclear features to distinguish between Grade II and Grade III, and the addition of microvascular proliferation and/or necrosis defining WHO Grade IV [1]. Nevertheless, several studies have shown that IDH-wildtype diffuse and anaplastic tumors, which would be classified as grade II and grade III, respectively, presented with overall survival (OS) quite similar to IDH-wildtype glioblastoma (GBM). On the other hand, the IDH status alone is insufficient to designate the tumor grade and prognosis, since other biologically more favorable CNS tumors, such as the pilocytic astrocytoma, pleomorphic xanthoastrocytoma and others also lack of IDH mutation [1, 3]. Therefore, the inclusion of the IDH status into the *Revised fourth Edition* of the WHO classification is complementary to the histological findings and will very likely be followed by the inclusion of other genetic markers in future classifications.

The present chapter purposes to discuss three of the most common astrocytomas: Pilocytic Astrocytoma, Diffuse Astrocytoma and Glioblastoma Multiforme, presenting the typical clinical history, physical examination, imaging, differential diagnosis, treatment options, complications and pears of each tumor.

17.2 Pilocytic Astrocytoma (WHO Grade I)

According to the current WHO Classification System, pilocytic astrocytomas (PA) represent approximately 5.1% of all gliomas, being more common in children [1, 4]. Males are slightly more affected than females, PA is the most common primary brain tumor in people aged 0 to 19, with an average annual age-adjusted incidence rate (adjusted for the US population in 2000) of 0.84 (per 100,000), which substantially decreases from the 15 to 19 age group in relation to the 10 to 14 group [5]. Other studies indicate an incidence rate of 4.8 per one million inhabitants / year in the United States [6].

PAs are responsible for 15.4% of primary CNS tumors in children and adolescents (0–19 years old) and 17.6% of primary childhood brain tumors (0–14 years old). PA, however, can occur at any age, becoming uncommon with advancing years [5]. PA can occur in any part of the CNS, although it does occur more frequently in the cerebellum (42%), followed by supratentorial compartment (36%), optic pathway and hypothalamus (9%), brainstem (9%) and cord spinal (2%) [4]. In children, the most commonly affected site is the cerebellum (67%), with only rare cases

developing in the supratentorial compartment; in adults, the incidence of the tumor in the supratentorial and cerebellar regions is 33% each [6, 7].

17.2.1 Clinical History

The symptoms will generally be insidious due to the slow growth of the tumor, and the identification of the first symptoms depends on the location and the age of the individual (younger children do not report sensory or visual symptoms as adults).

Common presentation symptoms for cerebellar tumors include ataxia, cranial nerves palsy and signs of increased intracranial pressure (ICP) as nausea, vomiting, drowsiness and headache. When present in the optical pathways, tumors can produce loss of acuity or visual field and, when located in the hypothalamus, can result in endocrinological syndromes such as *diabetes insipidus*, precocious puberty or hydroelectrolytic imbalance. Supratentorial lesions can also present as epileptic seizures [8].

The obstruction of the CSF flow can lead to hydrocephalus which may be asymptomatic or manifest with occasional headache, cognitive decline and gait disturbance. Acute hydrocephalus manifests in younger children with drowsiness, nausea, vomiting, head circumference growth, paralysis of the vertical conjugated gaze (constituting Parinaud's syndrome which in its classic form also includes mydriasis, absence of pupillary reaction to light and inability to convergence) and setting sun sign. In adult patients, symptoms such as, headache, nausea, vomiting and drowsiness are more frequent [8].

17.2.2 Physical Examination and Imaging

The screening test for expansive CNS lesions is usually tomography, in which the PAs usually appear as well-defined rounded or oval lesions, iso or slightly hypodense and usually with significant post-contrast reinforcement (Fig. 17.1a and b). Calcifications can be seen in 20% of exams [9].

On MRI, PAs are typically hypo or isointense in T1 sequences (Fig. 17.1c) with important contrast enhancement (Fig. 17.1d and f) and hyperintense in T2 or FLAIR images (Fig. 17.1e). They may contain cysts or consist of a cyst with a mural nodule tumor (the latter being particularly common for cerebellar and hemispheric tumors) [9].

Pilocytic astrocytoma involving the optic nerve and optic chiasm usually form spindle masses with enlargement of these structures. It is the most common bilateral tumors site in patients with neurofibromatosis type 1. In posterior fossa, the PA can involve the brain stem. In this location, in contrast to the diffuse intrinsic pontine

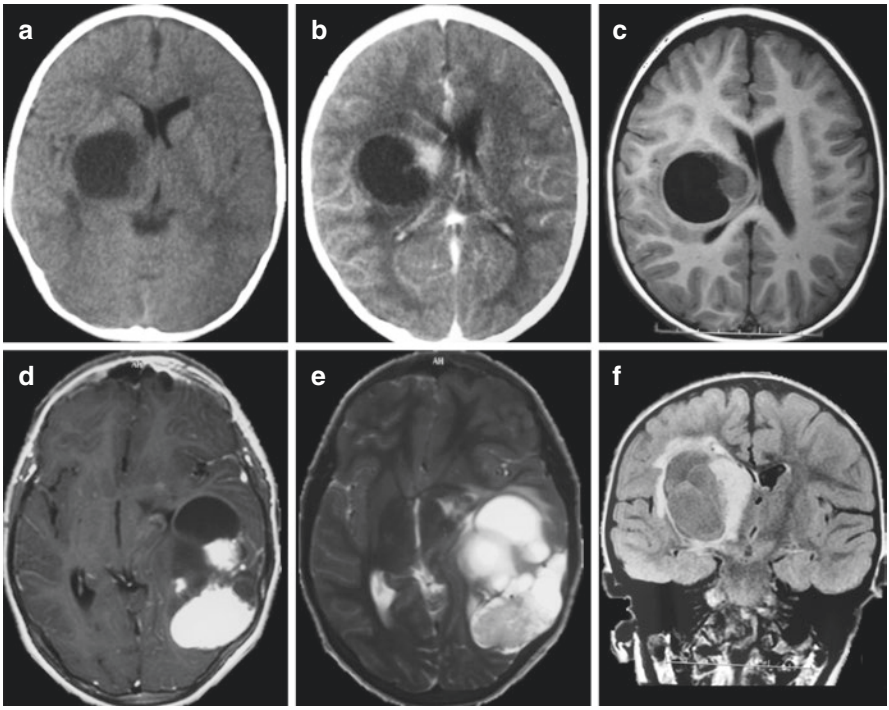

Fig. 17.1 (**a**–**f**) Pilocytic astrocytoma: (**a**) pre-contrast CT scan; (**b**) post-contrast CT scan; (**c**) T1-weighted non-contrast MRI scan; (**d**) T1-weighted post-gadolinium; (**e**) T2-weighted; (**f**) coronal FLAIR MRI scan

gliomas which infiltrate and expand, the PAs are usually located dorsally and have an exophytic growth pattern. The spinal cord is rarely affected [8].

17.2.3 Differential Diagnosis

The main differential diagnoses and their characteristics are explained below:

- *Abscess*: The cystic form of the PAs can be similar in the MRI and CT images, however, cerebral edema is more intense and the patient presents clinical and inflammatory / infectious markers;
- *Metastasis*: Isolated lesions can mimic PA both in solid and cystic form, especially in older adults. The diagnosis of metastasis can be addressed by the presence of another malignant neoplasm or lesions in other organs.
- *Hemangioblastoma*: Usually seen in adults. In children, frequently associated with von Hippel-Lindau disease. The wall of the cyst usually enhances contrast and there are no calcifications. Presents a smaller mural nodule with angiographic contrast blush;

- *Medulloblastoma*: usually arise from the midline (especially vermis and the roof of the fourth ventricle) and not from the cerebellar hemisphere. Usually seen in younger children (2–6 years old);
- *Ependymoma*: tends to fill the fourth ventricle and **protrude** out of the foramen of Luschka and Magendie, the cystic component is less common;
- *Amoebiasis, cysticercosis, hydatidosis*: May cause unique cystic lesions with post-contrast reinforcement, the clinical history of housing or travel to endemic areas is very important as well as the presence of eosinophilia and eosinophils in the CSF.
- *Demyelination / inflammation*: Optic neuritis in acute multiple sclerosis, acute disseminated encephalomyelitis can mimic PA with lesions of the optic nerve, however these lesions do not present the typical enlargement inside the orbit as in PA.

The differential diagnosis of a hemispheric PA with a cyst with a mural nodule is **ganglioglioma**. Gangliogliomas are generally cortical in origin and frequently calcify. **Pleomorphic xanthoastrocytomas** can present in the same way, but they are tumors of young adults and often incite meningeal reaction with a "dural tail" sign [8].

17.2.4 Treatment Options

PAs are treated mainly by surgery, seeking radical resection of the lesion. This can be followed by radiotherapy, especially in incomplete surgical resection. Chemotherapy can be discussed in cases where the tumor progresses and reoperation is not possible [10]. The most commonly used chemotherapeutic agents, vincristine and carboplatin, are not effective in every patient, therefore, the development of new therapies is urgently needed in order to improve clinical outcome [11].

In general, PAs are considered to have an excellent prognosis, with an overall 10-year survival greater than 90%. However, the prognosis is worse for tumors in the hypothalamic and chiasmatic region and tumors where complete surgical resection is not possible. In such cases overall survival is less favorable. In addition, the rare PAs that show leptomeningeal dissemination have a worse prognosis [12, 13].

In PAs (especially not associated with neurofibromatosis) a tandem duplication iat 7q34 leading to a fusion between KIAA1549 and BRAF is found in approximately 70% of patients. A mutation at the activation point at BRAF (V600E) is additionally found in 5% to 9% of these tumors. In general, changes in the RAF occur in approximately 80% of the PAs leading to subsequent constitutive activation of the MAPK oncogenic pathway [12, 14]. The use of BRAF inhibitors in the treatment of these tumors is still in clinical trials (ClinicalTrials.gov: NCT01677741 and NCT01748149).

17.2.5 Complications

Patients with tumors of the posterior fossa may develop hydrocephalus requiring an urgency or emergency endoscopic ventriculostomy or VP shunt.

The PAs rarely progress to malignancy, with the vast majority, even after multiple recurrences, keeping their morphology classified as WHO grade I. However, a small number of cases of malignant transformation have been documented [15].

The most important complications of PAs are related to the surgical procedure, the operating position and the individual's age. In relation to surgery the risk of postoperative infections is the same as any craniotomy, the risk of bleeding and CSF leaks, which is higher in the fossa lesions. Regarding the surgical positioning, the semi sitting position may be related to air embolism and care must be taking with bone hemostasis and use of transesophageal doppler.

Younger children may not tolerate blood loss and always have to be operated with RBC already available in the operating room. In the elderly, we must pay attention to the presence of cardiac and respiratory comorbidities and complications related to wound ulceration due to the greater fragility of the scalp.

17.2.6 Pearls

- PA is a more common tumor in the pediatric population;
- Classified by WHO as low grade (grade I);
- Strong association with NF1: 5% to 20% of patients with NF1 develops PA mainly in the optical pathway;
- MRI: Usually cystic lesion with a mural nodule, although it may be completely solid;
- And excellent prognosis with complete surgical resection in patients without neurofibromatosis; radiation and chemotherapy are not used routinely;
- Presentation typically with cerebellar changes and intracranial hypertension;
- Hydrocephalus that must be treated as soon as possible.

17.3 Diffuse Astrocytoma (WHO Grade II and III)

New developments have been quickly translated into further revised diagnostic categories of brain tumors. Molecular markers such as mutations in the isocitrate dehydrogenase gene (IDH) and 1p/19q status are now central for the differential diagnosis of brain tumors [1]. The molecular reclassification of gliomas contains more prognostic information compared with stand-alone classical histopathology. Diffuse astrocytoma (DA) is one type of LGG and historically classified as WHO grade II tumors. These are slow-growing tumors, which infiltrates brain parenchyma, posing challenges to gross total resection.

The median survival time of DA ranges from 3.9 to 10.8 years, according to the literature [16, 17]. Nevertheless, the inclusion of molecular analysis and genetic profile into the revised classification of astrocytomas has led to a paradigm shift regarding the classification, determination of prognosis and treatment of these tumors.

The changes in the newly revised classification of diffuse gliomas is certainly the most relevant for practicing neuro-oncology teams, as DA are the most frequent primary adult brain tumors [2, 17]. Here we aim to summarize key changes regarding the current classification and management of diffuse and anaplastic astrocytomas (WHO Grade II and III, respectively), including both IDH-mut and wildtype tumors [1]. Other types of gliomas, such as oligodendrogliomas, glioblastomas, diffuse intrinsic pontine glioma, optic pathway glioma are discussed separately.

17.3.1 Clinical History

Infiltrating diffuse astrocytomas typically present with seizures in young adult and middle-aged patients. Approximately 60% occur between 20–45 years of age. There is a predominance of affected males (M:F ratio, 1.18:1) [2]. DA may be located in any region of the brain; however, it occurs most frequently within the frontal and temporal lobes. Epileptic seizure is the most frequent initial presentation [2, 17, 18]. Some patients may present with progressive headache and signs of increased intracranial pressure due to mass-effect or hydrocephalus, although most patients will be oligosymptomatic at presentation. Nevertheless, subtle neurological symptoms such as behavioral, speech, visual and somatosensitive abnormalities may be present, according to the brain region involved [17].

17.3.2 Physical Examination and Imaging

Most patients may have a normal neurological examination at presentation, however, even in cases where no obvious neurological manifestation is observed, a more detailed cognitive and neuropsychological evaluation may be required to detect incipient functional abnormalities [2, 17, 19].

Concerning the neuroradiological evaluation, DAs usually appear as a homogeneous area of hypodensity on computed tomography (CT) scans, without contrast enhancement, whereas calcification and cystic changes may also be present [2, 16, 17]. Calcifications are not common in DA and may be rather related to oligodendrogliomas. Magnetic resonance imaging (MRI) often shows an ill-defined non-contrast-enhancing tumor mass, hypointense on T1-weighted and hyperintense on T2/Fluid-Attenuation-Inversion-Recovery (FLAIR)-weighted sequences, although gadolinium enhancement tends to indicate progression to anaplastic astrocytoma (WHO grade III) (Fig. 17.2). The so called T2-FLAIR mismatch appearance

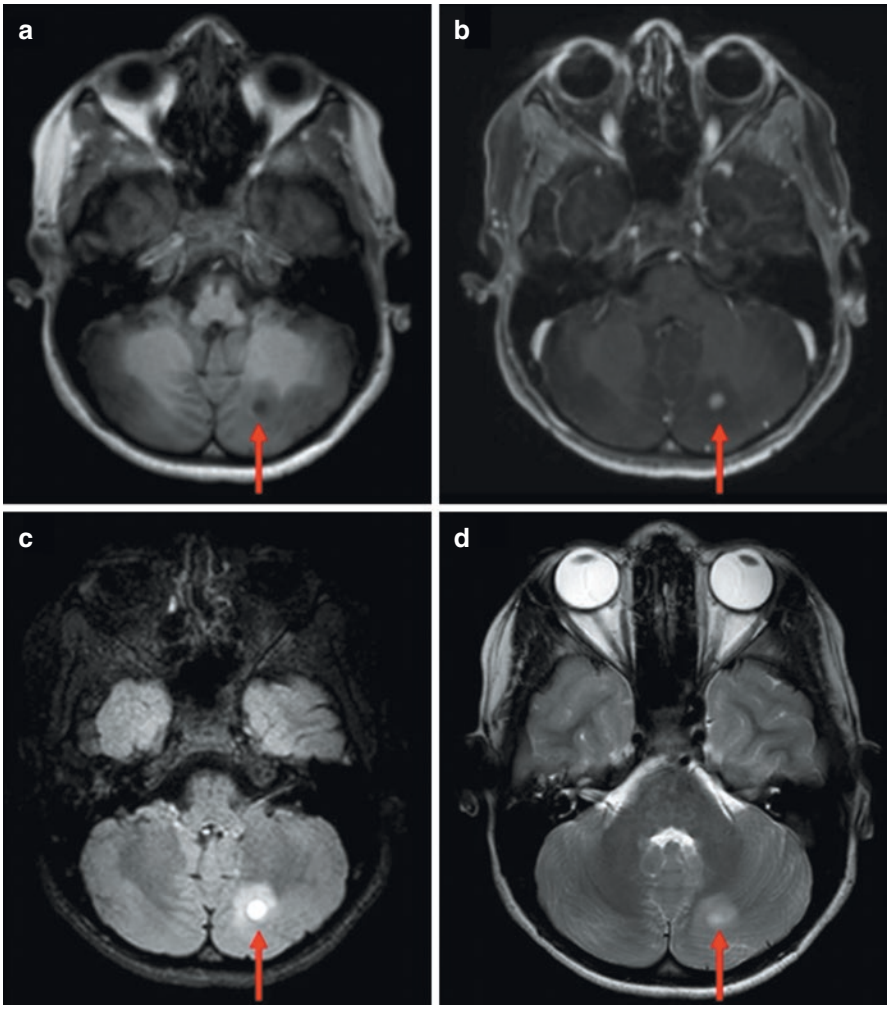

Fig. 17.2 (**a**)–(**d**) Diffuse astrocytoma (red arrow): (**a**) axial T1-weighted; (**b**) axial T1-weighted post-gadolinium; (**c**) axial MRI FLAIR; (**d**) T2-weigthed MRI

consists of a homogeneous high intensity signal on T2WI, which on T2-FLAIR appears relatively hypointense with a rim of hyperintensity, considered highly specific for DA as opposed to other LGG [17, 20].

The possibility of tailoring treatment options according to individual risk profile has gained attention in neuro-oncology. Modern neuroradiological modalities, such as spectroscopy (MRS), diffusion tensor and molecular imaging via *O*-(2-^{18}F-Fluorethyl)-L-tyrosine Positron Emission Tomography (^{18}F-FET-PET) may help to improve prognostic classification of brain tumor subtypes [21]. Lower Apparent Diffusion Coefficient (ADC) values, elevated choline:creatine ratio on MRS and elevated relative cerebral blood volume on MR perfusion may suggest progression

to a higher grade, according to WHO tumor classification [2, 17]. In line with that, amino acid PET may reveal areas of increased malignancy hypermetabolic. Thus, a recent study showed that the combination of ADC MRI and ^{18}[F]FET PET was able to detect glioma infiltration better than stand-alone standard MRI or ^{18}[F]FET PET in contrast-enhancing gliomas, possibly allowing better image-guided surgical resection, irradiation or a biopsy, whenever indicated [21].

17.3.3 Differential Diagnosis

One could discuss differential diagnosis of DA from the perspective of preoperative neuroradiological findings, as well as under the light of the postoperative morphological and genetic tumor profiles. Stroke, cerebritis, encephalitis, inflammatory and infectious processes of the central nervous system, other primary and secondary tumors should be considered as differential diagnosis in terms of preoperative assessment [2, 11, 17].

Regarding the neuropathological evaluation, DA is histologically synonymous with the previously described subtype of fibrillary astrocytoma. Gemistocytic astrocytoma remains a distinct subtype, whereas protoplasmic astrocytoma is no longer recognized as a separate entity by the WHO revised classification of CNS tumors [1]. Therefore, DAs are categorized primarily based on the presence of absence of an IDH mutation, and then also depending on histological findings into WHO grades II to IV (Fig. 17.3). The presence of IDH mutation determines a group of tumors with more favorable prognosis than IDH-wildtype tumors. IDH-mutation

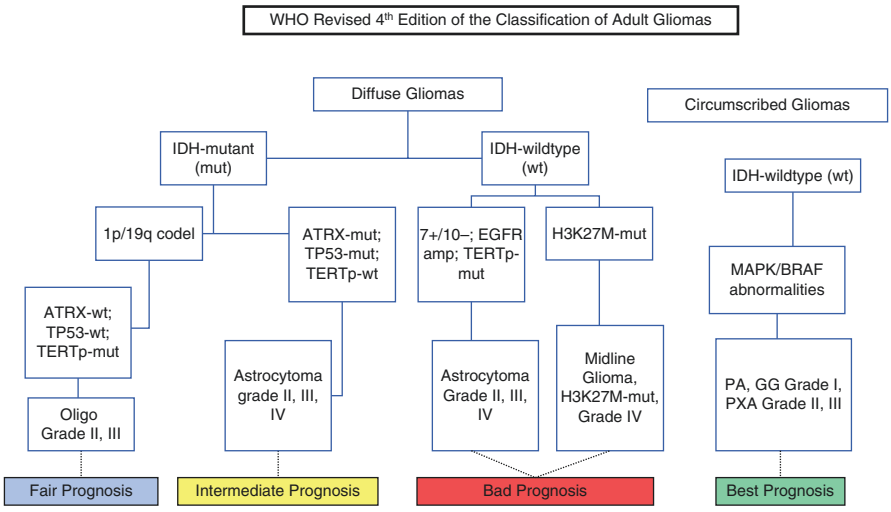

Fig. 17.3 Histological and genetic profile of gliomas

are found in nearly 90% of diffuse grade II and in 60% of diffuse grade III gliomas, in 5% of primary glioblastomas and are absent in other brain tumors [22].

Other genetic markers, such as 1p/19q status (presence or absence of codeletion), assessment of copy number alterations of chromosome 7 and 10, TERT promoter, BRAF, EGFR, PTEN and H3F3A mutations can be considered for routine testing [1, 17]. For instance, an IDH-wildtype DA with polysomy of chromossome7 and loss of 10q should be considered as a glioblastoma (WHO Grade IV) for prognostication and management. Furthermore, a tumor with oligodendroglial morphology, presenting an IDH mutation, but no 1p/19q codeletion, should be treated as an astrocytoma. On the other hand, a tumor with histological features of a glioblastoma, but IDH-mutated and 1p/19q codeleted will be designated an anaplastic oligodentroglioma. In line with that, the diagnosis of oligoastrocytoma has been excluded from the new classification, since the application of both genotype and phenotype has allowed to classify them either as astrocytoma or oligodendroglioma in almost all cases [1]. Unfortunately, molecular diagnostics are still not widely available. In cases where phenotypic and genotypic parameters cannot be integrated in order to define a tumor entity, diagnosis will be based on the histology and/or designated as "not otherwise specified" (NOS) [1, 17].

Despite of the importance of genetic information, a classification purely based on molecular diagnosis is currently not possible. In order to understand the nosological and clinical significance of specific genetic abnormalities, the morphological analysis remains essential. Finally, the denomination "diffuse astrocytoma" will eventually vanish, since it seems to represent a collection of tumors with astrocytic histological patterns, but distinctive genetic profiles [1, 22].

17.3.4 Treatment Options

The term "low grade glioma" may evoke false positive expectations for patients and caregivers faced with the burden of a progressive and debilitating disease [2, 16, 17]. The optimal management of DAs concerning the role of biopsy, indication and timing of surgical resection and oncological treatment with chemo- and radiotherapy are still under debate. Several ongoing prospective randomized studies aim to shed light on most of these questions and to assess the impact of new drugs and technologies in the management of diffuse gliomas. Although a randomized clinical trial to assess the impact of early radical resection versus watchful waiting in DA would probably not be feasible due to ethical reasons, several retrospective and prospective studies have shown increased OS associated with a greater extent of resection [2].

Recently, the Norwegian study analyzed in a prospective non-randomized design the impact of these different strategies showing that, in the population studied, surgical resection provided longer median overall survival (OS) (14.4 vs 5.8 years) [23]. Furthermore, the potential positive impact of surgical resection remained after stratifying and adjusting for molecular phenotype, e.g. IDH-mut 1p/19q codeleted

versus IDH-mut 1p19q non-codeleted versus IDH wild-type [23]. Furthermore, Englot et al. 2012 have shown in a comprehensive systematic review that gross total resection of LGG within the temporal lobe improved seizure control to a better extent than subtotal resection of the tumor [24].

More recently, Yordanova and Duffau 2017 advocated in favor of early diagnosis and supramaximal resection of LGG guided by detailed preoperative and intraoperative neurophysiological monitoring of functional brain networks, which may contribute to increased overall survival (OS), whilst decreasing the risk of malignant transformation and preserving the quality of life of the patients [25]. In line with that, although a randomized controlled trial to address open questions regarding the management of DAs is still required, [18] current international guidelines agree that surgery should be first-line therapy for gliomas, irrespective of genetic subtype, whenever safe and technically feasible [16, 22, 26].

Although gross total resection may not be always possible, there is evidence that the amount of residual tumor volume (RV) rather than the extent (percent) of resection (EOR) should be in focus, due to its association with overall survival [19, 27–29]. Concerning adjuvant treatment options and prognosis, besides molecular and histological profiles, tumor diameter (>6 cm), older age at diagnosis (>40 years), tumor crossing the midline, and the presence of neurological deficits seem to be associated with worse OS in DA (WHO Grade II), [30] whilst in anaplastic astrocytomas (AA, WHO grade III) age, Karnofsky performance status (KPS) and tumor diameter were the main prognostic factors [17]. The standard of adjuvant care for patients with LGG, including DA, has been recently revised, following the reclassification of brain tumors.

17.3.5 Complications

Surgical resection plays a central role in the management of DAs, currently [17]. Nevertheless, in the past, resection was not considered a feasible strategy for tumors located in highly eloquent brain regions, e.g. within the insula, motor cortex, corticospinal tract and speech areas. The development of preoperative functional assessments, intraoperative image-guidance and the application of real-time cortical and subcortical neurophysiological mapping of functional networks have completely changed the approach to brain tumor surgery [25, 31–33]. Chang et al. 2003, outlined the most common perioperative complications following first and second craniotomies among 788 patients enrolled in the Glioma Outcome Project [34]. Perioperative complications occurred in 24% and 33% of patients submitted to surgical management for the first and second time, respectively. Regarding the neurological status, although most patients were unchanged or better, more patients submitted to craniotomy for the second time displayed worsening (8% vs 18%) [34].

Frequently reported perioperative complications in glioma surgery were intracranial bleeding, infection, seizure, neurological worsening, deep vein thrombosis (DVT), pulmonar embolism (PE) and depression [2, 34]. Reported rates of DVT

and PE in glioma patients is strikingly as high as 25–39%, or up to 2% risk of events per month of survival, whereas nearly half occur within the postoperative period [35] Other commonly reported late complications related to the adjuvant treatment are adverse drug reaction, radio necrosis, brain edema, radiation-induced CNS tumors and cognitive issues [2, 17, 26].

17.3.6 Pearls

- The *Revised fourth Edition* of the WHO classification of CNS tumors has reshaped the approach to gliomas, now taking into account the genetic profile of these tumors allied to their histological phenotype, allowing a more appropriate and individualized management and prognostication.
- Maximum safe resection is recommended whenever feasible in all patients with newly diagnosed gliomas;
- Technological advances, such as preoperative and intraoperative functional brain mapping provide extra guidance for a safe tumor resection, even in highly eloquent areas;
- The role of tumor biopsy in the management of gliomas is still a matter of debate. However, most guidelines agree that allied to advanced preoperative imaging, it might be a useful strategy in the differential diagnosis of radio-necrosis and tumor progression. It might also be helpful to guide adjuvant treatment in cases where surgical resection is not feasible;
- Special attention should be given to the prevention of thromboembolic events in glioma patients. Preoperative ultrasound doppler, as well as pharmacological and non-pharmacological prophylactic measures should be routinely performed. In case of diagnosed DVT, inferior vena cava (IVC) filter should be considered in patients with contraindications to anticoagulation.
- Genetic and morphological histological profile of the tumor will determined the appropriate adjuvant treatment for individual cases, whenever indicated.

17.4 Glioblastomas (WHO Grade IV)

Glioblastoma (GBM) is the most common primary malignant tumor of the central nervous system in adults, with an estimated incidence of 2–3 cases per 100,000 individuals in North America and Europe [36].

GBM accounts for around 45.2% of malignant primary CNS tumors in adults, with a medial OS of 15 months [37]. They are slightly more prevalent in men (1.5:1) and often occur in the cerebral hemispheres, at average age of 53 years at onset and peak incidence between 65 and 74 years of age [38]. GBM has a 5-year survival rate of 3.3%, while lower grade gliomas, such as pilocytic astrocytoma, oligodendroglioma, and ependymoma have 5-year survival rates of over 70%. Not specified

astrocytoma, anaplastic astrocytoma, malignant glioma, and lymphoma have 5-year survival rates less than 40% [39].

GBM can be biologically separated into two subtypes, e.g. primary and secondary, according to their genetic profile. Primary GBM accounts for about 85% of them and typically occurs in patients older than 50 years [1, 3, 26, 37]. They are genetically characterized by EGFR amplification and mutation, loss of heterozygosity of chromosome 10q, gain of chromosome 7, mutation of the TERT promoter and PTEN tumor suppressor gene, and deletion of p16 [1, 3, 26]. Secondary GBM on the other hand, are much less common, occur in younger adults and present completely different genetic profile. Although they may also present loss of heterozygosity of chromosome 10q, p16 abnormalities and mutations in the TP53 tumor suppressor gene, the great majority of these tumors, derived from diffuse and anaplastic astrocytomas, have wildtype TERT promoter, mutant ATRX and a specific mutation of the isocitrate-dehydrogenase gene (IDH1 and IDH2) [1, 3, 26]. Pathways related to survival, proliferation, inhibition of apoptosis, invasion and angiogenesis may be common to both primary and secondary GBM [2, 3, 40]. Fig. 17.3 summarizes current histological classification and molecular diagnostics of gliomas.

17.4.1 Clinical History

Patients commonly present with headache and, not infrequently, with signs of intracranial hypertension, such as nausea, vomiting, drowsiness, blurred vision and diplopia. Similar to DAs, up to one-third of the patients diagnosed with a GBM present with epileptic seizure [2]. Due to nonspecific symptoms, physicians should have a high suspicion of malignance, bearing in mind the epidemiology of these tumors and a detailed clinical history.

17.4.2 Physical Examination and Imaging

The symptoms and signs of glioblastoma may be unspecific or vary according to tumor location in the brain. Neurological deficits when present, may be subtle, making early clinical diagnosis challenging. Rarely, GBM can present with intratumoral hemorrhage, causing stroke-like symptoms and signs. Computed tomography (CT) is widely available and usually the method of choice for the initial investigation at emergency departments. On CT scans they may appear as a contrast-enhancing tumor with irregular hyperattenuating thick margins and hypodense (necrotic) center, occasionally with hemorrhage and marked surrounding vasogenic edema.

Magnetic resonance image is the method of choice for planning both clinical and surgical management, as well as for follow-up and evaluation of patient's response to treatment. On MRI, GBM may present as a hypo to isointense mass within the

white matter, with marked contrast enhancement post-gadolinium on T1-weighted sequences. T2-weighted/FLAIR imaging shows a hyperintense tumor with vasogenic edema and occasionally flow voids, due to its high vascularization (Fig. 17.4).

GBM may also involve the corpus callosum, crossing the midline and resulting in a butterfly pattern on imaging. MR perfusion may show elevated rCBV compared to lower grade tumors, whereas MR spectroscopy may indicate high cell turnover and necrosis by increased choline, lactate and lipids, but decreased n-acetyl-aspartate and myoinositol. As previously discussed, FDG-PET may also be of advantage in the evaluation of GBM, allowing tailored image-guided surgical resection, irradiation or biopsy of these tumors, when indicated. Furthermore, recent studies have shown that quantitative PET/MRI in combination with dynamic susceptibility contrast perfusion MRI may be helpful in distinguishing radio necrosis from tumor recurrence of GBM [41].

17.4.3 Differential Diagnosis

The main differential diagnosis for high-grade gliomas are summarized, as follows:

- Brain metastasis: Often multifocal. Usually located in the grey-white matter transition;
- Primary CNS lymphoma: Homogeneous gadolinium enhancement. More frequent in immunosuppressed patients;

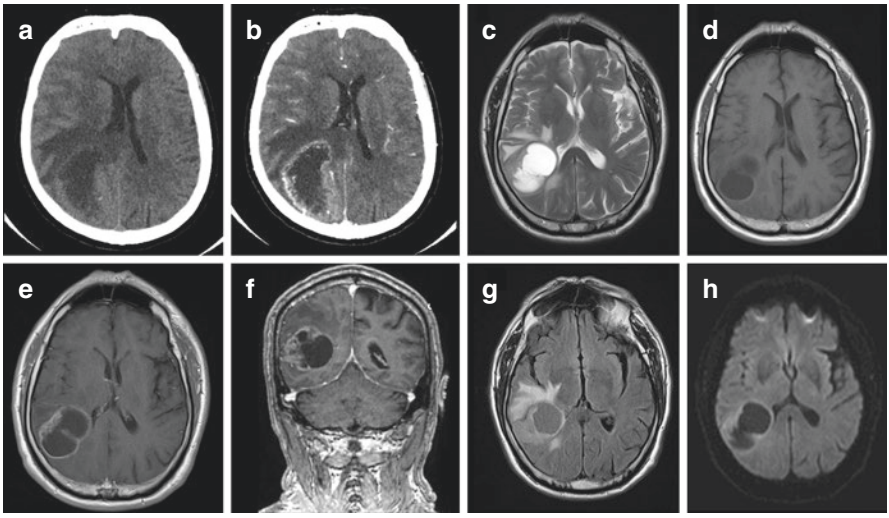

Fig. 17.4 (**a**)–(**h**) Glioblastoma (Grade IV): (**a**) Axial pre-contrast CT scan; (**b**) Axial post-contrast CT scan; (**c**) AxiaT2-weighted l MRI scan; (**d**) Axial T1-weighted non-contrast; (**e**) Axial T1-weighted post-gadolinium; (**f**) Coronal T1-weighted post-gadolinium; (**g**) Axial MRI FLAIR; (**h**) Axial MRI DWI

- Tumefactive demyelinating lesions: Ring-enhancing. Diffusely infiltrative. More frequent in young patients;
- Cerebral Abscess: High DWI signal present centrally. Central low-intensity on T1; Central and peripheral high-intensity on T2. MR spectroscopy with elevated lipids/lactate, succinate, acetate and amino acids.

17.4.4 Treatment Options

The treatment of patients with diagnosed glioma, including glioblastomas, should be preferably performed in reference centers, by an experienced multidisciplinary team, for holistic clinical and surgical management. The most common clinical issues when treating these patients are epileptic seizure, brain edema, thromboembolic events, fatigue, nauseas, cognitive dysfunction, and depression [42]. The prophylactic administration of antiepileptic drugs is not indicated for patients who have not presented epileptic seizure. Drugs that may interact with the coagulation performance and/ or with chemotherapeutic agents should be avoided [42]. The use of corticosteroids may be indicated in case of brain edema or during the adjuvant treatment, nevertheless, attention should be given to the complications associated, such as immunosuppression, wound problems, Cushing's syndrome and osteoporosis [26, 42]. Attention should be given to the screening and prevention thrombotic events, due to its high incidence among these patients during the course of treatment [2, 34].

Similar to that discussed for diffuse astrocytoma, surgery is also one of the main pillars in the management of glioblastomas. The main goals of microsurgical resection are I) to confirm histopathological diagnosis and genetic profile of the tumor; II) decrease mass effect; III) improve neurological symptoms and quality of life. Although there is a lack of level 1 evidence favoring maximal resection, increasing evidence indicates a positive correlation between extent of resection and overall survival, therefore supporting the concept that minimal residual tumor should be preferred instead of biopsy alone, whenever feasible [26, 27, 43–49]. For instance, in a large retrospective study which analyzed 1215 patients who underwent surgery for grade III and IV astrocytomas, extent of resection was an independent factor impacting on survival, independent of age, preoperative Karnofsky Performance, WHO grade of the tumor or type of postoperative treatment applied [49].

Currently, technological advances in terms of preoperative diagnostics and functional evaluation, as well as intraoperative armamentarium, i.e. neurophysiological evaluation, ultrasound, fluorescence-microscopy, neuronavigation and real-time imaging control, have made surgical intervention safer and more efficient [31, 33]. Therefore, most guidelines agree that biopsy alone should be reserved for cases where surgical resection is not feasible, or in the differential diagnosis of radionecrosis and tumor progression. Moreover, adjuvant or palliative care without histological confirmation of the diagnosis should be avoided, unless the risks are considered too high or patient's prognosis unfavorable despite of any treatment.

Although great advances have been achieved in understanding the biology and genetic profiles of these tumors, treatment alternatives have been developing in a slower pace. Since Stupp and colleagues 2005, [50] surgery followed by temozolomide (TMZ) concomitant to radiation therapy and adjuvant have become the mainstay in the management of glioblastoma [26, 50]. The Nordic trial and NOA 08 introduced the evaluation of MGMT promoter status in elderly patients in order to stratify the indication for TMZ or radiotherapy alone for those not eligible for combined modality treatment. In summary, patients with methylation of MGMT should receive TMZ alone, whilst those without MGMT methylation (or MGMT status unknown) should undergo hypofractionated radiotherapy only [51, 52].

Other pharmacological and non-pharmacological adjuvant approaches for the treatment of GBM have been under investigation. The role of local carmustine polymer wafers within the tumor resection cavity remains a matter of discussion. Westphal et al. (2003) showed increased survival with the administration of local carmustine compared with radiotherapy alone in patients with high-grade glioma (13.9 vs 11.6 months OS), however it did not improve outcome in glioblastoma [53]. In line with this, several studies supported that adding local carmustine polymer wafers to standard treatment did not improve outcome, despite of significant increase in toxicity and treatment-related complications, both for patients with newly diagnosed and patients with recurrent GBM [54]. A recent meta-analysis, on the other hand, has shown advantage of carmustine implantation in resection cavity for GBM, improving survival, in comparison with patients receiving TMZ alone [55]. Some centers advocate for its use as part of rescue therapy in case of tumor recurrence.

The utility of anti-angiogenic drugs have been also a controverse subject in the management of GBM [56]. Despite of strong evidence that bevacizumab prolongs progression-free survival (PFS) in newly and recurrent GBM, it does not significantly improve OS. The impact of anti-angiogenic drugs on quality of life (QoL) and real benefits remains unclear, however there may be a benefit in patients with large tumors, resistant to steroids, who might otherwise not tolerate radiotherapy [26, 56]. Bevacizumab is approved in some countries for recurrent GBM [26]. Tumor-treating fields (TTF) consists of a recently developed and FDA-approved non-pharmacological approach to brain tumors, where mild electrical fields pulse through the skin of the scalp, “disrupting” cancer cell’s ability to divide [57]. Following initial open label studies, other recent randomized clinical trials have showed an increase in PFS (7.1 vs 4 months) and OS (20.5 vs 15.6 months) favoring the use of TTF in comparison with standard chemo-radiation therapy [57]. There are still open questions regarding mechanism of action, data analysis and interpretation, cost-effectiveness and impact on QoL to be addressed though [26].

More recently, there has been huge efforts towards the development of personalized check-point inhibitors, target therapies and also of effective vaccines for the management of gliomas, including GBM [58, 59]. Several strategies have been evaluated for activity against GBM in clinical trials. For instance, an autologous tumor lysate-pulsed dendritic cell vaccine (DCVax®-L) was added to standard therapy for newly diagnosed GBM in a Phase 3 cross-over clinical trial, providing evidence that this strategy may extent survival, is feasible and safe in GBM [58]. Other approaches,

such as the Glioma Actively Personalized Vaccine Consortium (GAPVAC), has provided insights on the development of vaccines using unmuted tumor antigens and neoepitopes, showing sustained induced immunological response in glioblastoma patients [59]. Other approaches include peptide vaccines, heat shock protein vaccines, and adoptive immunological therapy [60]. The field has been rapidly evolving, leading to optimism that effective immunotherapy will improve outcome.

17.4.5 Complications

Commonly reported perioperative complications in the clinical and surgical management of glioblastoma were intracranial bleeding, infection, epileptic seizure, neurological worsening, deep vein thrombosis (DVT), pulmonary embolism (PE) and depression [2, 34]. Other commonly reported late complications related to the adjuvant treatment are adverse drug reaction, radio necrosis, brain edema, radiation-induced CNS tumors and cognitive issues [2, 17, 26].

17.4.6 Pearls

- Maximum safe resection is recommended whenever feasible in all patients with newly diagnosed glioblastoma;
- Technological advances, such as preoperative and intraoperative functional brain mapping provide extra guidance for a safe tumor resection, even in highly eloquent areas;
- Tumor biopsy should be reserved for high-risk patients, when resection is deemed not feasible and for the differential diagnosis of radio-necrosis and tumor progression in suspected recurrence;
- Concomitant and adjuvant TMZ associated with radiation therapy remains the mainstay following surgery in the management of GBM, regardless of its genetic profile. Biomolecular information may be helpful in terms of prognostication and prediction of response to adjuvant therapy.
- MGMT status testing should be considered in the elderly population in order to guide adjuvant therapy, according to results of the NOA-08 and Nordic trials.
- TTF may be of advantage in the management of GBM, however concerns have been raised regarding its high costs, limited health insurance coverage, impact on QoL and real net benefits;
- Special attention should be given to the clinical care of these patients, from the time of the initial diagnosis throughout the whole treatment, concerning the prevention and management of common issues, such as thromboembolic events, epileptic seizures, brain edema and depression;
- Immunotherapy seems to be a safe and promising approach in the management of GBM.

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Chapter 18
Embryonal Tumors

Jean-Paul Bryant and Toba N. Niazi

18.1 Introduction

Brain tumors are the most common solid neoplasms affecting pediatric patients and the leading cause of childhood cancer-related death [1, 2]. It is estimated that pediatric brain tumors comprise 15% to 20% of childhood malignancies, second only to leukemia [3]. Recent years have led to significant advances in the understanding of the molecular underpinnings of pediatric brain tumors, largely attributable to the progression of sophisticated genetic profiling techniques. These innovations have had a profound effect on embryonal brain tumors, which are a heterogenous group of neoplasms primarily affecting younger children or infants. For example, medulloblastomas which were once categorized into standard and high-risk subgroups are now comprised of four molecular subtypes with distinct tumor biology and clinical behavior. This knowledge has led to improved characterization and treatment strategies for these aggressive neoplasms.

As a whole, embryonal tumors comprise a genetically and biologically heterogenous group of neuroepithelial tumors composed of densely packed and mitotically active cells [4]. These tumors share a tendency to metastasize throughout the entirety of the neuroaxis. They are estimated to constitute 0.9% of total brain tumors while representing 13.3% of brain tumors diagnosed in children age 0–14 years, with a

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higher predominance in males than females [5]. Embryonal tumors represent the most frequently diagnosed brain tumor variant in children 0–4 years of age [5]. The estimated 5-year and 10-year survival rates of children diagnosed with embryonal tumors are 62.6% and 56.4%, respectively, but varies significantly by histological classification. Irrespective of histopathological characterization, embryonal tumors share an exceedingly aggressive phenotype, with all subtypes classified as malignant, World Health Organization (WHO) grade IV neoplasms [6].

The primary aim of this chapter is to discuss the epidemiological, histopathological, and clinical characteristics associated with each embryonal tumor. Further, we will discuss the expected clinical presentation in patients presenting with these neoplasms. Finally, this chapter outlines the typical radiographic findings associated with each tumor, while also discussing management and probable treatment outcomes.

18.2 Medulloblastoma

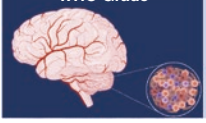
18.2.1 Epidemiology

Approximately 500 children each year in the United States are diagnosed with medulloblastoma [7]. Medulloblastomas are the most common primary malignant brain tumor diagnosed in children accounting for nearly 20% of all central nervous system (CNS) neoplasms [8, 9]. The annual incidence of medulloblastomas peaks in children 5–9 years of age, occurring at a rate of 0.58 per 100,000 population and further decreases with age [5]. In children aged 0–14 years, medulloblastoma accounts for 62.4% of all embryonal tumors diagnosed. Medulloblastomas demonstrate a modest male gender predominance in a ratio of 1.4:1, most notably in children younger than 4 years of age, but varies based on molecular classification (Table 18.1) [10]. While survival rates for embryonal tumors are dismal, medulloblastomas portend the greatest 10-year survival (64.9%) relative to embryonal tumors with multilayered rosettes (ETMR) and atypical teratoid/rhabdoid tumors (AT/RT). Approximately 5–6% of medulloblastomas occur secondary to a cancer predisposition syndrome including Li-Fraumeni syndrome, nevoid basal cell carcinoma syndrome (also known as Gorlin syndrome), or Turcot syndrome [11].

18.2.2 Clinical Presentation

Medulloblastomas are infratentorial, posterior fossa masses arising from the cerebellum (Table 18.1). Clinical signs and symptoms suggesting a diagnosis of medulloblastoma are typically related to hydrocephalus resulting from obstruction of the fourth ventricle. Obstruction occurs due to increased tumor size at the time of diagnosis as prior to clinical presentation patients are usually asymptomatic or

Table 18.1 Overview of embryonal tumor subtypes reviewed in the chapter based on data from the following references [6, 10]. Icons created with BioRender.com

Embryonal Tumor Type	Medulloblastoma	AT/RT	ETMR, C19MCaltered	Other CNS Embryonal Tumors
Age group 	Infants Children Adolescents Adults	Infants Children < 3 years	Children < 4 years	Infants Children Adolescents
Gender predominance 	Dependent on molecular subtype	No significant gender predominance	Estimated M:F ratio of 1.6-2:1	No significant gender predominance
Tumor Location 	Cerebellum	Majority in posterior fossa, may be supratentorial or infratentorial	70% Supratentorial (frontal, parietotemporal) 30% Infratentorial	Supratentorial (Non-specific, cerebral hemispheres)
Prognosis 	Very favorable-poor dependent on subtype	Poor	Very poor	Very poor
WHO Grade 	IV	IV	IV	IV

experience subtle symptoms [10]. Most children presenting with medulloblastomas will exhibit signs of increased intracranial pressure (ICP) such as morning vomiting and headache but may also experience significant nausea or altered mental status (AMS). At early stages of tumor development, the child will likely experience headache which is relieved by vomiting. As the tumor progresses, the temporal variation diminishes with symptoms becoming progressively constant.

Midline tumors are often associated with truncal instability or with diplopia secondary to sixth nerve palsy [12]. Tumors presenting laterally may cause appendicular ataxia or incoordination. Seizures are rarely a presenting symptom in children with medulloblastoma. Findings on neurological exam will largely depend on the tumor position within its typical posterior fossa location. Patients presenting with midline tumors may have difficulties with heal-to-toe walking, demonstrate a broad-based gate, or present with nystagmus. Those with lateral cerebellar tumors may exhibit finger-to-nose dysmetria, difficulty with heal-to-shin testing, or show a slight intention tremor.

The differential diagnosis for medulloblastoma includes pilocytic astrocytoma, ependymoma, and other embryonal tumors such as AT/RT and ETMR. Distinguishing between these entities based on symptomatology alone is difficult, however, non-embryonal brain tumors have slightly different initial clinical presentations. Children with ependymomas will usually describe a history of neck pain or stiffness while children with pilocytic astrocytomas tend to gradually develop symptoms over a longer duration of time than those with medulloblastoma. Variation also

exists based on the age of presentation. For instance, infants can present with macrocephaly due to their open sutures. Macrocephaly may also be accompanied by lethargy, bulging fontanels, and downward gaze caused by increased pressure on the tectum. Young children can better tolerate initial elevations in ICP secondary to hydrocephalus and as a result, tend to present later in their disease course with more severe symptoms including apnea, bradycardia, or AMS.

18.2.3 Radiographic Findings

While computed tomography (CT) is still used in the emergency setting for patients with suspected intracranial pathology, magnetic resonance (MR) imaging has become the modality of choice [13, 14]. MRI with gadolinium administration is the preferred method to evaluate suspected lesions of the posterior fossa [10]. Medulloblastomas will usually appear isointense or hypointense relative to the surrounding gray matter on T1-weighted images (Fig. 18.1). Gadolinium administration causes these lesions to become hyperintense on T1-weighted MRI. The signal on T2-weighted images is heterogenous where the solid portion of the mass is often isointense or hypointense in comparison to the gray matter (Fig. 18.1). Lack of tumor enhancement is an abnormal finding occurring in a minority of cases [15]. Leptomeningeal enhancement can be

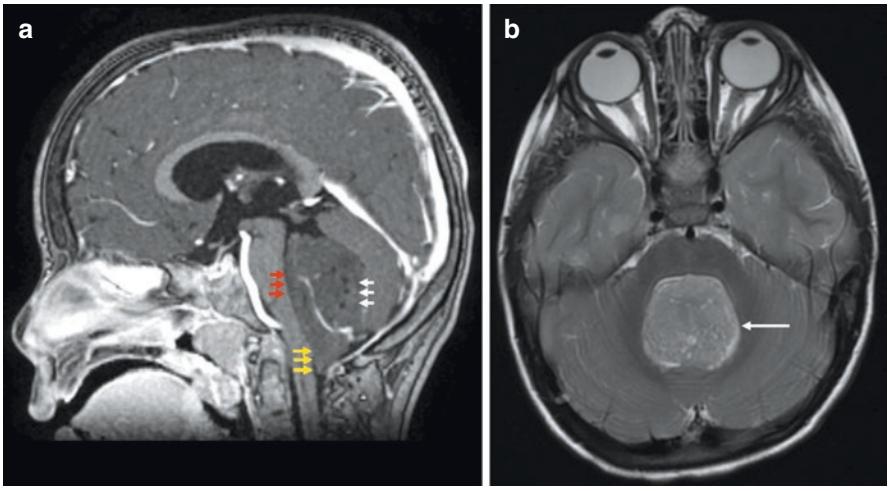


Fig. 18.1 MR images of a patient with medulloblastoma including (**a**) T1-weighted sagittal MRI brain with contrast and (**b**) T2-weighted axial MRI brain. Images demonstrate a well-defined, rounded mass in the posterior fossa, within the fourth ventricle (**b**, *arrow*). The mass extends through the foramen of Magendie into the cervical region and through the foramen of Luschka, bilaterally (**a**, *white arrows*). The signal intensity is low on T2, intermediate on T1 with restriction to diffusion. There is mass effect upon the brainstem (**a**, *red arrows*) and extension into the craniocervical junction (**a**, *yellow arrows*)

found on MR as well as the presence of cysts which are typically small and numerous. Tumor dissemination to the CSF is common and is best identified on T1-weighted sequences. Drop metastases present most usually as a contrast enhancing coating seen in the spinal cord or as distinct, strongly enhancing tumor foci in the spinal canal commonly along the posterior aspect. Diagnosing leptomeningeal invasion must be done with MRI of the spine prior to surgery as debris and blood may become difficult to distinguish from drop metastases post-operatively. Diffusion weighted MRI can be useful to distinguish medulloblastoma from other astrocytomas or ependymomas. Medulloblastomas exhibit diffusion restriction whereas ependymomas and pilocytic astrocytomas usually do not restrict diffusion [16].

The findings of medulloblastoma on CT are non-specific and cannot be definitively distinguished from ependymomas or AT/RTs. On CT without contrast, medulloblastomas typically appear as a hyperattenuating mass on the midline with surrounding vasogenic edema. Contrast administration causes homogenous enhancement of the lesion. Hydrocephalus is present on CT initially in most patients.

18.2.4 Pathology

To definitively diagnose medulloblastoma microscopic histopathologic examination is needed. The classic microscopic appearance of medulloblastoma demonstrates a small round blue cell tumor that is densely packed with prominent nuclei, abundant chromatin, and scant cytoplasm (Fig. 18.2). The most current WHO

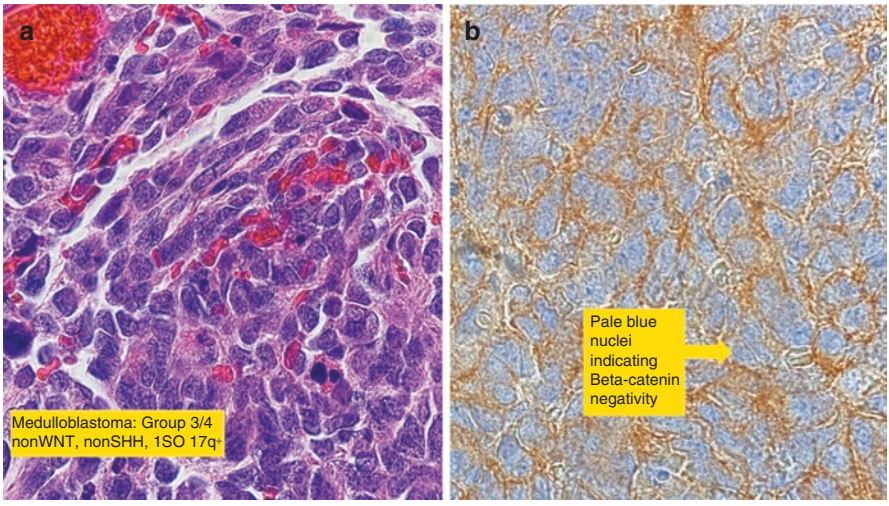


Fig. 18.2 Histopathological section including (**a**) H&E and (**b**) immunohistochemistry of a Group 3/4, nonWNT, nonSHH, 17q + medulloblastoma tumor sample likely reflecting the classic histological subtype. Cell nuclei stained negative for Beta-catenin which appear pale (**b**)

Classification of Tumors of the Central Nervous System divides medulloblastomas into four histological subtypes: classic, desmoplastic/nodular, medulloblastoma with extensive nodularity, and large cell/anaplastic [6]. Classic medulloblastoma accounts for the vast majority of histological subtypes reported (72%) and has the typical small round blue cell appearance (Fig. 18.2). Tumor cells are densely packed and undifferentiated with numerous mitotic figures, attributing to its high proliferative index. Homer Wright rosettes (pseudorosettes where differentiated cells surround the neuropil) may be appreciated. Desmoplastic/nodular medulloblastoma has been estimated to account for 20% of all cases, most commonly occurring in children under three years of age (~44% of medulloblastoma diagnoses in this age group) [17, 18]. Histological evaluation of the desmoplastic/nodular subtype is characterized by nodular, pale islands (reticulin free zones) surrounded by undifferentiated, densely packed cells with moderately pleomorphic nuclei and a dense, intercellular reticulin fiber network [19]. Tumor cells are glial fibrillary acidic protein (GFAP) positive. Synaptophysin staining is increased within tumor nodules while the Ki-67 index is increased outside of the nodules. Medulloblastoma with extensive nodularity is reported to comprise 3.2–4.2% of all medulloblastoma variants [18, 20]. This variant differs from the desmoplastic/nodular subtype in that its histoarchitecture is large and expanded. This expansion is caused by copious neuropil-like tissue in reticulin free zones. Small cells with round nuclei showing neurocytic differentiation can be seen in these reticulin free zones. Large cell/anaplastic medulloblastomas account for an estimated 10% of variants [20]. It is characterized by a lack of tumor cell size and shape variability. Tumor cells appear large and monomorphic with prominent nucleoli yet have the high rate of cellular turnover that traditionally characterizes anaplastic tumors.

There are four consensus molecular subgroups of medulloblastoma: wingless (WNT), sonic hedgehog (SHH), group 3, and group 4 (Table 18.2) [21]. The importance of these subgroups stems from their significant prognostic value and variation in overall survival. The WNT subgroup is defined by constitutive WNT pathway activation and tumor cells carrying mutations in the ß-catenin gene, *CTNNB1* [22, 23]. WNT activated tumors have favorable prognoses and usually occur outside of infancy primarily affecting children over four years of age and adolescents [9, 24]. WNT tumors represent the smallest molecular subgroup of medulloblastoma, accounting for approximately 10% of these neoplasms [25]. WNT activated tumors typically exhibit classic histology but may rarely have a large cell/anaplastic appearance.

The SHH subgroup is characterized by SHH pathway activation and has a bimodal age distribution primarily affecting infants and adults with desmoplastic/nodular tumors [10]. This subgroup is the second most prevalent variant accounting for 30% of medulloblastomas [25]. While it typically demonstrates the aforementioned age and histological predilection, tumors may arise in adults and can exhibit all histological variants [10]. SHH-activated tumors carry a favorable prognosis when presenting in infants but have a variable prognosis in other age groups.

Group 3 medulloblastomas have the worst prognosis and are associated with high rates of metastatic disease at the time of diagnosis (40–45%) [9]. They account for approximately 25% of all cases, occurring almost uniformly in infants and young children [9] [26]. The genetic aberration of group 3 medulloblastomas is usually

Table 18.2 Clinical and molecular characteristics of medulloblastoma subgroups, based on data from the following references [9, 10, 25]. Icons created with BioRender.com

Molecular Subgroup	WNT	SHH	Group 3	Group 4
% of Cases	10	30	25	35
Age group	Children > 4 Adolescents	Infants Adults	Infants Children	Children Adolescents
Gender Ratio (M:F)	1:1	1:1	2:1	3:1
Histology	Classic LCA (Rare)	Desmoplastic/nodular Classic LCA	Classic LCA	Classic LCA
Genetic mutation	*CTNNB1* mutation	*PTCH/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	*MYC* amplification	*CDK6* amplification *MYCN* amplification
Prognosis	Very favorable	Favorable in infants Intermediate in others	Poor	Intermediate
Estimated 5-year OS	95%	75%	<60%	60%-90%

characterized by *MYC* amplification, which confers a particularly short survival. Microscopically, group 3 tumors may exhibit classic or large cell/anaplastic histology. Group 4 medulloblastomas comprise the most prevalent subtype, accounting for approximately 40% of all cases [26]. They have an intermediate prognosis and are predominately diagnosed in children between 3–16 years of age with a strong predilection for males [27]. Group 4 medulloblastomas may demonstrate classic or large cell/anaplastic histology. The 5-year survival rate of group 4 medulloblastomas can reach greater than 90% in certain low-risk variants but can drop as low as 60% in high-risk variants [28].

18.2.5 Management and Outcome

The most commonly employed initial treatment for medulloblastoma includes gross total resection of the posterior fossa mass via suboccipital craniotomy. The goal of the procedure should be to resect as much of the tumor as possible while ensuring the resection is not extended into the brainstem. Medulloblastomas can be highly

vascular, thus care should be taken to prevent significant hemorrhage intraoperatively, especially in young children and infants. Ideally, postoperative MRI should be performed 72 hours following surgery to determine the extent of surgical resection. Imaging within this time window may cause obscuration by gliosis or blood products. The most common postoperative complication following tumor resection is posterior fossa syndrome (also known as cerebellar mutism) [29]. Posterior fossa syndrome has a classic triad of decreased speech or mutism, ataxia, and behavioral symptoms such as emotional liability or irritability [29]. These symptoms typically arise in patients 24–48 hours postoperatively. Bladder incontinence has been reported but is less common [30]. The pathophysiology of posterior fossa syndrome is not completely understood but has been attributed to disturbance of the dentothalamocortical pathway proximally caused by surgical resection.

Surgical resection is then often followed by radiation therapy and adjuvant chemotherapy in patients greater than three years of age with average-risk or high-risk disease [10]. In infants and young children, the treatment modality of choice is chemotherapy as to delay or eliminate the need for subsequent radiation. Radiation therapy is not recommended in this age group due to severe neurologic consequences including cognitive impairment, growth failure, and thyroid dysfunction. Children older than three years of age with average-risk disease have a reported 5-year survival rate of 85% with reduced dose chemotherapy and radiation following surgical resection. Children older than three with high-disk disease have a 70% survival rate with the same treatment regimen [31].

18.3 Atypical Teratoid and Rhabdoid Tumor (AT/RT)

18.3.1 Epidemiology

AT/RTs are rare entities comprising approximately 1.3% of CNS primary brain tumors in the pediatric population [32]. AT/RTs show a strong preponderance for children <3 years of age thus are estimated to account for over 10% of primary CNS primary brain tumors in infants (Table 18.1) [33]. An even greater proportion affects children younger than two years of age with 66% of all reported cases arising in this age group [34]. AT/RTs appear more commonly in males than females with an estimated male-to-female ratio of 1.6–2:1 (Table 18.1) [6]. AT/RTs are aggressive tumors with a dismal median overall survival rate ranging from 6 to 17 months [35]. The poor prognosis in children with AT/RTs is attributed to its early average age at diagnosis and propensity to metastasize through CSF.

18.3.2 Clinical Presentation

The clinical presentation of children with AT/RTs is variable and largely dependent on the age of the patient and location of the tumor. Infants and children younger than three years of age have shown to present with non-specific symptoms including

lethargy, failure to thrive, and vomiting [6, 36]. Most children present with symptoms consistent with the location of the tumor at the time of diagnosis. The majority of AT/RTs arise in the posterior fossa and consequently children may develop head tilts prior to other overt symptoms. Cranial nerve palsy involving the sixth and seventh nerves may also be seen on physical examination. Hemiplegia and headaches may occur as presenting symptoms most commonly in children older than three years of age [36].

The differential diagnosis in a child with a suspected AT/RT includes medulloblastoma and intracranial teratoma. Medulloblastomas tend to occur in an older age group and have a few differing radiographic characteristics in comparison to AT/RTs. AT/RTs may arise in an infratentorial or supratentorial location and more often involve the cerebellopontine angle than medulloblastomas [37]. Case series have also demonstrated that AT/RTs are more likely to present with signs of intratumoral hemorrhage on MRI [37]. Intracranial teratomas are uncommon neoplasms and typically present in the antenatal or newborn periods. These lesions are the most common fetal brain tumor accounting for approximately 50% of reported cases [38]. While age and imaging characteristics are potential distinguishing features, AT/RTs often resemble other embryonal tumors, thus histopathological examination is imperative.

18.3.3 Radiographic Findings

Like most intracranial neoplasms, MR is the imaging modality of choice when evaluating AT/RTs (Fig. 18.3). These tumors appear as heterogenous masses with areas of isointense to hyperintense signal relative to gray matter on fluid-attenuated inversion-recovery (FLAIR) images and demonstrate restricted diffusion [39]. Heterogeneous zones of variable signal intensity secondary to cystic and/or necrotic regions, previous hemorrhage, edema, or calcifications may be appreciated on T2-weighted images (Fig. 18.3). The vast majority of tumors show variable contrast enhancement on imaging. Leptomeningeal dissemination has been reported in as much as 25% of patients presenting with AT/RTs, highlighting their propensity to metastasize through the CSF [39]. AT/RTs most commonly arise in the posterior fossa but may appear in supratentorial regions and can be multifocal, presenting in both compartments [40]. CT images may show intermediate or slightly higher attenuation than that of gray matter with lower attenuation zones appearing secondary to cystic and/or necrotic changes.

18.3.4 Pathology

The gross appearance of these neoplasms tends to mimic medulloblastomas and other embryonal tumors. They appear pinkish-red with areas of necrosis and may be hemorrhagic. They tend to be soft in texture except when containing significant

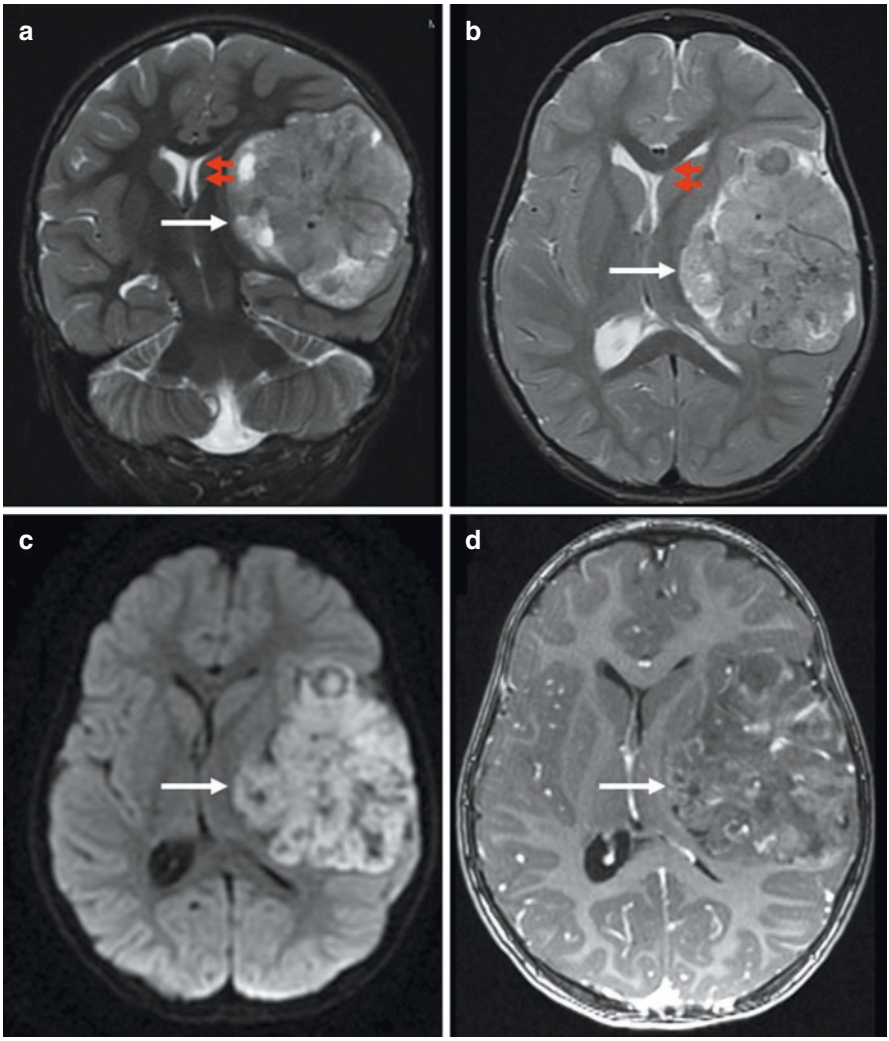


Fig. 18.3 MR images of a patient with AT/RT including (**a**) T2-weighted coronal MRI brain, (**b**) T2-weighted axial MRI brain, (**c**) axial diffusion MRI brain, and (**d**) T1-weighted axial MRI brain with contrast. There is a large heterogeneous mass in the left cerebral hemisphere, occupying the region of the sylvian fissure displacing and infiltrating the operculum (**a**–**d**, *white arrow*). Significant mass effect upon the adjacent brain is noted, with midline shift and near complete effacement of the left lateral ventricle (**a**, **b**, *red arrows*). There is partial effacement of the suprasellar cistern due to uncal herniation, with compression of the left cerebral peduncle (**a**). The lesion has very heterogeneous signal, with scattered hyperintense foci on T1-weighted image, a combination of mineralization and hemorrhage, several intralesional flow-voids and several irregular fluid-like areas within the tumor (**d**)

mesenchymal tissue and will instead be firm with dispersed tan-white regions. When arising from the cerebellopontine angle AT/RTs will typically wrap around cranial nerves and vessels with cerebellum and brainstem extension. Bone involvement is rare but has been documented [41].

On histology AT/RTs appear as heterogenous lesions with a complex of rhabdoid, epithelial, primitive neuroepithelial, and mesenchymal components (Fig. 18.4). The tissue heterogeneity and divergent histological patterns sometimes result in the misdiagnosis of AT/RTs and renders these lesions difficult to recognize based on histopathological criteria alone. The most easily discernible histological feature seen in many cases is characterized by tumor cells with archetypal rhabdoid features including: prominent eosinophilic nucleoli, abundant cytoplasm, eccentrically located nuclei with vesicular chromatin, and well-defined cell borders (Fig. 18.4). Lesions will typically have abundant mitotic figures. Tumor cells may range from having a classic rhabdoid phenotype to cells with less obvious atypia (Fig. 18.4). Whorled cytoplasmic globules of intermediate filaments are usually seen occupying the cell body on ultrastructural representation [42]. Small-cell embryonal components are present in two thirds of tumors while mesenchymal differentiation is a much less common finding. When a mesenchymal component is present, areas with spindle cell features may be appreciated [6]. Epithelial differentiation is the least frequently encountered histologic feature, presenting as adenomatous regions or papillary structures.

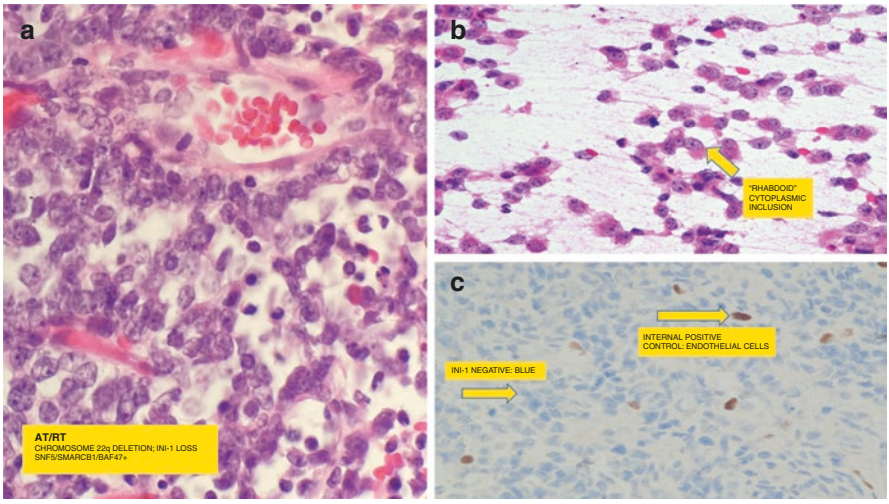


Fig. 18.4 Histopathological section including (**a**) H&E staining, (**b**) Touch preparation cytology, and (**c**) immunohistochemical staining of a C19MC altered-ETMR tumor sample. Typical appearing rhabdoid cells with rhabdoid cytoplasmic inclusions are seen (**b**). Blue appearing cells on immunohistochemistry demonstrates negativity for INI-1 (**c**)

AT/RTs may occur sporadically or as a result of rhabdoid tumor predisposition syndrome (RTPS). RTPS occurs primarily in infants and children under three years of age [43]. The genetic hallmark of AT/RTs involves a germline deletion or mutation of the *SMARCB1* gene and loss of SMARCB1 protein expression in nearly all cases. A smaller proportion of tumors also have mutations or loss of the *SMARCA4* gene, which in addition to *SMARCB1*, encodes proteins involved in the SWI/SNF complex [43, 44]. The most infrequent genetic profile of AT/RTs involves intact SMARCB1 protein expression with aberrant *SMARCA4* expression. This rare genetic permutation is seen in very young patients and has an exceedingly poor prognosis [45].

18.3.5 Management and Outcome

There is currently no standard therapy in treating patients with AT/RTs. These tumors are challenging to treat due to their large size and associations with nearby blood vessels in a patient population that is highly sensitive to fluctuations in blood volume. There is growing evidence supporting the use of neoadjuvant chemotherapy in the management of children with AT/RTs [34, 46, 47]. Reports have cited that neoadjuvant chemotherapy increases tumoral fibrosis facilitating the formation of a clearer surgical plane between the tumor and the surrounding normal brain [34, 48]. Further, neoadjuvant chemotherapy has shown to reduce tumor size and intraoperative blood loss in highly vascular tumors due to increased collagenization of tumor supplying vessels [46, 49, 50].

Overall survival of AT/RTs is poor, despite aggressive multimodal therapy, with some reports citing a median survival as low as 9 months (Table 18.1) [51]. For patients presenting with metastatic disease the prognosis is dismal, with an estimated median survival of only three months [52]. Gross total resection is among the few strategies that has consistently shown to lengthen survival [53]. Given the large size and vascularity of these tumors, the benefit of resection must be weighed against the risk of surgery. Additionally, chemotherapeutic regimens must be carefully administered as tumor specific complications such as intratumoral hemorrhage and chemotherapy-induced thrombocytopenia have been reported [47].

18.4 Embryonal Tumor with Multilayered Rosettes (ETMR), C19MC-Altered

18.4.1 Epidemiology

ETMRs, previously termed embryonal tumor with abundant neuropil and true rosettes (ETANTR), are rare entities first described by Eberhart et al. in 2000 [54]. An accurate incidence rate of C19MC-altered EMTRs is difficult to determine as

these tumors are rare, difficult to distinguish from other embryonal tumors, have varied terminology, and require genetic profiling. Embryonal tumors previously classified as ETANTR, ependymoblastoma, and medulloepthilloma are now included in this tumor subtype which share a common genetic aberration [6]. Case reports are the predominate study design published regarding ETMRs with the largest series detailing the tumor characteristics of nearly 100 samples [55]. These tumors almost uniformly affect children under four years of age with the overwhelming majority occurring within the first two years of life. ETMRs do not exhibit any gender predominance with an almost equal male-to-female ratio of 1.1:1 (Table 18.1) [6].

18.4.2 Clinical Presentation

The clinical presentation of ETMRs varies based on the anatomical structures affected by the tumor. Tumor location in the majority of cases described is supratentorial, with approximately 30% of cases affecting the cerebellum and brainstem [56]. Lesions affecting the cerebral hemisphere typically involve the frontal and parietotemporal regions (Table 18.1). Infratentorial lesions may protrude into the cerebellopontine cistern in some cases, however, this location is observed less frequently. ETMRs localized to the spinal cord have been described but are rare [57]. The most common clinical presentation reflects signs and symptoms of increased ICP such as nausea, vomiting, and headache. Focal neurological deficits, such as limb ataxia or unilateral weakness typically affect older children or manifest in patients with infratentorial lesions. Other clinical signs reported in children with ETMRs include confusion, seizures, cerebellar syndrome, torticollis, and visual impairment however, these symptoms occurred less commonly than signs of increased ICP and unilateral weakness [57].

18.4.3 Radiographic Findings

MR sequences are most commonly used to image patients with suspected ETMRs which are often radiologically misdiagnosed as medulloblastoma, AT/RT, ependymoma, or pilocytic astrocytoma. On MR, these tumors appear as large, heterogenous solid masses which may contain a cystic component. Microcalcifications also may be appreciated. These tumors typically demonstrate patchy or no contrast enhancement with decreased intensity on T1-weighted images and decreased intensity on T2-weighted images (Figs. 18.5 and 18.6). They are accompanied with little edema and restrict diffusion owed to their high cellularity. Many cases of ETMR with dural attachment have been reported [55, 56, 58–60].

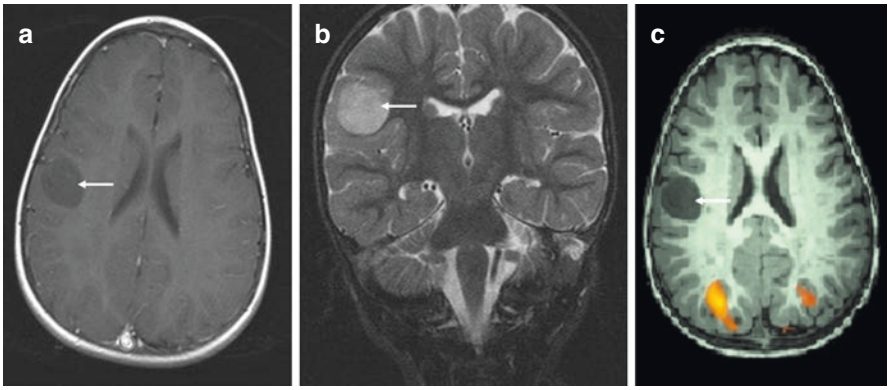


Fig. 18.5 MR images of a patient with C19MC-altered ETMR including (**a**) T1-weighted axial MRI brain with contrast, (**b**) T2-weighted coronal MRI brain, and (**C**) T1-weighted axial functional MRI brain. Images display a well-circumscribed lesion in the inferior right precentral gyrus, involving the cortex and subcortical region (**a–c** *arrow*). Hypointensity on T1-weighted images and hyperintensity on T2-weighted images are seen (**a–c**). Subtle restricted water diffusion is seen with no significant enhancement (**c**)

18.4.4 Pathology

On gross examination ETMRs are typically gray-pink, well circumscribed masses with areas of necrosis, hemorrhage, and/or less commonly, microcalcifications. Cystic components may be present. The C19MC-altered ETMRs all share a common molecular alteration characterized by amplifications and fusions in the C19MC locus at 19q13.42, however, they are distinguished by some histopathological features. Similarly, all variants typically will display rosettes comprised of multilayered and mitotically active pseudostratified neuro-epithelium (Figs. 18.7 and 18.8). The lumen may be central, round, or slit-like and is empty or contains eosinophilic debris. Rosette nuclei are usually pushed away from the lumen towards the outer cell border. The rosettes usually do not possess a well-defined outer membrane.

The three histopathological subtypes of C19MC-altered ETMR are hypothesized to represent points on a spectrum of morphology or the varied differentiation which may be present within a single tumor. These subgroups include ETANTR, ependymoblastoma, and medulloepithelioma. ETANTRs show a biphasic architecture characterized by densely packed clusters of small tumor cells with round or polygonal nuclei and scant cytoplasm (Fig. 18.8) [54, 60]. Large neuropil-like areas are often seen and may contain neoplastic, neurocytic, and ganglion cells however this finding is infrequent (Fig. 18.8) [54]. Areas of hypercellularity contain cells with high mitotic activity and apoptotic bodies. Multilayered rosettes are typically present in aggregates of small cells (Fig. 18.8). Ependymoblastomas feature sheets and clusters of poorly differentiated cells with abundant multilayered rosettes. This ETMR pattern typically lacks neuropil-like areas and ganglion cell elements. The

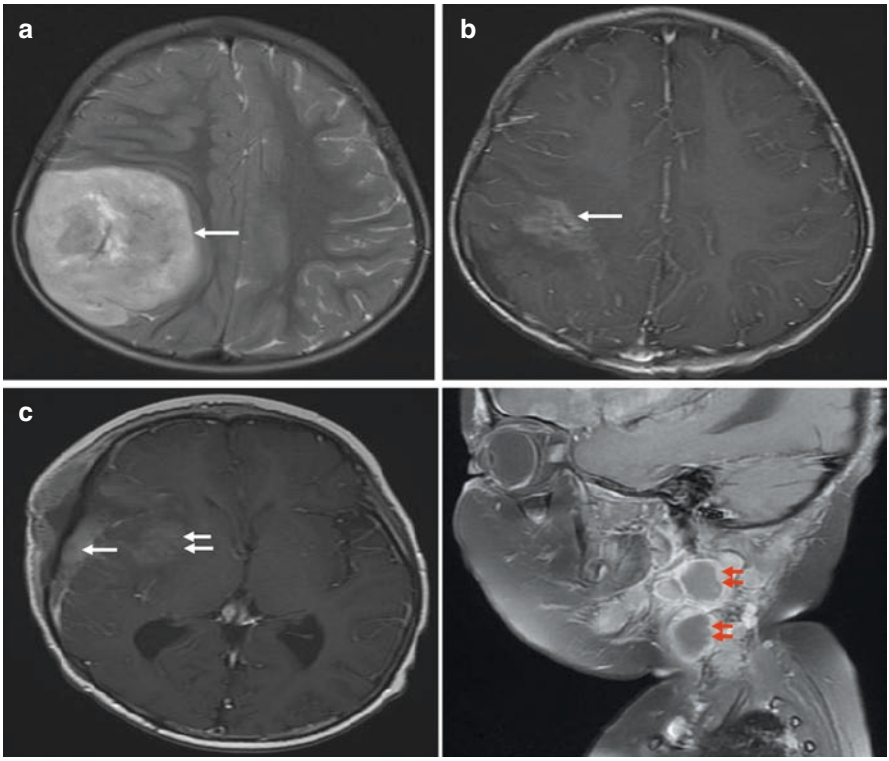


Fig. 18.6 MR images of a patient with C19MC-altered ETMR, ETANTR subtype including (**a**) initial MRI of the brain with contrast showing enhancing lesion in the right parietal lobe (*arrow*), (**b**) MRI brain at 10 months after initial surgery showing recurrence in the resected cavity (*arrow*), and (**c**) MRI brain and neck after 1 year of second surgery revealed local recurrence (arrow) with right temporal soft tissue enhancement (*white arrows*) with parotid gland and cervical lymph node involvement on the same side (*red arrows*)

rosettes are often interspersed with intermediate sized embryonal cells containing a high ratio of nucleus-to-cytoplasm. Medulloepitheliomas are perhaps the most histologically distinguishable variant and presents as a distinct mass in young children. These lesions are characterized by tubular, trabecular, and papillary patterns of pseudostratified epithelium. Abundant mitotic figures are seen and are typically near to the luminal surface. Found away from the distinct papillary and tubular structures are large sheets of poorly differentiated cells containing hyperchromatic nuclei with a high ratio of nucleus-to-cytoplasm. Dispersed clusters of multilayered rosettes are sometimes present within this region. Tumor cells span from embryonal to mature neurons or astrocytes. Mesenchymal differentiation or tumor cells containing melanin pigment has been reported in this subtype but is a rare finding [61]. The genetic hallmark of these tumors is characterized by C19MC amplification. In the series by Korshunov et al., 96% of 97 ETMR tumor samples contained this particular genetic aberration as revealed by fluorescence in-situ hybridization (FISH),

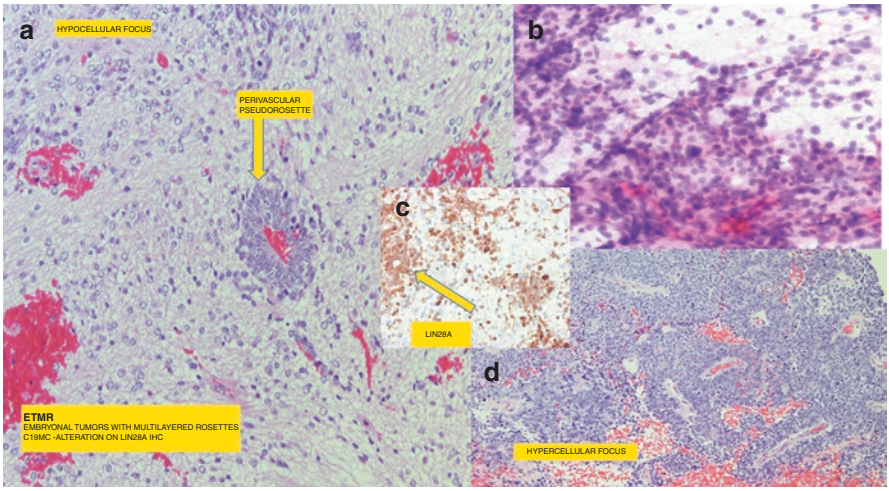


Fig. 18.7 Histology including (**a**, **d**) H&E staining, (**b**) Touch preparation cytology, (**c**) immunohistochemical staining of a C19MC altered-ETMR tumor sample. The tumor displayed both hypocellular (**a**) and hypercellular (**d**) foci demonstrating the heterogeneity of the tumor. A perivascular pseudorosette is seen on H&E staining (**a**)

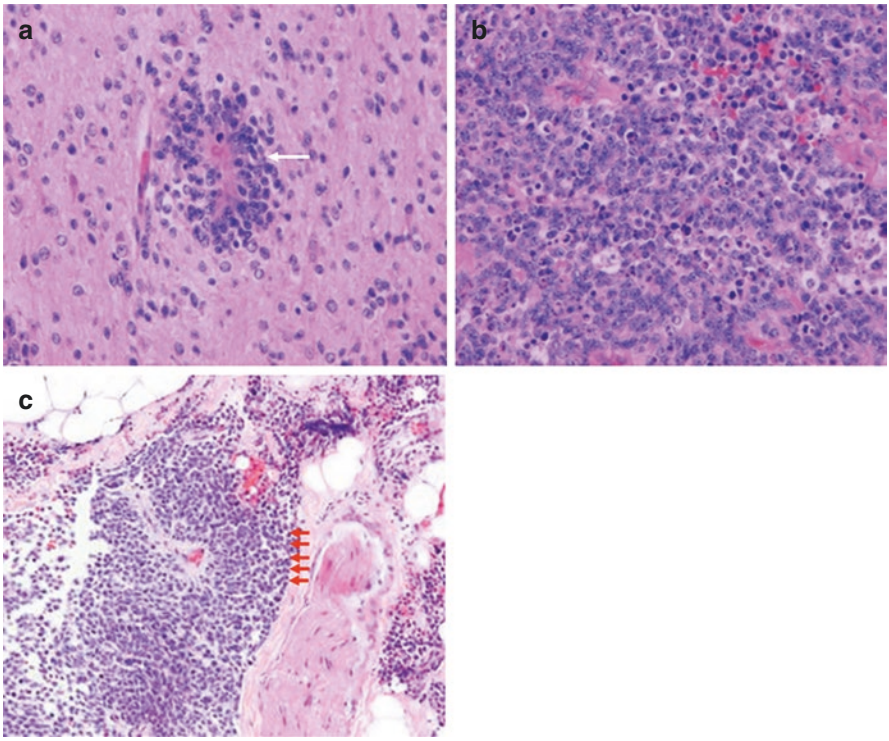


Fig. 18.8 (**a**–**c**) H&E histology photomicrographs of C19MC-altered ETMR, ETANTR subtype showing true a rosette surrounded by abundant neuropil (**a**, *white arrow*), malignant embryonal component of ETANTR (**b**), and metastasis of ETANTR to the lymph node (**c**)

regardless of histopathological classification [55]. Consequently, FISH is a particularly useful tool for diagnosing ETMR in the clinical setting.

18.4.5 Management and Outcome

A standard treatment protocol for the management of ETMRs has yet to be described. Investigators have recommended maximal resection to reduce ICP with subsequent systemic chemotherapy and craniospinal radiotherapy when necessary [57]. Extension of the surgical resection up to 1 cm into the surrounding infiltrated cerebral tissue has shown to moderately improve patient outcomes [62]. Craniospinal irradiation and high-dose chemotherapy following surgical resection has also demonstrated some benefit. The study by Horwitz et al. reported a 1-year event free survival (EFS) rate of 36% and an OS rate of 45% using this treatment regimen [57]. Conversely, treatment strategy relying on only high-dose chemotherapy following surgery had an estimated a 1-year EFS of 16% with 14% OS [55]. Histological variation and recurrent chromosomal aberration have not shown to significantly affect clinical outcome [6].

ETMRs are rapidly growing neoplasms and are associated with an aggressive clinical course. Survival averages approximately one year following multimodal therapy. Recurrence usually results from local tumor regrowth with a smaller number of patients developing distant, systemic metastases through leptomeningeal dissemination or extracranial invasion into soft tissue. Some case reports have described long-term disease free survival post-treatment, however, this is an extremely rare outcome [56].

18.5 Other CNS Embryonal Tumors

In their latest update, the WHO categorizes medulloepithelioma (non-C19MC altered), CNS neuroblastoma, and CNS ganglioneuroblastoma into a tumor subgroup which lacks specific histopathological characteristics or genetic aberrations that are present in other CNS tumors [6]. These tumors are poorly differentiated, exceedingly rare, and are neuroectodermal in origin (Fig. 18.9). The classification of ETMR, C19MC-altered subtype has since complicated surveillance of embryonal tumors without identified genetic mutations. This change in diagnostic criteria has rendered the gathering of exact epidemiological information difficult. Nevertheless, these tumors are estimated to account for approximately 1% of all brain tumors but 13% of tumors arising in children 0–14 years of age (Table 18.1) [5]. The tumor biology of these neoplasms is similar, with most lesions arising in the cerebral hemispheres and rare cases of tumors with brainstem and spinal cord origin [63, 64]. MRI imaging usually reveals T1-hypointensity relative to gray

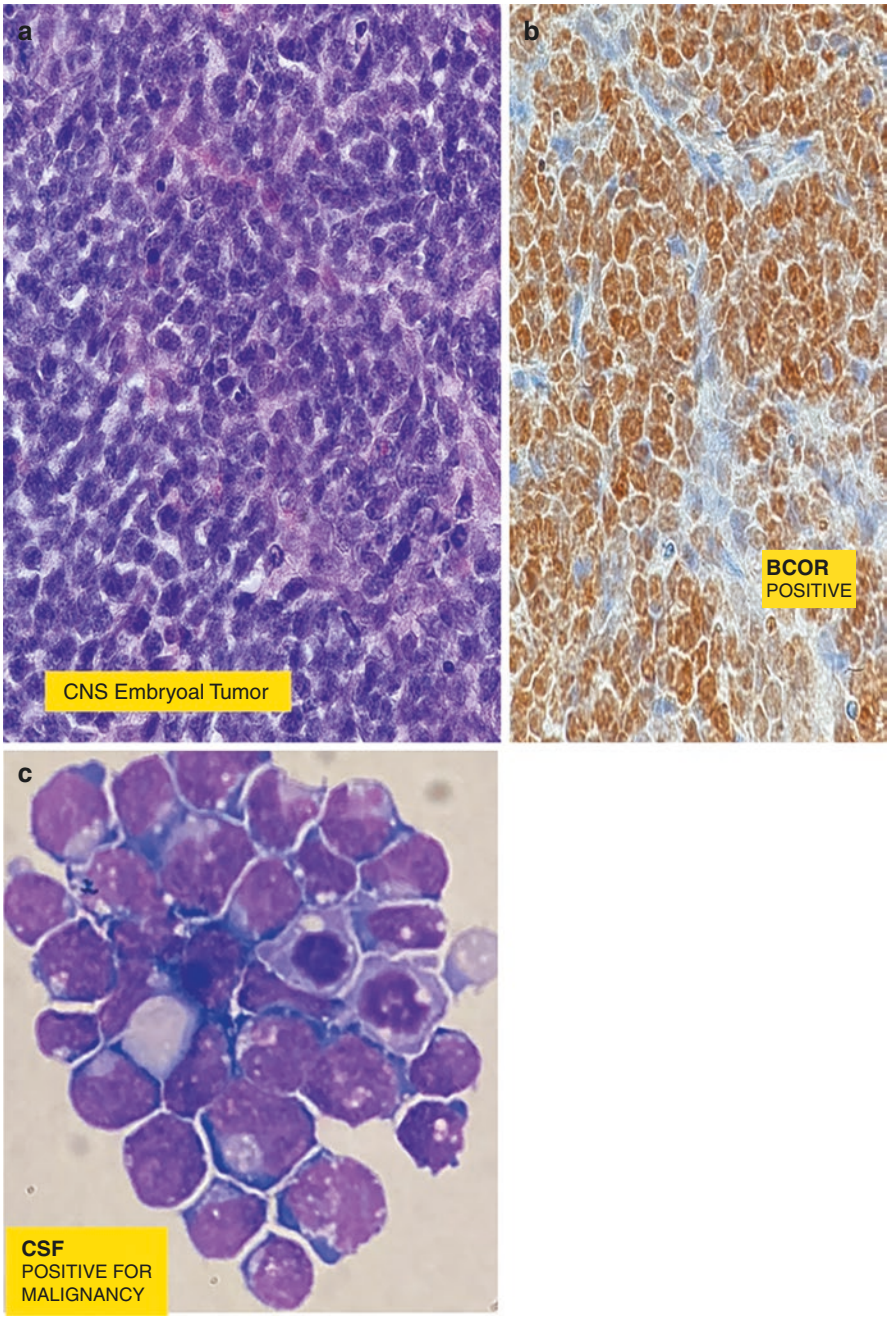


Fig. 18.9 Cellular analysis including H&E staining (**a**), immunohistochemical staining (**b**), and CSF analysis (**c**) of a CNS embryonal tumor sample. Tumor cells were positive for BCOR (**b**) and the CSF sample contained malignant cells suggesting metastatic seeding (**c**)

matter and T2-hypointensity with cystic or necrotic areas appearing hyperintense. Contrast enhancement is seen with gadolinium administration.

Metastatic dissemination occurs in approximately 25% of tumors at presentation, typically seeding in the subarachnoid space with extension through the spinal canal. This highlights the importance of diagnostic lumbar puncture for cytology and spinal MRI which are both imperative for all patients with suspected CNS embryonal tumors [65]. Management typically includes maximal surgical resection followed by adjuvant chemotherapy [66]. Given the extraordinarily young average age at diagnosis, radiotherapy has little utility in treating this patient population due to potential adverse developmental side effects. The clinical behavior of CNS embryonal tumors is very aggressive and consequently, these tumors have an exceedingly poor prognosis (Table 18.1). Multiple relapses and leptomeningeal spread are common. The five-year survival rate for children with CNS embryonal tumors is estimated to be 29–57% [6].

18.6 Conclusion

Embryonal tumors present unique challenges to the pediatric neurosurgeon. Overall, they tend to exhibit aggressive clinical behavior, with the most intrusive tumor subtypes demonstrating widespread leptomeningeal dissemination. The OS of most embryonal tumors is unfortunately dismal, owed to their early age of diagnosis, tumor locations near eloquent cerebral structures, and tendency for these neoplasms to relapse even after surgical and chemotherapeutic treatment. While gaps in the literature undoubtedly exist regarding the characterization and best treatment practices of these tumors, recent years have elicited impactful genetic and biological information. Further, the advancement of adult brain tumor management with innovative treatment modalities such as immunotherapy has already expanded to the pediatric population in both the pre-clinical and clinical settings [67, 68]. Conceivably, continued investigations will lead to improved treatment outcomes, therefore reducing the physical and psychological burden placed on children and their families.

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Chapter 19
Ependymal Tumors

Georgios Alexiou and Neofytos Prodromou

19.1 Introduction

Brain tumors occur almost as frequently as leukemia in children and for the ages 0–14 years, brain tumors are the most important cause of death. The overall incidence rate of central nervous system (CNS) tumors is 5.37 cases per 100.000 population for children age 0–14 years [1]. Ependymomas are the third most common CNS tumor in children after pilocytic astrocytoma and medulloblastoma [2]. Ependymomas account for 5.7% of all tumors and are more common in males [1]. Ependymomas are believed to arise from radial glial cells throughout the neuraxis. The majority arise in the posterior fossa (2/3 of cases), followed by supratentorial location. Spinal cord ependymomas account for 10% of all cases. Based on the latest World Health Organization (WHO, 2016) classification they are classified into 3 grades of malignancy [3]. Among hereditary tumor syndromes, ependymomas occur in 1/3 to 1/2 of patients with neurofibromatosis type 2 (NF2). NF2 related ependymomas are usually of grade II and most frequently located in the posterior fossa and cervicomedullary region of the spine [4]. To date conflicting data exist on the prognostic significance of grading in ependymomas, thus molecular studies have been conducted to better elucidate ependymoma's features. Recently, a genetically defined ependymoma variant has also been included, the *RELA* fusion–positive, which involves the majority of supratentorial pediatric ependymomas [3]. Gross total resection is the treatment of choice.

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19.2 Clinical Features

The mean age at diagnosis is 4–6 years and one third of ependymomas are diagnosed in children under the age of three. Ependymomas can be found infratentorial, supratentorial and in spinal cord or cauda equina. Ependymomas outside of the CNS can also be found, mainly in the sacrococcygeal region, but are exceedingly rare. They usually present as palpable soft-tissue masses and should be differentiated from pilonidal cyst, lipoma, spina bifida, abscess and other rare neoplastic lesions [5]. Spinal ependymomas are discussed in detail in spinal tumors section. Infratentorial ependymomas are the most frequent and are usually associated with symptoms of increased intracranial pressure due to fourth ventricle obstruction. They may also present with ataxia and cranial nerves dysfunction. These tumors are thought to arise from the floor, the lateral aspect, and less frequent from the roof of the fourth ventricle. Supratentorial tumors are rare, usually not associated with the ventricular system and are commonly localized adjacent to the cortical surface. Headache and epilepsy are the most common presenting symptoms and papilledema the most common sign [6].

19.3 Pathological-Genetics Features

The key features of ependymomas are presence of perivascular pseudorosettes and ependymal rosettes. There is immunohistochemical positivity for glial fibrillary acidic protein (GFAP), S100, vimentin and epithelial membrane antigen (EMA). DNA methylation profiling of ependymomas revealed at least 9 distinct molecular subgroups and many additional subtypes. Three subgroups for each compartment (supratentorial, posterior fossa and spinal) that constitute separated entities have been identified (Table 19.1) [7]. Supratentorial ependymomas with *RELA* fusion have been found in 70% of supratentorial ependymomas and are considered a distinct entity. These tumors are usually located in the cerebral cortex with cystic predominance. The *RELA* fusion has an oncogenic function by activating the NFKB pathway. To date seven different *RELA*-fusion variants have been reported [8]. Tumors with *RELA* fusion morphologically demonstrate clear cells and branching capillaries and are associated with unfavorable prognosis.

Recently, ependymomas with *YAP1-MAMLD1* fusion have been reported as another distinct entity in the supratentorial compartment. These tumors were

Table 19.1 Pediatric ependymomas molecular subgroups

Supratentorial	Infratentorial	Spinal
Sub-ependymoma	Sub-ependymoma	Sub-ependymoma
YAP1 fusion	EPN-A	Myxopapillary
RELA fusion	EPN-B	EPN

usually large in size, located intra or periventricular, multinodular with cystic areas and heterogeneous contrast enhancement. Most often occur in females under 3 years of age and contrary to tumors with *RELA* fusion they are associated with good prognosis [9]. Histological features are round nuclei with finely granular chromatin and cells with dot-like cytoplasmic expression of EMA [9]. Posterior fossa tumors are characterized as group A and B. In group A there is EZ-HIP overexpression and somatic mutations. These tumors have dismal prognosis with about 50% 5-year survival. Group B tumors occurs in older children and adults, rarely recur or exhibit metastasis, they have chromosomal instability and are associated with favorable prognosis [10].

19.4 Imaging Features

The classic radiological appearance of a posterior fossa ependymoma is of a fourth ventricle heterogeneous mass with solid and cystic components, hemorrhage, areas of necrosis and calcifications. Extension in the cerebellopontine angle, through the lateral recess of the fourth ventricle, is a characteristic finding. Group A ependymomas usually arise from the lateral recess of the fourth ventricle, extend to the cerebellopontine angle (CPA) and displace the brainstem laterally, whereas group B arise from the inferior floor of the fourth ventricle, may infiltrate the obex and displace anteriorly the brainstem [11] [Fig. 19.1].

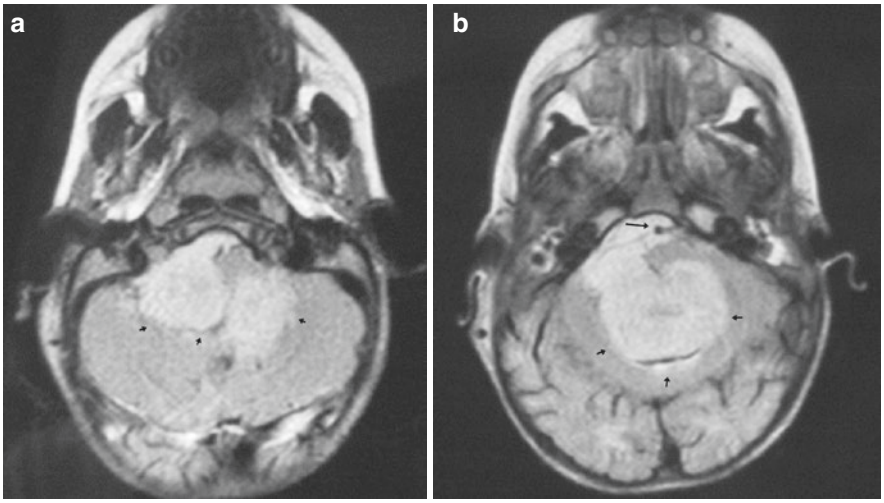

Fig. 19.1 Fluid attenuated inversion recovery MRI (**a**, **b**) of an ependymoma (arrowheads) displacing the brainstem and extending into cerebellopontine angle. Encasement of the basilar artery is seen (arrow). The lesion was totally excised via a transvermian approach

Supratentorial ependymomas more frequently occur in the frontal lobe followed by parietal lobe [6, 12]. Their mean diameter is about 6 cm, often extending from pial surface to the margin of the lateral ventricle and less frequent are intraventricular [12, 13]. Supratentorial ependymomas are heterogenous in appearance with solid and cystic areas. Calcifications can be seen in half of the cases. These tumors are usually hypo or isointense on T1-weighted images and hyper or isointense on T2-weighted images and they have relatively well-defined margins [Fig. 19.2]. In advanced MR techniques there is similarity with other high-grade gliomas, with increased perfusion indices, restricted diffusion, multiple intratumoral susceptibility foci and increased choline/N-acetyl aspartate ratio [13].

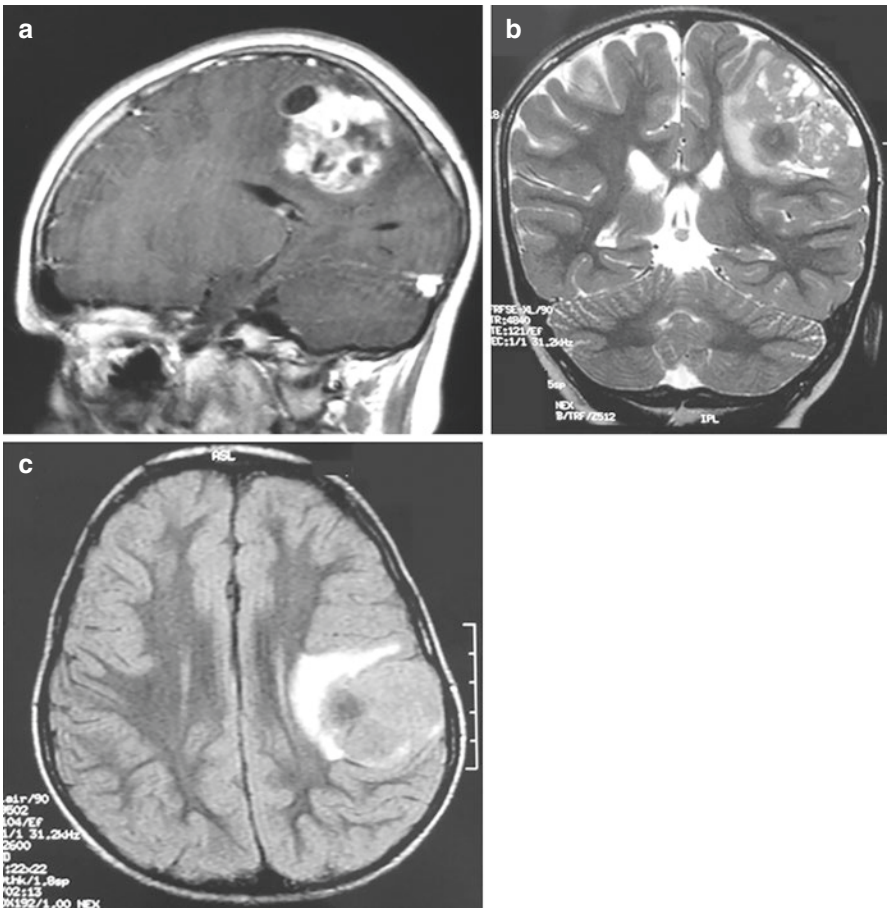

Fig. 19.2 A case of a 10-year-old boy presented with a 2 week history of headache and vomiting. (**a**) Sagittal gadolinium-enhanced T1-weighted MRI of a supratentorial ependymoma exhibiting areas with solid and cystic components. T2-weighted (**b**) and FLAIR MRI (**c**) showing peritumoral oedema

19.5 Treatment

19.5.1 Surgery

Extent of surgery is the most important prognostic factor in ependymomas. For patients with initial subtotal resection, repeat resection for achieving gross total resection should be considered. For tumors located in the fourth ventricle either a sitting or prone position can be utilized. Both procedures have been found safe. The sitting position allows for better visualization and orientation and decreased bleeding, however complications such as venous air embolism and hemodynamic instability have been reported [14]. Posterior fossa tumors can be approached via a transvermian or telovelar approach [15]. The latter is associated with minimal damage to neural tissue since there is no incision of any part of the cerebellum. However, for large tumors that compress the vermis or tumors at the rostral half of the fourth ventricle a transvermian approach might be better [16]. Teloverian approach permits early visualization and protection of the floor of the fourth ventricle. Although this approach has been considered to reduce the incidence of postoperative cerebellar mutism syndrome, which may occur in nearly one third of cases, this has not been proven in later studies [16]. Tumors of the CPA or filling the ventral brainstem may encase neurovascular structures and are associated with significant morbidity [17]. Other common complications after excision of fourth ventricle tumor are cranial neuropathies, gait abnormalties, diplopia and sensory deficits, whereas complications that require reoperation, such as hematoma needing evacuation, CSF leak or infection, are rare (<5%) [16]. 5-Aminolevulinic acid (5-ALA) has been also utilized for maximizing the resection of pediatric ependymomas. Strong fluorescence has been reported in the majority of ependymomas, both of grades II and III [18].

19.5.2 Adjuvant Therapy

Although major advances in our understanding of biology of ependymomas, treatment options remain limited. Radiotherapy has been proven to increase survival [19]. Historically radiation therapy is usually reserved for children over the age of 3 because of the neurocognitive, learning outcomes and endocrinological sequala. Nevertheless, very young children that underwent GTR or NTR and received immediate postoperative conformal radiation therapy (CRT) exhibited more than twice event-free and overall survival compared to other strategies that withhold the use of radiotherapy. Regarding posterior fossa ependymomas that received surgery and CRT, those patients without 1q gain had the best prognosis [20]. Thus, after gross total excision focal radiotherapy is the standard treatment. For ependymomas that present with dissemination there is a need for surgery to confirm diagnosis and craniospinal irradiation is usually ensued [20]. The benefit of chemotherapy remains largely unproven for ependymoma.

19.6 Prognosis—Future Perspective

Extent of surgical excision and age at diagnosis is the most important prognostic factors. Children under the age of 3 harbor a dismal prognosis because of delay in radiotherapy or lower radiation doses. Tumor recurrences usually occur in tumor bed with a median time to recurrence of 13–25 months [21]. In relapse gross total resection should be the goal of treatment and is associated with significant better 5-year overall survival of 48.7% compared to 5.3% in less than gross or near total resection. Radiotherapy has a positive effect only when gross or near total resection could not be performed [22]. Radiosurgery or hypofractionated stereotactic radiotherapy for recurrent tumors is a viable option that is well tolerated and with no significant adverse effects [23]. On the topic of neurocognitive, academic and functional outcomes patients with relapsed tumors had significant lower measures of full scale IQ, perceptual reasoning, word reading, numerical operations and measures of quality of survival [24].

Ependymomas are generally refractory to chemotherapy and temozolomide showed almost no effect and disease progression occurred in the majority of cases [22]. Epidermal growth factor receptor (EGFR) has been reported in a considerable number of tumors and might be involved in the neoplastic transformation [25]. EGFR can be also serve as a therapeutic target. Recently, CXorf67, a protein that suppresses DNA repair, was found highly expressed in posterior fossa (EPN-A) ependymoma. These tumors have a poor prognosis and tumors with high CXorf67 expression showed increased sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors and augmented effect when combined with radiotherapy [26]. Recently in recurrent ependymomas three cell-surface targets, EPHA2, HER2 and interleukin 13 receptor α2, were found to selectively expressed in tumor cells. In multiple metastatic mouse models the administration, in cerebrospinal fluid, of chimeric antigen receptor T cells with or without azacytidine, was an effective therapy [27]. In conclusion, maximal safe removal followed by local radiotherapy is a mainstay of treatment and offers a survival benefit, since these tumors are generally resistant to chemotherapy. A reoperation should be considered if first excision does not result in gross total excision.

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Chapter 20
Neuronal and Mixed Neuronal-Glial Tumors

Marios Lampros, Georgios Alexiou, and Neofytos Prodromou

20.1 Introduction

Neuronal and mixed neuronal-glial tumors comprise a rare heterogeneous group of pure neuronal tumors or tumors with a mixed neuronal and glial component. These neoplasms are generally benign, slow-growing, and usually occur in childhood or early adult life. It is estimated that they account for approximately 10% of brain tumors in the pediatric age group. Epilepsy is a typical clinical manifestation of these neoplasms, with many epilepsies being drug-resistant. These tumors can be found anywhere in the Central Nervous System (CNS), although the temporal lobe is predominantly affected [1, 2].

In the 2016-World Health Organization (WHO) classification of CNS tumors, the term "Neuronal and mixed neuronal-glial tumors" encompasses the following neoplasms: Ganglioglioma (Grade I/ WHO), Anaplastic Ganglioglioma (Grade III/ WHO), Gangliocytoma (Grade I/ WHO), Dysembryoplastic neuroepithelial tumor (Grade I/ WHO), Dysplastic cerebellar Gangliocytoma (Lhermitte- Duclos disease) (Grade I/ WHO), Desmoplastic infantile astrocytoma and ganglioglioma (Grade I/ WHO), Papillary glioneuronal tumor (Grade 1/ WHO), Diffuse leptomeningeal glioneuronal tumor (Low grade, not currently assigned), Central neurocytoma (Grade II/ WHO), extraventricular neurocytoma (Grade II/ WHO), Cerebellar lipo-neurocytoma (Grade II/ WHO), Rosette-forming glioneuronal tumor (Grade I/ WHO) and Paraganglioma (Grade I/ WHO). All neoplasms of this group are low grade (Grade I or II /WHO), except for anaplastic ganglioglioma, which is a Grade III/ WHO neoplasm [3].

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Patients' overall prognosis with neuronal or glioneuronal tumors is very favorable, with approximately 75–90% 5-year survival, except for anaplastic ganglioglioma, which is related to poor survival. Surgical resection is generally sufficient as treatment, and adjuvant therapy is utilized in patients with tumor recurrence or the presence of metastatic lesions. Herewith, this chapter will discuss the clinical, pathological, imaging, and treatment features of these tumors [1, 2, 4].

20.2 Gangliogliomas and Gangliocytomas

20.2.1 General

Gangliogliomas (GGs) and Gangliocytomas are rare low-grade mixed glioneuronal tumors comprising 2–4% of all pediatric CNS neoplasms. Children and young adults are mainly affected, and patients' mean age at diagnosis is 12 years. There is a slight male predilection, with the male to female ratio being 1.5:1. In 50–70% of the cases, the neoplasm is located in the temporal lobe. Nevertheless, they may occur anywhere in CNS, including other lobes, brain stem (5%), and spinal cord (3%) [5].

20.2.2 Pathological Features

In the 2016 WHO classification of CNS tumors, GGs are assigned as low Grade (Grade I/WHO) neoplasms, except for anaplastic GG, which is considered high grade (Grade III/WHO). Criteria for Grade II have been proposed but yet to be recognized from WHO. The vast majority of GG are low grade, with the anaplastic form being exceedingly rare. Histopathological features typically found in GGs are large clusters of dysplastic neurons with loss of normal cerebral architecture, Nissl bodies aggregation, and binucleated cells. Additionally, a neoplastic glial component (mainly from astrocytes) is observed, and its presence is necessary for GG diagnosis. Otherwise, in the absence of a neoplastic glial component, the diagnosis of gangliocytoma is established. Other histological features found in GG include eosinophil granular bodies (EGB), rosenthal fibers, and calcifications. The presentation of anaplastic features in the glial component, such as increased mitotic activity and cellular atypia, set the diagnosis of anaplastic GG. Anaplastic GG may occur as de-novo lesions or malignant transformation of a previously low-grade GG in 10% of the cases. Immunochemistry markers for MAP2, synaptophysin, CD34 antigen, and neurofilaments are utilized to highlight the presence of neoplastic neurons. The neurons' presence is very significant in the differential diagnosis of anaplastic GGs from Glioblastomas (a pure glial neoplasm). Immunochemistry for

Glial-fibrillary-acidic-protein (GFAP) and $BRAF^{V600E}$ is positive in the cells of the glial component [1, 3].

20.2.3 Clinical Manifestations

The clinical picture is related to the location of GGs. Epilepsy is the most common clinical manifestation observed in 70–80% of patients with cerebral GGs. GG is considered the leading cause of tumor-related epilepsy in children. Focal deficits, weakness, and symptoms of raised intracranial pressure from obstruction of cerebrospinal fluid (CSF) flow such as headache, nausea, and vomiting may be observed. Cranial nerve palsy, paresis, and sphincteric dysfunction may occur in brainstem GGs. Back pain and myelopathy are found in GGs located in the spinal cord. GGs are generally slow-growing tumors, and the period from the onset of symptoms to diagnosis is approximately 7–12 months in low-grade GGs. In anaplastic GG, this time is significantly shorter, usually a few weeks, due to their rapid growth and infiltrative nature [5, 6].

20.2.4 Imaging

In magnetic resonance imaging (MRI), GGs usually appear as well-circumscribed cystic lesions with a small mural nodule or solely as solid lesions. The signal is low in T1- Weighted images (WI) and high in T2-WI. Enhancement of the mural nodule is usually observed after Gadolinium (Gd) administration. Mild perifocal edema and hydrocephalus findings from obstruction of CSF flow may be present. GGs' differential diagnosis from pilocytic astrocytoma may be challenging when based solely on imaging features. In computed tomography (CT), GGs appear with clear margins and varying degrees of attenuation. Calcifications may be observed in 20% of the cases [4].

20.2.5 Management/Prognosis

Surgical resection is the optimal treatment of GGs and is an essential factor in patient survival. Gross Total Resection (GTR) of the tumor, if possible, should be attempted in all GG cases and is related to excellent survival and low recurrence rate. In a series of 12 gagliogliomas no tumor recurrence was noted after a mean 4.4 years follow-up period [2]. GTR rate in all GGs is approximately 75%, with the rate being lower in spinal cord and brainstem GGs (50%). In cases where GTR is not achieved, the maximization of surgical resection (with concern to normal parenchyma) is still of crucial significance because a tumor resection of over 95% is

related to a significantly lower recurrence rate and more favorable survival. The extent of resection is the most important prognostic factor also in the case of anaplastic GGs. The role of radiotherapy and chemotherapy in the treatment of GGs is discussable. Recent studies support that there is no observable survival benefit after the use of radiation. Adjuvant treatment is utilized in tumor recurrence cases, in the anaplastic form, and in cases where surgical treatment is not possible (still with no clear benefit in overall survival). The prognosis of children with low-grade GGs not located in the brainstem is excellent, and the overall 5-year survival rate is approximately 95%. As discussed above, the extent of resection is another factor that influences patients' survival because it minimizes recurrence risk. Finally, the prognosis is fair in patients with anaplastic GGs (65% 5-year survival rate), in GGs located in the brainstem (GTR is rarely achieved, except if the tumor has an exophytic component), and in GGs that occur in children under 1 year [5–8].

20.3 Dysembryoplastic Neuroepithelial Tumors

20.3.1 General

Dysembryoplastic Neuroepithelial Tumors (DNET) are low-grade (Grade I/WHO) mixed glial-neuronal neoplasms, accounting for 0.5% of all pediatric CNS tumors. The histogenesis of DNET is still controversial. Nevertheless, there is some evidence that it is originated from cells of the secondary germinal layer. As with GGs, children and young adults (with a slight male predominance) are mainly affected, and epilepsy is the most common clinical manifestation [2]. DNET is predominantly located in the temporal lobe (50–60%) or in other supratentorial structures (usually in the cerebral cortex) or even intraventricular [Fig. 20.1] [9].

20.3.2 Pathological Features

Currently, three histological subtypes of DNET are recognized: the simple, the complex, and the non-specific type. The presence of the specific glioneuronal element is the main factor that determines DNET classification. Specific glioneuronal element refers to columns from oligodendroglial-like cells in a perpendicular orientation to the cerebral cortex. A mucinous matrix is present, and floated neurons are observed between the bundles of oligodendroglia-like cells. In the simple type, the specific element is the only feature observed in the biopsy specimen. The presence of glial nodules or/and adjacent focal cortical dysplasia together with the specific element is observed in the complex type, while in the non-specific type, the specific element is absent, but glial nodules or cortical dysplasia exist. The differential diagnosis of DNET from ganglioglioma may be very challenging. Immunochemistry markers are utilized and may assist in the diagnosis of DNET. Staining for NeuN,

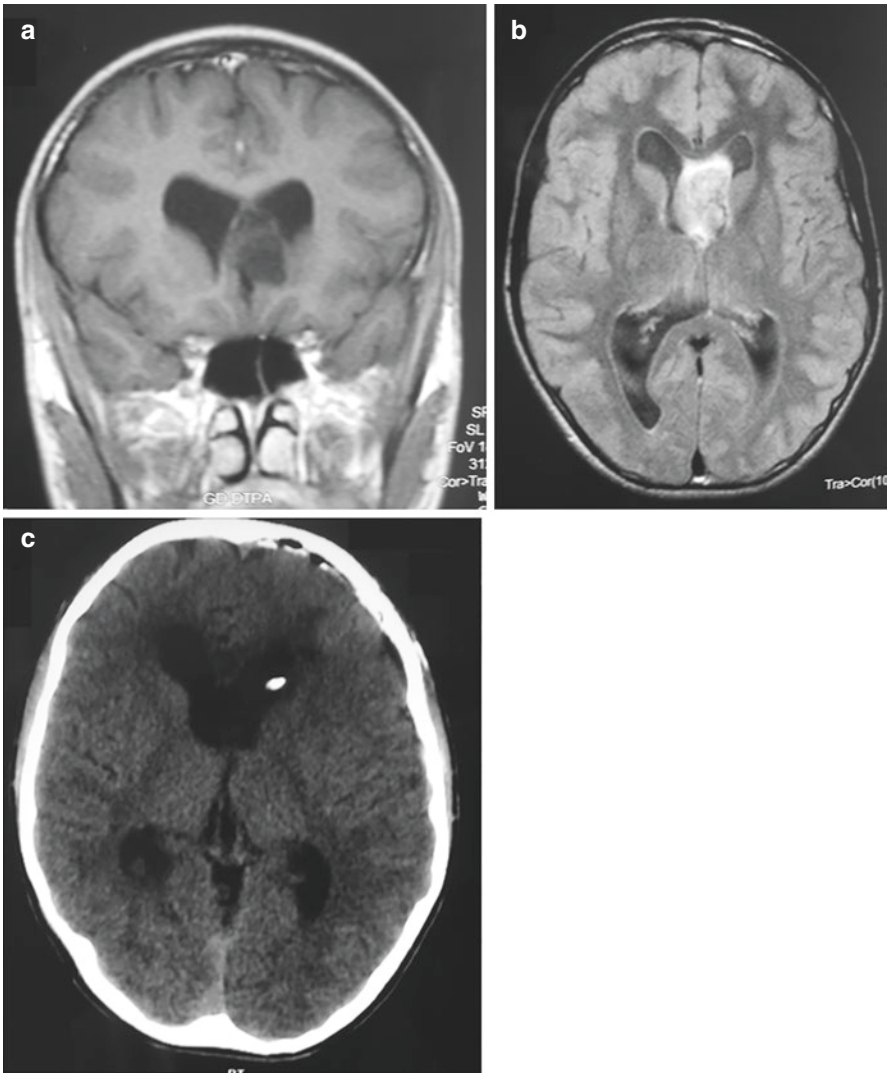

Fig. 20.1 A case of a 12-year-old boy with intractable epilepsy. MRI revealed an intraventricular mass that exhibited no enhancement after gadolinium administration (**a**). Increased signal intensity in FLAIR sequences was observed (**b**). The patient was operated on via a left frontal transcortical approach to the tumor and the lesion was totally excised (**c**). Pathology revealed the presence of a DNET. The Ki-67/MIB-1 index was 1–2%

MAP2, and Neurofilament are utilized to highlight the neurons in a specific element, while staining for GFAP may highlight the glial nodules in complex and non-specific types. Staining for CD 34+ is usually positive in the non-specific type and may contribute to the differential diagnosis of DNET from astrocytic or other glial neoplasms [1, 9, 10].

20.3.3 Clinical Manifestations

DNETs in the majority of cases are manifested with intractable partial complex seizures in a previously healthy patient with no progressive neurological deficits and account for 20–30% of all brain lesions removed for the treatment of epilepsy. The mean age of seizures onset in the pediatric age group is approximately 8–10 years. Neurological deficits and symptoms of raised intracranial pressure are usually absent. Neurofibromatosis type I and Jacobs' syndrome are considered possible risk factors for the development of DNT [9].

20.3.4 Imaging

In MRI, DNET typically appears as a cortical lesion, with little to no peritumoral edema and mass effect. The signal is usually low in T1-WI and high in T2-WI, while the enhancement varies. An MRI classification of DNT has been proposed, and apart from its diagnostic significance, it can also be utilized in pre-operative planning. In this classification, three types are recognized: type 1, where the DNT appears as a cystic/multi-cystic lesion with low signal in T1-WI, type 2, where the lesion appears nodular with heterogeneous signal, and type 3, where the lesion appears dysplastic with poor delineation and iso/low signal in T1-WI. The simple and complex histological types are related to type 1, while the non-specific types are related to Imaging types 2 and 3 [4, 9].

20.3.5 Management/Prognosis

Surgical resection of the neoplasm is the optimal treatment, and after total resection, the patient is usually cured of seizures. It is estimated that the rate of seizure-free results after surgery is approximately 80–90%. The extent of resection differs between the three MRI subtypes. In type 1, the epileptic zone is found inside the lesion, so resection is sufficient. In type 2, the epileptic zone may extent in the cortex surrounding the lesion, so the resection should be extended into the peritumoral cortex. The epileptic zone in type 3 may occupy large cortical areas, and thus anterior temporal lobectomy or amygdalo-hippocampectomy may be required. Electrocorticography is another tool that can help the surgeon localize the epileptic zone and determine the extent of resection. Adjuvant therapy is generally not utilized in the treatment of DNET [4, 9].

20.4 Central and Extraventricular Neurocytoma

20.4.1 General

Central Neurocytoma (CN) and Extraventricular Neurocytoma (EVN) are rare low-grade (Grade II/WHO) neuronal tumors and account for 0.3–0.5% of all intracranial neoplasms. They are neuroepithelial neoplasms from uniform round cells with neuronal differentiation. CN and EVN have the same histological appearance, but CN is by definition located in the lateral ventricles, close to Monro's foramen, while EVN refers to intraparenchymal lesions predominantly found in frontal and parietal lobes. These neoplasms chiefly affect young adults in the third decade of their lives, while there is no significant sex predilection. CN is approximately three times more common than EVN [10, 11].

20.4.2 Pathological Features

CN and EVN have a histological resemblance to oligodendrogliomas with small uniform cells and a characteristic perinuclear halo. Calcifications are present in approximately 50% of the cases. Additionally, a fibrillary stroma is observed, while immunochemistry is usually positive for synaptophysin, neurofilaments, and NeuN. GFAP positive areas are not uncommon and represent trapped astrocytes. Ganglioid differentiation is uncommon and, if present, is usually observed in EVN. Anaplastic features and necrosis are exceedingly rare [11, 12].

20.4.3 Clinical Manifestations

CN usually occurs with raised ICP (headache, nausea, vomiting) due to the obstruction of CSF flow at foramen of Monro. The prodrome period of symptoms is short (duration less than six months). The clinical manifestations of EVN are non-specific and related to their location. EVNs usually occur with seizures, focal deficits, and symptoms of raised ICP [12, 13].

20.4.4 Imaging

In MRI, CN appears as a well-defined intraventricular lesion with iso to low heterogeneous signal in T1-WI, while the signal is high in T2-WI. Multiple small cysts may occur as a result of neoplastic degeneration. EVN typically appears as a cystic lesion with a solid nodule located in cerebral parenchyma. After Gd injection, CN

and EVN display moderate or significant enhancement of their solid component. On CT, CN and ENV are usually hyperattenuating well-demarcated lesions, and calcifications are present in half of the cases [13].

20.4.5 Management/Prognosis

GTR is the optimal treatment in CN and, if achieved, is related to an excellent prognosis and low recurrence rate [Fig. 20.2]. Nevertheless, the GTR rate in CN is approximately 40%, and the risk of recurrence is high after STR. Thus, adjuvant radiotherapy is utilized in cases of STR. The role of chemotherapy is debatable and is preferred in cases of tumor recurrence. GTR or STR combined with radiotherapy is also performed in EVN, but despite their histological similarity to CN, they tend to have more aggressive biological behavior and are related to less favorable survival [11–13].

20.5 Dysplastic Cerebellar Gangliocytoma (Lhermitte-Duclos Disease)

20.5.1 General

Dysplastic cerebellar Gangliocytoma (DCG) or Lhermitte Duclos disease is an uncommon benign lesion which by definition affects the cerebellum. Fewer than three hundred cases have been reported worldwide. This lesion is probably hamartomatous rather than neoplastic in nature and is strongly associated with the Cowden syndrome (multiple hamartoma syndrome), a phacomatosis related to mutations in the *PTEN* gene. Despite that, the sporadic form of DCG is more common. Young adults are predominantly affected, with no sex predilection [14, 15].

20.5.2 Pathological Features

Enlargement of the cerebellar folia (unilateral) is usually present with significant thickening of the cerebellum molecular layer. The layer of Purkinje cells is absent, while the granular layer's architecture is significantly altered from the infiltration of large neuronal cells [15, 16].

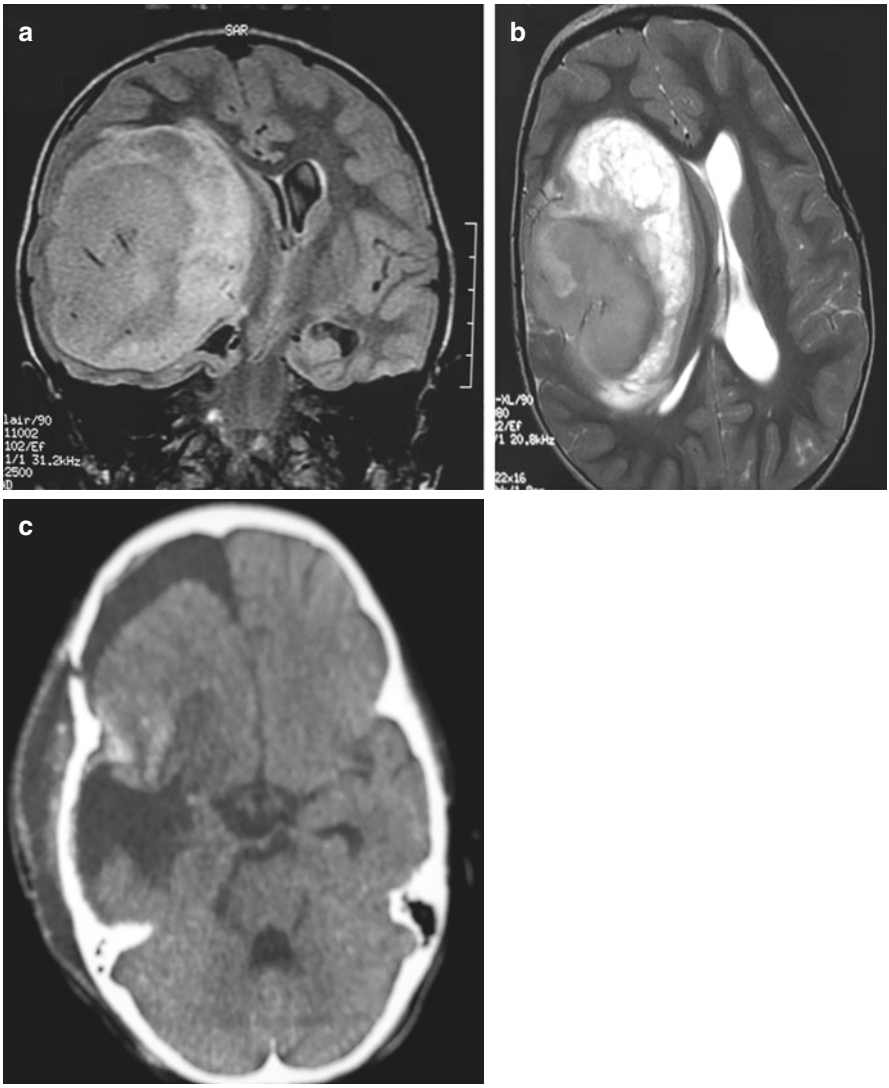

Fig. 20.2 A case of a giant extraventricular neurocytoma in a 4-year-old girl presented with hemiparesis (**a** and **b**). The patient was operated on and gross total excision was performed (**c**)

20.5.3 Clinical Manifestations

DCG has a slow growth rate, with many patients remaining asymptomatic for years, and the progress of symptoms is usually slow. Clinical manifestation varies and includes cerebellar dysfunction symptoms such as ataxia, nystagmus, or raised ICP from obstruction of CSF flow at the fourth ventricle level [15, 16].

20.5.4 Imaging

MRI is of crucial significance and can set the diagnosis of disease without the need for biopsy. The signal of the lesion is usually low in T1-WI and high in T2-WI. The presentation of cerebellar gyri is characteristic and facilitates disease diagnosis. The lesion does not display contrast enhancement, and if present other differential diagnoses should be considered [4, 16, 17].

20.5.5 Management/Prognosis

Treatment of the disease depends on the patient's clinical status. In asymptomatic patients, imaging follow-up may be sufficient without any intervention due to the disease's slow growth. In patients with raised ICP, treatment of hydrocephalus should be performed, while in the presence of severe neurological symptoms, tumor resection should be attempted. Total resection may not be possible because the lesion's borders might not be well-demarcated, and the transition to normal cerebellar parenchyma may be gradient. Despite that, partial resection of the lesion may improve the patient's symptoms and treat the hydrocephalus [16, 17].

20.6 Desmoplastic Infantile Astrocytoma and Desmoplastic Infantine Ganglioglioma

20.6.1 General

Desmoplastic infantile astrocytoma (DIA) and desmoplastic infantine ganglioglioma (DIG) are exceedingly rare neoplasms that almost exclusively affect infants. They are low-grade (Grade 1/WHO), usually supratentorial tumors located superficially in the brain parenchyma, and are adjacent to the dura mater. The tumor is predominantly located in the frontal and parietal lobes. Cases of spinal or infratentorial DIG and DIA have been reported but are unusual. They comprise less than 1% of all CNS tumors, but they probably account for 5–10% of all primary CNS neoplasms of infancy. A slightly male predilection has been observed [18, 19].

20.6.2 Pathological Features

DIG/DIA have a solid component adjacent to the dura matter and a large uni or multilobulated cystic component located inside the brain parenchyma. Desmoplastic features are characteristic and are observed in the solid nodule and the adjacent

leptomeninges. The presentation of spindle-shaped cells is characteristic in desmoplastic areas with reticulin fibers surrounding them. The feature that differentiates DIG and DIA is that DIG has a neuronal component in addition to the neoplastic astrocytic component, while in DIA, the neuronal component is absent [1, 18, 19].

20.6.3 Clinical Manifestations

Clinical manifestations include abnormal growth of head circumference, bulging fontanelle, and raised intracranial pressure symptoms. Seizures are observed in about 15–20% of the children. The onset of symptoms is usually short, and the mean duration until diagnosis is less than 3–6 months [18, 19].

20.6.4 Imaging

In MRI, a uni or multilobulated lesion with a solid nodule is observed. The tumor is located superficially in the cerebral parenchyma and is adjacent to dura matter. The signal intensity in the cystic component is low in T1-WI and high in T2-WI. The solid nodule's signal is low in both T1 and T2 sequences, but displays significant enhancement after contrast administration. In CT, the cystic component is usually hypodense, while the solid nodule is iso to high dense and displays significant enhancement after contrast administration. Areas with hemorrhages or calcifications are rarely present and may indicate a malignant transformation of the glial component [1, 18, 19].

20.6.5 Management/Prognosis

Total resection of the tumor is the optimal treatment, but the presentation of adhesions in meninges and parenchyma may limit the extent of resection. Aspiration of the cystic component may be performed prior to tumor removal in large DIG/DIA cases to decompress the brain and prevent herniation during surgical manipulations. In cases of STR, there is a possible role for adjuvant chemotherapy, while the role of radiotherapy is contentious and is performed in selected cases (usually in older children). The prognosis of children with DIG/DIA is very favorable, with the mortality rate being approximately 5%. In cases of STR, recurrence-free survival may range from months to years, so a close follow-up is suggested. Cases of tumor dissemination have been reported and are probably related to malignant transformation in the astrocytic component. Histological factors suggestive of a metastatic potential are the presentation of necrosis and increased mitotic activity [18, 19].

20.7 Papillary Glioneuronal Tumor

20.7.1 General

Papillary glioneuronal tumors (PGT) are low-grade (Grade I/WHO) mixed glial-neuronal neoplasms of CNS, and only a few cases have been reported. They are located in supratentorial structures with a predilection for the temporal lobe and usually around the ventricular system. The neoplasm probably arises from multipotent subependymal stem cells with the ability for glioneuronal differentiation, but the exact histogenesis of the tumor is still unclear. Patients of all ages may be affected, including children and elderlies, but the tumor frequency is higher in young adults, while sex predilection has not been observed [20].

20.7.2 Pathological Features

The PGT displays characteristic histological features, including a glial component from neoplastic astrocytes and a neuronal component from cells with neuronal differentiation (mainly neurocytes). The astrocytes are forming pseudo-papillary structures with a single or pseudostratified layer from cuboidal cells surrounding hyalinized vessels. Between the papillary structures, nodules from neuronal cells are present. Tumor borders may display features of reactive gliosis. Areas with neovascular proliferation or necrosis are typically not observed. Immunochemistry is positive for GFAP in the glial component and synaptophysin and NeuN in the neuronal component. Lately, the utterly benign nature of the lesion has been doubted by some authors [21].

20.7.3 Clinical Manifestations

Clinical manifestations are atypical and include symptoms of raised ICP (30–40% of the cases), seizures (30%), focal deficits, and confusion [20, 22].

20.7.4 Imaging

The tumor macroscopically is well-circumscribed and has a combination of cystic and solid components, while the presentation of cysts-mural nodule complex is not unusual. The solid component has a low signal in T1-WI and a high signal in T2-WI, and heterogeneous enhancement of the nodule may be observed after contrast administration. The tumor causes mild to no peritumoral and mass-effect. On CT,

the lesion is well-defined and iso to hyper attenuative to the normal parenchyma. The wall of the cystic component is enhanced after iodine administration, and calcifications may be observed [1, 20, 22].

20.7.5 Management/Prognosis

GTR of the tumor is usually feasible in the majority (around 80%) of cases, but tumor recurrence cases are increasingly reported in the last years, so a close follow-up is suggested. The high mitotic index is a possible prognostic factor of tumor recurrence. Adjuvant chemotherapy and radiotherapy are usually performed after tumor STR, tumor recurrence, or in the presence of a high proliferative index. Despite that, in cases of tumor recurrence, reoperation should be considered as the first treatment option [20, 22, 23].

20.8 Cerebellar Liponeurocytoma

20.8.1 General

Cerebellar Liponeurocytoma (CLN) is another rare CNS neoplasm, with fewer than 100 cases reported worldwide. In most cases (around 80%), it is located in the cerebellum as suggested by its name. Nevertheless, tumor cases with similar features to CLN have been described in supratentorial structures (mainly around or inside the ventricular system). In the 2016 WHO classification of CNS tumors, it is assigned as a grade 2 neoplasm. In previous WHO classifications, it was classified as a Grade 1 neoplasm, but the high recurrence rate of tumors reported in the literature led to this grade modification. CLN can occur in all age groups, but there is a predominance for patients in the fifth decade of their life, with the mean age being 45 years. A slight (but probably not significant) female predominance is observed [24, 25].

20.8.2 Pathological Features

The presentation of cells with neuronal differentiation and of foci from astrocytes and cells with lipomatous differentiation are the typical histological features observed in CLN. The lipomatous cells are probably neuroepithelial cells with lipid content rather than mature adipose (mesenchymal) cells. The mitotic index in cells of CLN is typically low, and malignancy features are absent. A differential diagnosis from medulloblastoma with lipidized cells should be considered in the presence of a high mitotic index [1, 24, 25].

20.8.3 Clinical Manifestations

Patients with CLN may develop cerebellar dysfunction symptoms such as ataxia, unsteadiness, or symptoms of raised ICP (nausea, vomiting, headache) from obstruction of CSF flow [24, 26].

20.8.4 Imaging

On MRI, CLN appears as a well-circumscribed cerebellar lesion with iso to low T1 signal (80% of the cases) or with a high signal that corresponds to tumor areas dense in lipid content. The signal is high in T2-WI. After contrast administration, it displays heterogeneous enhancement. On CT, the CLN is hypodense or isodense to normal parenchyma and has heterogenous enhancement. Peritumoral edema and calcifications are uncommon, and if present, other differential diagnoses should be considered [24, 25].

20.8.5 Management/Prognosis

GTR is the optimal treatment and is achieved in approximately two third of the cases. The recurrence rate is low (around 15%) after GTR, while tumor recurrence is observed in half of the cases after STR. In a systematic review performed by Gemburch et al., no tumor recurrence was observed after a combination of GTR and adjuvant radiotherapy, while the recurrence rate after STR only without adjuvant radiotherapy was approximately 80%. Therefore, the extent of tumor excision and the use of adjuvant radiotherapy are probably the most important prognostic factors for tumor recurrence [24–27].

20.9 Diffuse Leptomeningeal Glioneuronal Tumor

20.9.1 General

The term DLGNT was first described by Gardiman et al. in 2010, but the entity was recognized and included in the WHO classification of CNS tumors just in the latest 2016 revision. Gardiman et al. described four patients with a tumor with morphological and immunohistochemical features suggestive of a glioneuronal neoplasm. The neoplasm had unique characteristics, different from the other known glioneuronal tumors, so they suggested that it should be defined as a new

separate entity. Currently, no grade has been assigned to this neoplasm. Epidemiological features are not known to a great extent due to the new definition of the term. Nevertheless, DLGNT cases may have been previously reported in the literature with different terms such as diffuse leptomeningeal oligodendroglioma or misdiagnosed as tuberculous meningitis or meningeal carcinomatosis. The tumor usually occurs in young children with a mean age of 4 years, with a slight male predilection [3, 28].

20.9.2 Pathological Features

The tumor probably arises from precursor cells entrapped in leptomeninges during the primitive migration, as suggested by Gardiman et al. A biphasic population from neuronal and glial cells is observed in the tumor specimen, and characteristically, the tumor cells invade the leptomeninges. The neoplastic cells are monotonous and form straight lines or small lobules. DLGNT cells have histological resemblance with those observed in oligodendrogliomas with round nuclei and perinuclear haloes. Leptomeningeal stroma is typically thickened and fibrous (desmoplastic) or myxoid. Therefore, the neoplasm shares remarkable histological features with oligodendrogliomas and extraventricular neurocytomas. The mitotic index is typically low, and a higher mitotic index is related to the more aggressive nature of the neoplasm [3, 28, 29]. Immunochemistry is usually positive for synaptophysin, OLIG-2, MAP2, S-100, and negative for NeuN, Epithelial Membrane Antigen. The chromosomic 1p deletion or 1p/q19 codeletion are frequently seen in tumor cells. The presence of 1pq19 codeletion, together with the presence of oligodendroglia-like cells, are the main reasons this tumor was previously described in the literature as an oligodendroglia-like leptomeningeal tumor. Nevertheless, cells of DLGNT do not display the IDH mutations observed in oligodendrogliomas, which provides a definite way for differential diagnosis from oligodendrogliomas [1, 3].

20.9.3 Clinical Features

Clinical manifestations are not specific, and except for symptoms of raised ICP, the rest of the symptoms vary among the patients are related to the CNS site predominantly affected. Patients usually complain of headache, nausea, vomiting. An increased head circumference is observed in young children. Symptoms of cerebellar dysfunction, cranial nerve palsy, focal deficits, seizures, and gait imbalance may occur [29, 30].

20.9.4 Imaging

Three typical but not pathognomonic imaging features are observed in patients with DLGNT. The first such feature is the presence of diffuse intracranial and intraspinal nodular leptomeningeal thickening that is more intense in basal cisterns, cerebellum, and the spinal cord. The leptomeninges are densely enhanced after contrast administration. The second feature observed in patients of DLGNT is the presence of multiple non-enhanced small cysts around the cerebellum, brain stem, and spinal cord with a high signal in T2-WI. These cysts probably represent dilation of perivascular (Virchow - Robin) spaces. The third imaging feature in DLGNT is the absence of a primary intraparenchymal CNS lesion, although a solid component may be observed in the spinal cord. This component is probably due to perivascular infiltration from tumor cells. Nevertheless, cases not displaying these features have been described, and the absence of some of these features should not exclude DLGNT diagnosis. Communicating tetraventricular hydrocephalus may be present in 40–80% of the cases [28, 30].

20.9.5 Management/Prognosis

The optimal management of DLGNT is complex, and the primary treatment goals are to treat the hydrocephalus and stabilize the disease's progression. Treatment of hydrocephalus is performed with the placement of a ventriculoperitoneal shunt. Stabilization of the disease progress is achieved with long-term chemotherapy agents, usually temozolomide or carboplatin/vincristine combination. Surgery may be performed to obtain a biopsy specimen, while resection of the tumor is not feasible due to the diffuse spread of the disease. The role of radiotherapy is debatable. The lesion usually has an indolent growth, but the morbidity and mortality rates are increased due to the onset of severe neurological dysfunction and hydrocephalus [28–30].

20.10 Rosette-Forming Glioneuronal Tumor

20.10.1 General

The rosette-forming glioneuronal tumor (RGT) is a rare low grade (Grade I/WHO) CNS glioneuronal neoplasm. In most cases (around 60%), it is located in the fourth ventricle. Other locations include cerebral hemispheres, thalamus, spinal cord, and the pineal region. Young adults are mainly affected. The mean age of patients is 33 years, while there is a female predilection [31].

20.10.2 Pathological Features

RGT is a mixed glial-neuronal neoplasm. The glial element is predominant and forming histological features that resemble those observed in pilocytic astrocytomas. The neuronal element is forming characteristic perivascular pseudorosettes or neurocytic rosettes. Immunochemistry is positive for glial markers as GFAP and S100 in the glial component and positive for NSE and MAP in the neuronal component [31–33].

20.10.3 Clinical Manifestations

Symptoms of raised ICP may be present due to CSF flow obstruction in the fourth ventricle level. The tumor typically has an indolent growth. Other symptoms related to the tumor location may occur [32, 33].

20.10.4 Imaging

The tumor is usually well-defined and may be solid, cystic, or have a combination of solid and cystic components. The signal of the solid component varies, while cysts display a high signal in T2-WI. Heterogenous enhancement of the solid nodule is observed after contrast administration [1, 32].

20.10.5 Management/Prognosis

GTR is the optimal treatment. The tumor's location in the fourth ventricle makes the tumor removal challenging, and postoperative neurological deficits may occur. No adjuvant therapy is needed after successful tumor resection, and the prognosis is very favorable [1, 32, 33].

20.11 Paragangliomas

20.11.1 General

Paragangliomas are rare neoplasms that arise from cells of the paraganglion system. These cells belong to the diffuse neuroendocrine or Amine Precursor Uptake Decarboxylase (APUD) system. In CNS, paragangliomas usually occur from

paraganglion cells of filum terminale. Intracranial paraganglioma is exceedingly rare and usually occurs as a result of a glomus jugulare paraganglioma with an intracranial extension. Nevertheless, primary intracranial paragangliomas have been reported (mainly in the pineal region and the posterior fossa). CNS paragangliomas usually occur in adults in the sixth decade of their life and are exciddinlgy rare in children [1, 34, 35].

20.11.2 Pathological Features

The pathological features of CNS paragangliomas are similar to those located outside the CNS, with nests of neuronal type1/chief cells (Zellballen) surrounded by sustentacular (type 2) cells. The tumor is usually soft, well-demarcated, and may have significant vascularity. Immunochemistry in type 1 cells is positive for NSE and synaptophysin and type 2 for S-100 and GFAP [1, 34].

20.11.3 Clinical Manifestations

Clinical features are related to tumor location. Spinal paragangliomas are usually occurring with back pain (80–90%) or sciatic pain (70–80%). Cauda-equina syndrome is another less frequent manifestation of spinal paragangliomas. Patients with intracranial paragangliomas may complain of tinnitus, neurological deficits, and hearing loss. CNS paragangliomas are typically not functional, but cases of functional (catecholamine excretive) spinal paragangliomas have been reported and manifested as flush attacks. [34–36].

20.11.4 Imaging

In MRI, spinal paragangliomas appear as well-demarcated lesions with iso to low signal in T1-WI and high signal in T2-WI. A hemosiderin-cap as a result of hemorrhage may be present in T2-WI. As previously noted, intracranial paragangliomas are usually secondary from a glomus jugulare paraganglioma. In MRI, these tumors display the “salt and pepper” sign created by the small tumoral hemorrhages and the flow-void due to the increased blood flow. After contrast injection, spinal and glomus jugulare paragangliomas are markedly enhanced [34].

20.11.5 Treatment/Prognosis

Total tumor resection is the optimal treatment, and the GTR rate is higher in spinal paragangliomas, while in glomus jugulare paragangliomas, the GTR rate is lower due to the complex anatomy and the tumor extension at the time of diagnosis. Other interventions include radiation treatment and vascular embolization. The recurrence rate is low in the spinal location, and no tumor metastasis is expected, but half of the patients with glomus jugulare paraganglioma will have tumor recurrence, and metastatic lesions may be observed in 3–5% of the cases [1, 34, 35].

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Chapter 21
Craniopharyngioma and Other Sellar Tumors

Amets Sagarribay Irañeta

21.1 Pituitary Gland: Development, Anatomy and Function

Embriological basis of pituitary gland development may help in pituitary tumours understanding. Pituitary gland is a master neuroendocrine organ located at midline within the sella turcica recess of the sphenoid bone [1, 2]. It has an essential role in maintenance of homeostasis and reproductive function [3], regulating production and secretion of peptid hormones to develope and functioning of many organs, including thyroid, adrenal glands, gonads, mammary gland and liver [2].

The pituitary gland forms around the middle of the fourth embryonic week from an invagination of the oral ectoderm (stomodeum) to the rudimentary primordium (Rathke's pouch) [3]. Neurulation, neural plate development from ectoderm, occur at 3 weeks of gestation [4]. The anterior part of neural plate will grow to develope the forebrain, optic nerves, hypothalamus, anterior and posterior pituitary lobe [1]. To understand pituitary gland development the murine model has been used because is similar to other vertebrates and humans [5–7]. In the murine model pituitary organogenesis begins around E8.5 (embrionic day 8.5) with the appearance of Rathke's pouch, an invagination of the anterior pituitary placode from oral ectoderm. The dorsal portion of the pouch contacts the midline of the ventral diencephalon, evagination of which (around E10) acts as the main organizer for its patterning and differentiation of its cells [8]. So the hypothalamus (part of diencephalon derived from neural ectoderm) influences and regulate hypophysis gland development (derived from ectoderm) [7]. After 24 h of primordium Rathke's pouch development infundibulum (ventral diencephalon) invaginate to contact Rathke's pouch at the time that it severed from oral ectoderm achieving a fully developed definitive pouch [1].

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The final pituitary gland is composed of three lobes: the endocrine hormone-producing anterior and intermediate lobes originated from the oral ectoderm (Rathke's Pouch) and the posterior lobe (neurohypophysis) developed from the overlying neural ectoderm as does pituitary stalk [1].

The adenohypophysis (pituitary anterior lobe) produces six different hormones: corticotropin or adrenocorticotropic hormone (ACTH) by corticotrophs cells, growth hormone (GH) by somatotrophs cells, thyroid-stimulating hormone or thyrotropin (TSH) by thyrotrophs cells, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by gonadotrophs and prolactin (PRL) by lactotrophs cells [1, 2]. The production and secretion of all six hormones is controlled by factors synthesized and released from the axonal terminals of hypothalamic neurons to the hypophyseal portal system [9, 10] so the hypothalamus regulates posterior lobe but also anterior. Hypothalamus secretes: corticotropin-releasing hormone (CRH) that controls ACTH, GHRH that regulate GH secretion, thyrotropin-RH (TRH) for TSH, and gonadotropin-RH (GnRH) for LH and FSH; dopamine inhibits PRL secretion. All of them are trophic factors, releasing hormones (RH), that regulate the function of the anterior pituitary through modulation of cell proliferation, hormone synthesis, and secretion [9].

The neurohypophysis (pituitary posterior lobe) contains axonal terminals from hypothalamic and secretes oxytocin and vasopressin. These hormones are synthesized by neurons from hypothalamus and transported to the axonal terminis. Neurons from posterior lobe are surrounded by pituitocytes (astroglia) [9].

21.2 Pituitary and Sellar Tumours

As described previously, pituitary tumours are rare neoplasms in children. Incidence and prevalence of all CNS tumours in children in the United States showed 4.9 new cases per 100.000/year and 35.4 cases per 100.000, respectively [11]. Some series in literature estimate that up to 15% of all intracranial tumours in children are craniopharyngiomas [9] but, in general, it seems to be much less frequent neoplasm accounting for 1.2–4% of all intracranial tumours in children [12], so we can estimate an incidence around 0.06–0.2 cases per 100.000 patient/year and prevalence of 0.4 to 1.4 cases per 100.000 children. Pituitary adenomas are the second most common tumours in pituitary fossa although less frequent than craniopharyngioma.

21.2.1 Craniopharyngiomas

The first description of a craniopharyngioma was in 1857 by Zenker but the term craniopharyngioma was introduced in 1932 by Cushing [13]. They are the most frequent of all pituitary fossa tumours in children comprising 80–90% [9].

Incidence of craniopharyngiomas has bimodal distribution. First peak is between 5 and 14 years old and the second in the fift decade of life [14, 15].

Craniopharyngiomas are benign tumours that are probably the result of metaplastic changes in vestigial epithelial cell rests along the tract of the involuted hypophyseal–pharyngeal duct or Rathke's pouch that forms the adenohypophysis and glandular portion of the pituitary stalk (derived from an stomodeum diverticulum) [16].

There are two distinct histological patterns: adamantinomatous (children and adults) and squamous papilar (almost in adults). There are two theories to explain craniopharyngiomas development related to embriology of pituitary gland as described before. The embryogenetic theory: adamantinomatous craniopharyngiomas arise from epithelial remnants of the craniopharyngeal duct or Rathke's pouch (derived from parts of the stomadeum that form tooth primordial). The metaplastic theory: squamous papillary tumors arise from metaplasia of squamous epithelial cell rests (remnants of that portion of the stomodeum that contributed to the development of the buccal mucosa) [16–19].

Nowadays, genetic and epigenetic studies showed different mutation and pathway signaling between both craniopahryngioma subtypes, so there might be new therapeutic strategies in the next future to treat or control tumor growth and progression [15].

21.2.1.1 Clinical Presentation

Clinical presentation in children is related to mass effect or endocrine disturbances. Initial symptoms of craniopharyngioma are frequently unspecific, and the diagnosis can be made relatively late. The most frequent symptoms before the diagnosis in children are headache (68%), followed by visual impairment (55%), growth failure (36%), nausea (34%), neurologic deficits (23%), polydipsia/polyuria (19%) and weight gain (16%) [12, 20, 21]. The period from initial symptoms to the diagnosis does not correlate with tumor size, hypothalamic involvement, functional capacity or survival [22]. It is important to investigate children that show weight gain and growth retardation because they may be early signs of craniopharyngiomas in children. Acute presentation with signs and symptoms of raised ICP or acute vision loss secondary to obstructive hydrocephalus are associated with bad prognosis with lower 10-year overall survival [22].

21.2.1.2 Diagnosis

Imaging: craniopharyngioma can be located in the sella, and/or partially or entirely suprasellar. Craniopharyngioma classic CT scan image in a child is an enhancing sellar/suprasellar mass that is calcified (90% of craniopharyngiomas calcify in children) and cystic. When two out of these three features are present, craniopharyngioma is the most likely diagnosis [23, 24]. Usually the solid focus is in the sella and

cystic components arising above it [24]. On MRI usually demonstrates T1 high intensity, reflecting the protein or cholesterol content of the "motor oil-like" fluid found in the tumor cysts [25]. Other causes of T1 hyperintensity in craniopharyngiomas have been described—fat, hemorrhage, or even mild calcification [26]. On T2-weighted sequences, including Fluid Attenuated Inversion Recovery (FLAIR), the solid portion is again usually heterogeneous, whereas the cysts are invariably hyperintense. The use of contrast show almost invariable contrast enhancement of the solid portion and the peripheral rim of the cystic portion on both CT and MR (Fig. 21.1).

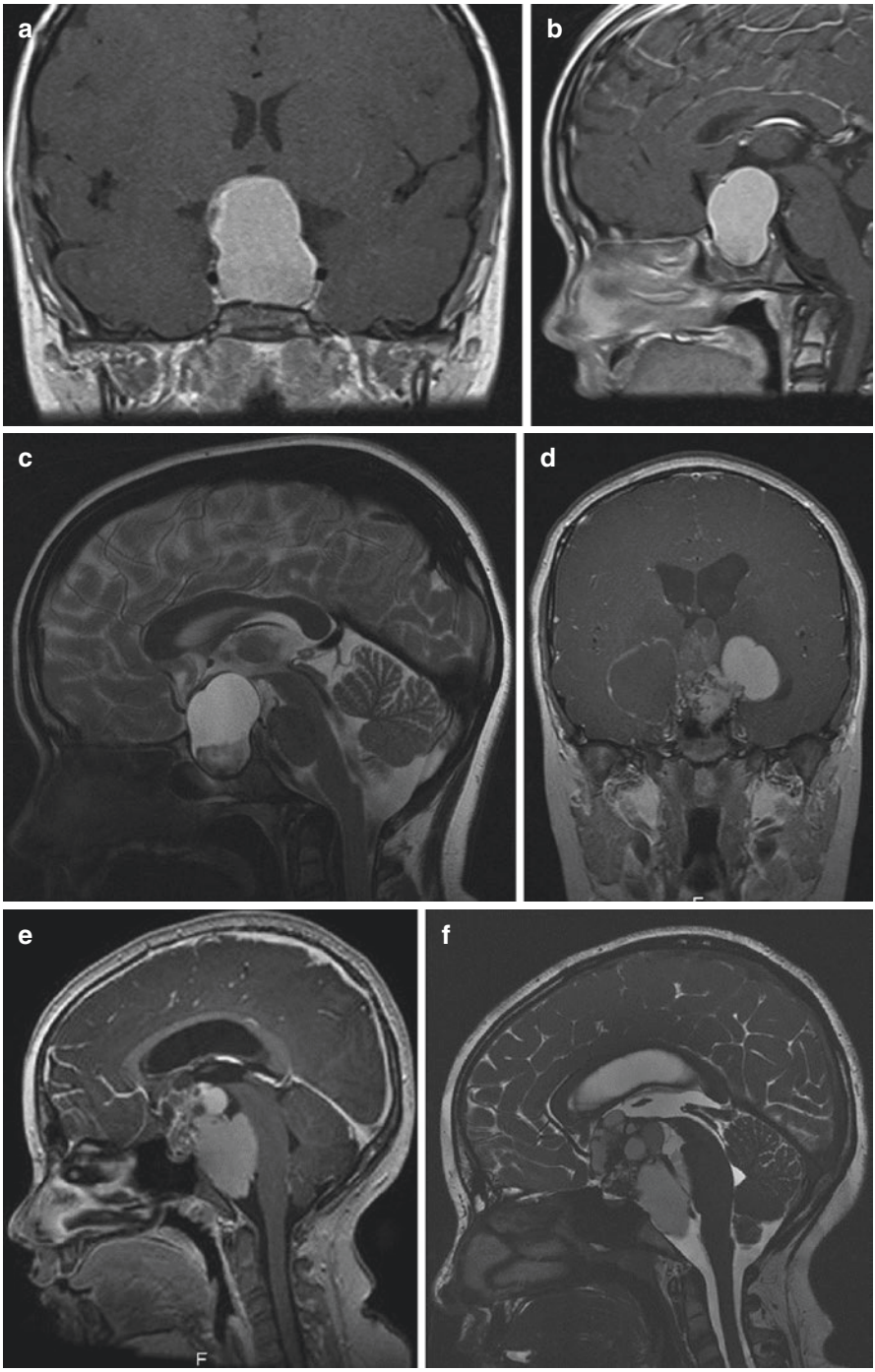
The most common differential diagnosis of craniopharyngioma are pituitary adenoma, hypothalamic or optic pathway glioma, Rathke's pouch cyst and Epidermoid tumor. Pituitary adenomas are noncalcified lesions, have a tendency to expand into the sella and have less superior extension. If cystic component is present it usually has low intensity signal on T1 images [27]. Hypothalamic or optic pathway gliomas rarely have a sellar component (only large lesions), rarely calcify, are usually isointense on T1 and usually lack a cystic component [24]. Large Rathke's cleft cysts typically do not contain a solid component, do not enhance, and are not calcified. With small lesions it may be difficult to differentiate [28]. Epidermoid tumors are rare in the suprasellar region and may be identified by restricted diffusion as they have high signal. Peripheral rim enhancement is less common in epidermoids [29].

Hormonal and hypothalamic assessment: endocrine deficits might be present in 52%–87% of children at the time of presentation as the result of disturbances to the hypothalamic-pituitary axes. They affect growth hormone secretion (75%), gonadotropins (40%), adrenocorticotropic hormone (ACTH) (25%), and thyroid-stimulating hormone (TSH) (25%) [30]. 17%–27% have been reported to have diabetes insipidus neurohormonalis [31–33]. So all hypothalamus-pituitary axis, urine output and water intake must be tested at the time of diagnosis.

Symptoms of hypothalamic dysfunction have been found in 35% of craniopharyngioma patients at diagnosis. They are obesity, behavioral changes, disturbed circadian rhythm and sleep irregularities, daytime sleepiness, and imbalances in regulation of body temperature, thirst, heart rate and/or blood pressure [33]. Rapid weight gain and severe obesity are serious neuroendocrine complications due to hypothalamic involvement and difficult to control. 12%–19% of patients reported to be obese at presentation [31, 32, 34, 35] and often occur years before diagnosis [36].

Ophtalmological examination: Craniopharyngiomas commonly induce visual impairment in children so ophthalmological examination and referral might be done

Fig. 21.1 Craniopharyngioma MRI features: (**a**) 7 years old boy with sellar and suprasellar craniopharyngioma and no hypothalamus involvement, mostly cystic, coronal T1-weighted image; (**b**) (same patient) sagital T1-weighted image with contrast enhancement; (**c**) (same patient) Sagital T2-weighted-image; (**d**) 9 years old girl, with sellar, suprasellar and parasselar craniopharyngioma with suspected hypothalamus involvement, coronal T1-weighted image with contrast enhancement; (**e**) (same patient) sagital T1-weighted image with contrast enhancement; (**f**) (same patient) sagital T2-weighted image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at diagnosis [37, 38]. Almost 50% of children may have visual impairment at diagnosis: decreased visual acuity (41.3%), visual field loss (38.3%), papilledema (25.8%) and optic nerve atrophy (44.8%). Abnormalities in orthoptic examination such strabismus, diplopia and cranial nerve deficits were seen in 12.5% of cases [37].

21.2.1.3 Treatment

Treatment of craniopharyngiomas in children is under continuous debate because the optimal treatment strategy for craniopharyngioma is controversial [39, 40]. Although craniopharyngiomas are benign lesions and, historically, gross total resection has been the preferred treatment approach, tumor's proximity, encasement and invasion to vital structures such as hypothalamus, frontal lobe, ventricles, cranial nerves, and circle of Willis makes complete tumour resection unfeasible and unsafe in many cases and may lead to high rates of hypothalamic-pituitary and/or optic impairment [41–45].

Perioperative fatal complications are reported in up to 3% of craniopharyngioma surgery [52]. The rate of neuroendocrine hypothalamic dysfunction increases seriously following radical surgical treatment, up to 65%–80% in some series [30, 33, 34]. The degree of obesity of affected craniopharyngioma patients is positively correlated with the degree of hypothalamic damage [53–55] and rapid weight gain typically occurs during the first 6–12 months after treatment [35, 55, 56]. The prevalence of severe obesity is higher in comparison with pretreatment status, reaching up to 55% [30]. Obesity and eating disorders result in increased risks of metabolic syndrome [57] and cardiovascular disease [55], including sudden death events [58], multisystem morbidity and death [59].

The rate of post-surgical pituitary hormone deficiencies increases due to the tumor's proximity or even involvement of hypothalamic-pituitary axis [30, 32, 33, 36, 60–64]. Transient post-surgical diabetes insipidus occurs in up to 80%–100% of all cases [30, 34, 60] and the rate of permanent post-surgical diabetes insipidus ranges between 40% and 93% [30, 32–35, 60, 61, 65]. Growth hormone deficiency following treatment is found in about 70%–92% of patients [30, 36, 53, 66, 67].

Last twenty years many groups reviewed their results retrospectively to design new strategies in order to reduce mortality and morbidity secondary to surgical treatment [13, 40, 46–51].

Some classifications emerged based on preoperative clinical and imaging but focused in craniopharyngioma relationship/invasion of hypothalamus and sparing during surgical procedures [13, 21, 49, 68–71]. Nowadays it is accepted that craniopharyngioma with no hipothalamus involvement and "safety" neurovascular dissection might be treated by surgery with the goal of complete removal. When hypothalamus sparing is not possible more conservative surgical management is the rule with association of radiotherapy for tumour remnant. This new approach for craniopharyngioma treatment has shown good long-term disease control and survival with much less morbidity and mortality mainly related to hypothalamus sparing [13, 40, 41, 48–51, 53–56, 62, 63].

Surgical technique may be by craniotomy (pterional transsylvian fissure, interhemispheric transcallosal, midline subfrontal, supraorbitary subfrontal), by endoscopic transnasal transsphenoidal approach or expanded endonasal approach but also by transventricular endoscopic approach. There are also some radiotherapy approaches to craniopharyngioma adjuvant treatment. Detailed description of surgical technique and radiotherapy options are beyond the scope of this chapter.

Overall survival rates reflect the benign origin of craniopharyngiomas but also the complexity and consequences of treatment options, mainly when hypothalamus is affected. Overall survival described in children series show: from 83% to 96% at 5 years, 65%–100% at 10 years and averaging 62% at 20 years. It is not only survival but also quality of life affected by craniopharyngiomas when there is hypothalamus involvement so treatment recommended strategy, in this cases, is limited hypothalamus-sparing surgery followed by radiotherapy [46].

21.2.2 Pituitary Adenomas

Pituitary adenomas are very rare in children. Data from autopsy studies show that pituitary adenomas were present in 17–25% in general population and data from radiological imaging studies show similar incidence, up to 20% of people [72–74]. Only 3.5 to 8.5% of pituitary adenomas are diagnosed in people under 20 years of age accounting for 3% of all intracranial tumours in children [75–78]. However many adenomas presenting in early adult life probably originated in childhood [79].

Pituitary adenomas in children, in comparison to adenomas in adults, are more frequently functioning (80–97%). Adrenocorticotropin (ACTH)-secreting adenomas (Cushing disease) are the most common in early childhood, followed by prolactin (PRL)- prolactinoma- and growth hormone (GH)- secreting adenomas [80]. Prolactinomas predominate in older children and adolescents [3, 81, 82]. Except for corticotroph adenomas, the majority of pituitary adenomas are macroadenomas (diameter > 1 cm) and are frequently invasive.

Although the majority of these tumors are sporadic they can be part of a genetic condition predisposing to pituitary and other tumors. Even sporadic tumors have genetic abnormalities: most pituitary tumors are monoclonal lesions and modifications in expression of various oncogenes or tumor suppressor genes. In recent years many genetic defects have been identified, including genes involved in cell signaling or cell growth and proliferation [79, 81, 83–87]. Other factors and genetic events seem to be implicated in pituitary cell clonal expansion, and oncogene activation is necessary to propagate tumor growth [3, 83, 85]. Familial cases account for 5% of pituitary adenomas [79, 81, 86, 87]. Some genetic syndromes have been associated with pituitary adenomas: MEN-1, McCune- Albright, Carney complex and familial isolated pituitary adenomas (FIPA) [88].

Clinical and laboratory diagnosis depend on tumour secreting hormone (adenoma subtype). Pituitary MR imaging is the modality of choice for detecting pituitary adenomas. Main sequences are T1 weighted spin-echo MRI of the pituitary

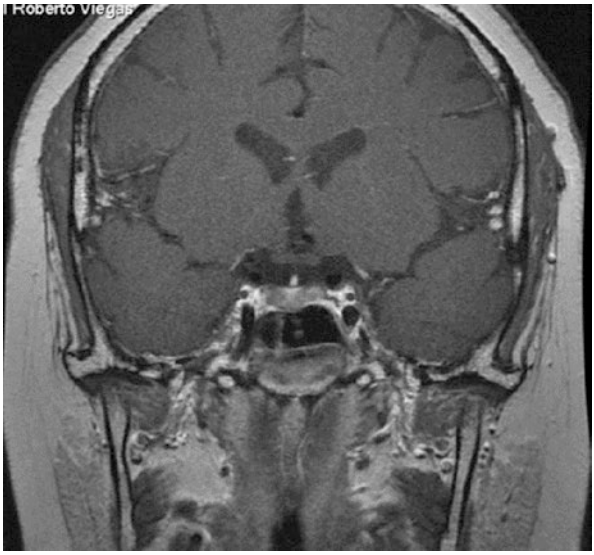

Fig. 21.2 Pituitary adenoma MRI features. Coronal T1-weighted image with contrast enhancement showing hypointense adenoma surrounded by contrast enhanced pituitary gland

before and after administration of gadolinium (Gd). Adenohypophysis (anterior pituitary gland) is normally iso-intense with the rest of the brain. Adenomas appear as hypoenhancing lesions because normal pituitary issue enhance faster than adenoma (Fig. 21.2). Deviation of the pituitary stalk away from the side of the tumor and an asymmetrical increase in the vertical height of the gland are less specific signs for adenoma diagnosis [89]. Dynamic MR techniques rely on rapidly repeated scans, which capture the wash-in and wash-out of contrast to demonstrate a time-dependent pattern of early gland enhancement, followed by delayed adenoma enhancement, optimizing visualization of the lesion [88].

Prolactinoma (Prolactin-secreting adenomas): It arises from acidophilic cells of adenohypophysis. These cells are derived from the same embryonic lineage as the somatotropes and thyrotropes so tumours might secrete also GH and, rarely, TSH [3, 89]. Prolactinomas are the most common adenoma in children accounting for 48%–52% of tumors in general but is much more prevalent in second decade. In fact, ACTH-releasing tumors (Cushing disease) are much more common in the first decade than prolactinomas (71% vs 16%) [90]. Prolactinomas become significantly more frequent than corticotropinomas in late childhood, adolescence and adulthood [3]. Girls are more affected than boys (1.9:1 to 4.5:1, depending on age) [79].

Clinical presentation in prepubertal children is a combination of headache, visual disturbance, and growth failure. Due to suppression of gonadotropin secretion by hiperprolactinemia or local compression/destruction of pituitary gland pubertal females frequently present with symptoms of pubertal arrest, hypogonadism and, sometimes, galactorrhea. Clinicians may ask but also express the breast to rule out galactorrhea because teenagers may not spontaneously talk about this symptom and it may not occur spontaneously. In males macroadenoma are more frequent at presentation so may present with headaches and/or visual impairment. Presentation

may be also pubertal arrest or growth failure but is less frequent maybe due to the fact that gonadotropin release is sensitive to the effects of hyperprolactinemia, enabling earlier detection of the tumor in females [89, 91–93].

Basal prolactin levels has a high diagnostic value and correlates with the size of the tumour [80, 94, 95] but, due to pulsatile secretion, at least two determinations on different days and 2–3 samples separated by 20 min should be obtained [96, 97]. It is important to rule out physiologic (nipple stimulation, chest wall lesions, physical or emotional stress), iatrogenic (medication as phenothiazines, metoclopramide, centrally acting antihypertensive) and pathologic causes (tumors and infiltrative disease of the pituitary, infundibulum, hypothalamus) of secondary hyperprolactinaemia [79, 89]. Supranormal PRL levels below 100 ng/mL may be attributable to the so-called "stalk effect", above 100 ng/mL, prolactinoma is relatively assured and certain above 200 ng/mL—although results below these thresholds do not exclude the possibility of a true secreting prolactinoma [88, 97, 98].

Management of prolactinoma is mostly medical with dopamine agonists in order to reduce prolactin levels and reduce tumor volume, unless there is an acute threat to vision, hydrocephalus, cerebrospinal fluid leak or other surgical emergency [79, 89]. D2 agonists can achieve control of PRL in 80–90% of patients in the majority of cases in the first 6 months of therapy [97, 99]. There are mainly two options of medication, cabergoline (0.5–3.5 mg/week) or bromocriptine (2.5–15 mg/day). In the first year of treatment, up to 80% microadenomas and 25% of macroadenomas my show tumour volume reduction. Medical treatment must be continued at least two years after normal prolatin values and tumor desappearance on MR.

If hyperprolactinaemia persists after 3 months of maximal dose treatment and tumour reduction is <50% can be concluded tumour resistance to medical treatment and pituitary surgery should be considered. Radiotherapy may be an option after medical and surgical treatment failure [96, 97].

Corticotropinomas (ACTH-secreting adenomas, Cushing disease): adenomas causing Cushing's disease are the most common pituitary adenomas in prepubescent children [3] accounting for 54.8% of adenomas from age 0 to 11 years, and 29.4% from 12 to 17 years [80]. Beyond the first 5 years of life, ACTH-secreting adenomas account for 80–90% of children who develop Cushing's syndrome [89]. Male predominance is observed in prepubertal subjects [101, 102] accounting for 63% of cases [103]. Corticotropinomas are significantly smaller than other types of pituitary tumors (usually 3 mm or less) and rarely invade the cavernous sinus or grow into the subarachnoid space [3]. There are also case reports of tumors that originate in the posterior lobe [101].

The classic presentation is one of rapid weight gain with striae, hypertension, headaches, growth failure, pubertal failure or arrest, delayed pubertal development and amenorrhea despite often significant virilization and hirsutism and premature pubarche in prepubertal children [3, 89]. Insulin resistance is common, although frank diabetes occurs infrequently [89]. Features of paediatric Cushing disease show some differences compared with adult patients [79] as children and younger adolescents do not typically report problems with sleep disruption, muscle weakness, or problems with memory or cognition [3]. Instead of depression, memory

problems, and sleep disturbances, children with Cushing's syndrome frequently tend to be obsessive and are high performers at school [89].

The diagnosis of an ACTH-secreting adenoma needs the demonstration of ACTH-dependent hypercortisolaemia of pituitary origin [79]. Although microadenoma is the cause of most Cushing syndrome differential diagnosis must be done with primary adrenal tumors (more frequently seen in first 3 years of life), ectopic ACTH production (bronchial or thymic carcinoids), and, very rarely, ectopic CRH-producing tumors [89]. First step in diagnosis is to confirm Cushing's syndrome with several 24-h urine free cortisol (UFC) measurements and correct values for body surface area and normal range of each laboratory. Failure of the serum cortisol to suppress to less than 3 mg/dL the morning after receiving low dose of dexamethasone at midnight is another important data [89].

To establish that the Cushing's syndrome is due to an ACTH-secreting pituitary adenoma more tests are needed: stimulation of ACTH and cortisol following injection of ovine-CRH (increase after injection) and suppression of cortisol by more than 50% after high dose of dexamethasone given at midnight. The latter test has a sensitivity that is 85% and able to be done as an outpatient [89].

If laboratorial tests suggest corticotropinoma and the pituitary MRI shows adenoma the diagnosis is already done. If MRI is negative, then ovine-CRH-stimulated bilateral inferior petrosal sinus sampling can be used to confirm that the ACTH is coming from the pituitary gland and can also assist in lateralizing the tumor with approximately 75% accuracy. The sensitivity of this test at confirming pituitary ACTH dependence is 97% [89] (Fig. 21.3).

Cushing disease treatment in childhood is always surgical mainly by transsphenoidal adenomectomy [3]. The cure rate is significantly greater in those patients

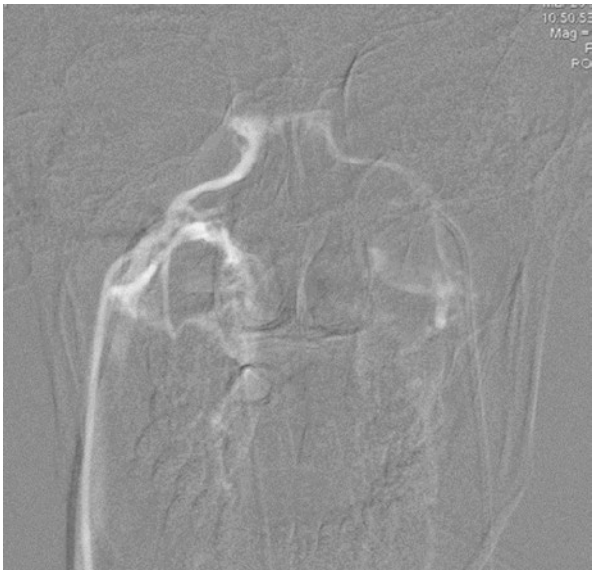

Fig. 21.3 Inferior petrosal sinus sampling for Cushing's disease diagnosis

who have noninvasive microadenomas and is successful in over 90% of the cases, with a recurrence rate of less than 10% [3, 89]. If the tumor is surgically unresectable, or after a second recurrence, fractionated radiation or gamma-knife therapy will produce normalization of cortisol in the majority of patients, although delayed plurihormonal hormone deficiency is expected [3, 89, 104, 105]. Cure rate of radiotherapy is approximately 70–80% of children [106]. Bilateral adrenalectomy may be considered for inoperable or recurrent cases; however it is associated with a significant risk of development of Nelson's syndrome [3, 107].

Somatotropinomas (GH-secreting adenomas, gigantism/acromegaly): Somatotroph GH-secreting adenomas account for 5–15% of pediatric pituitary tumors with a higher prevalence in males (59%) and median ages at symptom onset of 9 years and at diagnosis of 14 years [79, 108]. Approximately 90% of cases are macroadenomas, 30–60% being invasive [3]. Excess GH production in children may result from an adenoma or secondary to somatotroph hyperplasia, which occurs by stimulation of somatotroph in certain genetic conditions such as McCune-Albright syndrome, MEN-1 or Carney complex. Almost very rare, another cause of GH excess can be hypothalamic or ectopic tumors that secrete GHRH or by dysregulation of GHRH signaling that may occur as a result of a local mass effect [3, 89].

Somatotrophs are believed to have the same ancestral embriologic lineage as the lactotrophs and thyrotrophs so may stain for and secrete any or all of these hormones but it does not imply that the tumor secretes this hormone in clinically significant amounts [3, 89].

Clinical presentation varies depending on whether the epiphyseal growth plate is open or not [3, 79, 88, 89]. Before epiphyseal closure or fusion, acceleration of growth velocity with prominent height deviation above 2SDs may be the rule, a condition also known as "gigantism". As epiphyseal fusion approaches clinical symptoms become similar to those in adults (acromegaly) such as coarse facial features, broadened nose, large hands and feet, obesity, organomegaly, sweating, nausea and glucose intolerance [3, 79, 89]. Unlike adults, there have been no reports of a significant increase in colonic polyposis or malignancy or thyroid nodules [89]. Since somatotropinomas are often macroadenomas, headaches and visual disturbances are also frequently reported [3, 89, 109, 110]. Weight gain and delayed puberty can also occur [79].

Diagnosis is based on clinical, laboratorial and imaging results. Laboratorial diagnosis is based on the detection of increased IGF-I and GH levels for age and gender in blood tests. Further investigation include oral glucose tolerance test. Somatotropinomas patients show failure of GH suppression or a paradoxical rise in GH after an oral glucose load of 1.75 g/kg although this test alone may result high false positive rate [89, 111]. Identification of a pituitary adenoma on MRI scan is needed for final diagnosis [79, 100].

First-line of treatment for somatotropinomas is transsphenoidal surgery for intrasellar microadenomas and noninvasive macroadenomas with biochemical control reported in 70% of microadenomas and 50% in noninvasive macroadenomas [100, 108, 112]. In large and invasive tumors surgery might be indicated to maximal

removal and decompression but persistent disease is very common so medical therapy and/or radiotherapy may be necessary [3]. Pharmacologic agents such as long-acting somatostatin analogs (octreotide or, more recent, lanreotide) are often indicated both before and after surgery, when surgical cure is unlikely or when surgery fails to achieve biochemical control, and have been shown to be effective at shrinking tumor size and normalizing IGF-1 levels in 56% of cases [79, 100, 113–119]. D2 agonists can be used in patients with associated hyperprolactinaemia, or as adjuvant therapy if no biochemical control observed under high doses of somatostatin analogs [79, 100, 108, 112, 118]. Pegvisomant (GH receptor antagonist) has shown to be effective therapy for normalization of IGF-1 levels with less side effects [120]. Some groups has shown very good results in combined therapy with pegvisomant and long-acting somatostatin analogs [121]. Unfortunately there is limited data on pegvisomant treatment in children [3].

With the development of improved GH assays, the definition of cure of GH-secreting tumors has become increasingly rigorous, from an initial definition of an unsuppressed GH value of less than 10 mg/dL to the current definition that requires a return of the IGF-I levels to normal, with glucose-induced suppression of GH to less than 1 mg/dL (immunoradiometric assay) [89].

Radiotherapy is considered to be the third-line therapy. Hypopituitarism may occur in 30–50% of patients after radiotherapy [79]. Follow-up and monitoring of patients consists in measurement of IGF-I and post-oral glucose tolerance test GH levels together with MRI pituitary imaging [79, 100, 108, 112].

Thyrotropinomas (TSH-secreting adenomas): Thyrotropinomas are very rare during childhood and adolescence accounting for 0.5–2.8% of pituitary adenomas in children [79, 81, 122]. Only few cases reported in literature and described as macroadenomas (almost 90%) with symptoms as headache, visual disturbance, and symptoms and signs of hyperthyroidism [79, 89]. Laboratory tests show elevated free T4 and T3 with no TSH supression. The differential diagnosis might be with isolated central thyroid hormone resistance. Medical suppression of thyroid hormone synthesis may result in increased tumor growth [89].

Again transsphenoidal surgery is the treatment of choice for these tumors but may require adjunctive radiation therapy because its invasiveness and volume. Treatment with octreotide can normalize thyroid hormone levels in 80–90% and produce tumor shrinkage in up to 50% [123, 124].

Gonadotropinomas (FSH/LH-secreting adenomas): extremely rare in children, with few cases in literature, mostly FSH-secreting adenomas so clinical presentation is related to FSH secretion with precocious puberty, ovarian cyst or macroorchidism [81, 125]. Diagnosis is based on signs and symptoms, high levels of FSH and inhibin B, normal or low LH and testosterone, an increased FSH response to gonadotropin-releasing hormone stimulation and detection of a pituitary mass on MRI [125]. Nevertheless diagnosis is usually delayed until the appearance of symptoms related to tumour mass or pituitary hormone deficiency [79].

Non-functioning pituitary adenomas (no hormone secretion): non-functioning pituitary tumors are very rare in children accounting for only 4 to 6% of pediatric cases. In adults they represent 33 to 50% of the total number of pituitary

lesions [77, 126, 127]. These tumors are believed to arise from gonadotroph cells and are frequently macroadenomas at diagnosis, may be invasive and presenting with growth and/or pubertal failure, symptoms of hyperprolactinaemia or hypogonadism especially in young females or with headaches and visual disturbances [3, 79, 89, 122, 128]. In some cases large adenomas may obstruct the foramen of Monro and cause hydrocephalus, but also may expand to cavernous sinus resulting in cranial nerve palsies or cavernous sinus syndromes [3].

Non-functioning pituitary adenomas may show hormone deficiencies: GH deficiency in up to 75%, LH/FSH in 40%, or ACTH and TSH deficiency in 25% [129]. Hyperprolactinemia is seen in less than 20% of patients secondary to stalk compression. Diabetes insipidous is only seen 9 to 17% of cases [3].

Surgery is the first line treatment in symptomatic or growing tumours but observation in small ones. Recommendation for surgical excision of intrasellar tumor or cyst depends on the tumor size, location, and potential for invasiveness [3, 89].

21.3 Other Sellar Tumours

As described at the begining of this chapter pituitary tumors are very rare in children. Craniopharyngioma and adenomas are the most frequent tumors in pituitary fossa, accounting for 90–95% of cases. Other lesions are even rarer than pituitary tumors in children. Some of them are described in summary.

Rathke cleft cyst: are non-neoplastic cystic lesions containing mucoid material in the sellar region accounting for less than 1.2% of pituitary lesions [130–132]. As craniopharyngiomas both have their origin from the remnants of the embryonic Rathke pouch [131, 132] and both may represent a continuum from the simpler Rathke cleft cyst to the more complex craniopharyngiomas [133]. Little data are available on the presentation or treatment outcomes but headache, hypopituitarism and growth delay were the most frequent presentation in a large serie [134]. On CT scanning, cysts usually are hypodense, non-enhancing by contrast and lack of calcification. In MRI, the cyst signal often is similar to cerebrospinal fluid on T1- and T2-weighted images [135]. Surgery is the treatment of choice when symptomatic.

Epidermoid and dermoid cysts: Epidermoid and dermoid cysts result from the inclusion of epithelial elements during embryogenesis. The contents of dermoid lesions are desquamated epithelium, sebaceous material, and, sometimes, dermal appendages, whereas epidermoid cysts contain a white cheesy material (keratin) within a thin capsule [136]. They appear as hypodense cysts with no enhancement in CT or hypointense in MRI [137] and show restriction to diffusion in diffusion-weighted images.

Chordomas: are slow-growing tumors of midline that arise from notochordal remnants in the clivus, usually producing sphenoid basis destruction and invasion. Chordomas of the sellar region are rare but may extend along the entire skull base and the sella (usually is destroyed instead of expanded), so location, bone destruction, and calcification differenciate from pituitary adenomas. Symptoms are

headaches, visual deficit, neck pain, diplopia, and nasopharyngeal obstruction. Surgery is the treatment of choice associated with adjunctive radiotherapy due to complete removal difficulty [135–137].

Germinomas: are malignant intracranial tumors of granulomatous infiltrate around germ cells. They are the most frequent tumour of germ cell tumours group and usually appear at pineal region in children and adolescense (with male preponderance) but another locations may be hypothalamus, anterior III ventricle and intrasellar (not clear gender preponderance) [138, 139]. Diabetes insipidous is a common symptom seen in 80% of cases [136]. Another signs and symptoms may be visual symptoms, including failure of upper gaze and obtundation, delayed sexual development, hypopituitarism and precocious puberty [140–142]. Nowadays a combination of biopsy, chemotherapy and Radiotherapy are the gold standard of treatment with good prognosis depending on dissemination previous to diagnosis [139, 140].

Teratoma: are classified in three different subtypes included in the germ cell tumours group: mature, imature and mature with mailgnant transformation [138]. These tumors are found most commonly in the pineal region, followed by the suprasellar and hypothalamic regions, and rarely in the sellar region [136]. They derive from the pluripotential cells from all three embryologic layers (ectoderm, mesoderm, and endoderm): mature teratoma from two fully differentiated embryologic layers, immature teratoma by embryonic elements from one or two layers. Teratomas can involve the pituitary gland primarily or secondarily, by invasion [136]. Signs and symptoms are similar to germinomas (*see previous description*). Teratoma appear in imaging assessments as a well-delineated mixed cyst with calcification [136]. Treatment may be a combination of surgery alone when mature subtype or surgery plus chemotherapy plus radiotherapy in imature and mature with malignant transformation [139].

Langerhans cell histiocytosis: Langerhans cell histiocytosis is a histiocytic disorder derived from myeloid progenitor cells that express CD34 surface antigen belonging to the monocyte-macrophage complex [136, 143] with an incidence of 3–4 cases/million/year in children younger than 15 years old and male peponderance (2:1) [144]. Anterior pituitary dysfunction is less frequent than diabetes insipidous that may be present in 10–50% of cases. The most common findings on MRI are pituitary stalk thickening and absense of neurohypohysis bright spot in T1-weighted images [136]. The diagnosis may be based on symptoms, imaging techniques (to rule out systemic disease) and surgical biopsy of other involved sites. Biopsy of pituitary stalk is reserved to growing lesions or no other diagnosis possibility [145]. The main treatment is chemotherapy.

Arachnoid cyst: pathogenesis is not known but it is believed to arise from an arachnoid herniation into the pituitary fossa as a result of incompetence of the diaphragma sellae (embriology defect, after trauma or adhesive arachnoiditis) so true sellar arachnoid cyst is very rare [136]. MRI show cystic lesion with same intensity as cerebrospinal fluid in all sequences and no contrast enhancement [135, 137, 142] (Fig. 21.4).

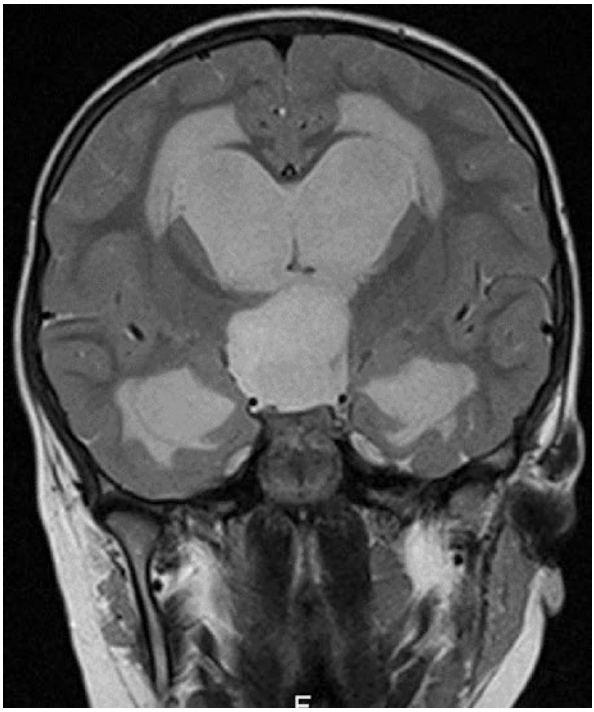

Fig. 21.4 Sellar and suprasellar arachnoid cyst. Coronal T2-weighted image

Optic pathway glioma: Optic pathway gliomas account for 3–5% of all pediatric CNS tumors and represent the most common intrinsic optic nerve tumor [146]. 30% are associated with neurofibromatosis type 1 [136, 146]. Presentation in children varies depending on location into the optic pathway [146]. The most common symptoms are visual loss, headache, and proptosis [136]. Patients with lesions extending to the hypothalamic region may present with hydrocephalus, diencephalic syndrome, precocious puberty or endocrinological deficits [146]. The diencephalic syndrome associates emaciation, growth acceleration, hyperkinesis and euforia [135, 146]. Imaging examinations show a tumor with origin in chiasm or optic nerve, classically a hypointense lesion on T1 images with contrast enhancement. Although optic pathway gliomas are low-grade tumors, their behavior can be aggressive, and their management is often challenging including observation, surgery, chemotherapy and radiation [146].

Other extremely rare lesions in pituitary fossa: inflamatory diseases (sarcoidosis, xanthogranuloma), tumours (astrocytoma, ependymoma, gangliocytoma, hamartoma, metastasis, lymphoma, meningioma), vascular lesions (aneurysm) or infectious diseases (pituitary abscess, tuberculosis, fungal infections) [136].

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Chapter 22
Pediatric Brainstem Tumors

Ariana Barkley and Jason Scott Hauptman

22.1 Introduction

Central Nervous System (CNS) tumors are the most common solid tumors in the pediatric population with brainstem tumors specifically comprising 10–20% of all pediatric CNS malignancies and 20–25% of infratentorial tumors [1–4]. Average age at diagnosis in the pediatric population is 6–9 years without an overall gender predilection [1]. Brainstem tumors are a diverse group of pathologies whose heterogeneity has resulted in multiple subclassification schemes drawing from either anatomical, radiographic or histological characteristics. Historically, the majority of these lesions have been categorized as diffuse idiopathic pontine gliomas (DIPG) which constitute 75–80% of these tumors [5] and portend a median survival time of 9–11 months, making them the leading cause of brain tumor death in children [1].

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22.2 Evolution of Surgical Intervention and Classification Schemes

Brainstem tumors were considered generally inoperable until surgical intervention was first introduced by Alvisi et al. in 1962. In this report 16 patients underwent either surgical resection, biopsy, cyst evacuation or decompression alone during the 1950s; a time without access to CT scans and thus without the ability to pre operatively classify the tumor aside from using air encephalograms [6]. In this study, they alluded to a specific subclassification of brainstem tumors with obvious resection planes that exhibited improved survival time and quality of life after resection [6]. Similarly, Pool et al. in 1968 described three cases: one intrinsic and two exophytic lesions in patients who underwent surgical decompression followed by radiotherapy with longer overall survival time than traditionally quoted in the literature of the time [7]. Latimer et al. in 1971 utilized air encephalography to identify 34 patients with suspected brainstem tumors that were ultimately taken for surgical exploration. In 11 patients, they were able to either subtotally resect an exophytic lesion extending laterally or into the fourth ventricle or evacuate a large neoplastic cyst that resulted in prolonged survival lending further argument to the utility of surgical intervention. Growing interest in the histopathological characterization of these tumors added arguments in favor of biopsy [8] and with the advent of CT scans in 1978 Hoffman et al. reported that surgical resection of lesions protruding into the fourth ventricle led to prolonged survival in the 10 patients who underwent excision with no patients demonstrating tumor progression in 1 and 5 year follow up [9]. This ultimately culminated in the refinement of surgical intervention based on radiographic classification introduced by Epstein in 1985 and association of resected tissue with a histopathologic grading system in attempts to predict prognosis [10].

First attempts at classification schemes were largely based on radiographic characteristics defined by CT or MRI imaging modalities, with the latter becoming the gold standard for diagnosis (Table 22.1) [3, 10–13]. In 1985 Epstein et al. subdivided brain stem tumors into three categories based on MRI morphological characteristics: disseminated, exophytic -with diffuse, focal and cervicomedullary subdivisions, and intrinsic-with cerebellopontine angle, branchium pontis and fourth ventricle subdivisions [10]. In his 1986 report, Epstein stated that all the disseminated tumors were high-grade gliomas based on the World Health Organization histopathologic classification (WHO III–IV), all the cervicomedullary tumors were low-grade gliomas (WHO I–II), and the major focal tumors were low-grade tumors [14]. Stroink et al. similarly emphasized morphology but in contrast based his four classifications on CT findings with exophytic, diffuse intrinsic, focal intrinsic cystic and focal intrinsic solid divisions [15].

Anatomical associations were not incorporated into classification schemes until the 1990s. Barkovich et al. combined anatomical origin with guidelines based on growth patterns and radiographic characteristics of brainstem tumors [16]. The classification scheme was based on location-midbrain, pons, and medulla, focality-diffuse or focal, direction and extent of exophytic growth, degree of brainstem

Table 22.1 Historical classification schemes

Author	Imaging modality	Classification scheme
Epstein et al. (1985)	MRI	Disseminated Exophytic: Diffuse, focal, Cervicomedullary Intrinsic: Cerebellopontine angle, brachium pontis, fourth ventricular
Stronik et al. (1986)	CT	Exophytic Diffuse intrinsic Focal intrinsic: Cystic, solid
Barkovich et al. (1990)	MRI	Location: Midbrain, pons, medulla Focality: Diffuse, focal Direction of growth Degree of brainstem enlargement Hydrocephalus Hemorrhage or necrosis
Fischbein et al. (1996)	MRI	Midbrain: Diffuse, focal, tectal Pons: Diffuse, focal Medulla
Albright et al. (1996)	MRI	Focal: Midbrain, pons, medulla Diffuse
Choux et al. (1999)	MRI	Type 1: Diffuse intrinsic Type 2: Focal intrinsic Type 3: Dorsal or lateral exophytic Type 4: Cervicomedullary

enlargement, evidence of hydrocephalus, and presence of hemorrhage or necrosis [16]. Similarly, Fischbein et al. subclassified brain stem tumors into midbrain, pontine and medullary categorizations [13] and Albright et al. merged anatomical and radiographic morphological characteristics by dividing brain stem tumors into diffuse and focal with midbrain, pontine and medullary subdivisions for the latter [17]. This attempt was continued by Choux et al. in 1999 with classifications into types 1 through 4: diffuse intrinsic, focal intrinsic, dorsal or lateral exophytic, and cervicomedullary tumor respectively [18].

The histological characteristics of these tumors were introduced by the World Health Organization (WHO) with the first edition published in 1979. In 2016, they incorporated genetic characteristics in CNS tumor classifications for the first time and introduced the classification of H3 K27M diffuse midline glioma in lieu of the DIPG subcategory.

22.3 Current Classification

Current anatomic and radiographic classification discussed in the literature include mesencephalic (midbrain), dorsal exophytic, cervicomedullary, focal and diffuse intrinsic brainstem tumors. WHO histopathologic diagnoses range from low to high grade astrocytoma, H3K27M midline gliomas and more rarely, ganglioglioma, hemangioblastoma, primitive neuroectodermal tumors (PNET), atypical teratoid rhabdoid tumors (ATRT) with differing probabilities of either depending on anatomic and radiographic characterizations.

22.3.1 Mesencephalic

22.3.1.1 Clinical Presentation

Mesencephalic brainstem tumors are relatively rare comprising only approximately 5% of brainstem tumors [19]. The mesencephalon, or midbrain, is divided grossly into a ventral tegmentum and dorsal tectum which encircle the aqueduct of Sylvius, a corridor for CSF egress form the third to fourth ventricle. The tectum contains the inferior and superior colliculi which are involved in auditory and visual reflexes respectively, but does not structurally involve sensorimotor white matter tracts.

Tectal lesions are more commonly discussed in the literature when considering mesencephalic brainstem tumors therefore by nature of the involved anatomy, pediatric patients tend to present with symptoms of obstructive hydrocephalus secondary to aqueductal compression. Parinaud's syndrome characterized by lid retraction (Collier's sign) secondary to damage to posterior commissure levator inhibitory fibers, light-near dissociation, upward gaze palsy and convergence-retraction nystagmus may also be observed, but long tract sensorimotor or lower cranial nerve deficits are rarely seen [19–21]. Symptom duration can range from acute on the order of days to longer term with some studies reporting up to 9 years [21–23].

22.3.1.2 Radiographic Characteristics

Imaging of symptomatic mesencephalic brainstem tumors characteristically demonstrate aqueductal compression with triventricular obstructive hydrocephalus. On CT, ventriculomegaly can be seen and occasionally tectal calcification in an isodense non contrast enhancing thickened collicular plate that is isodense compared to grey matter [24, 25]. On MRI they are commonly T1 hypo or iso intense, T2 hyperintense, with high flair signal and rarely contrast enhance. Lesion borders are commonly ill defined and result in a thickened collicular plate. Very rarely is there thalamic extension or exophytic growth into the adjacent quadrigeminal cistern, which is more commonly seen in higher grade or pineal region tumors respectively

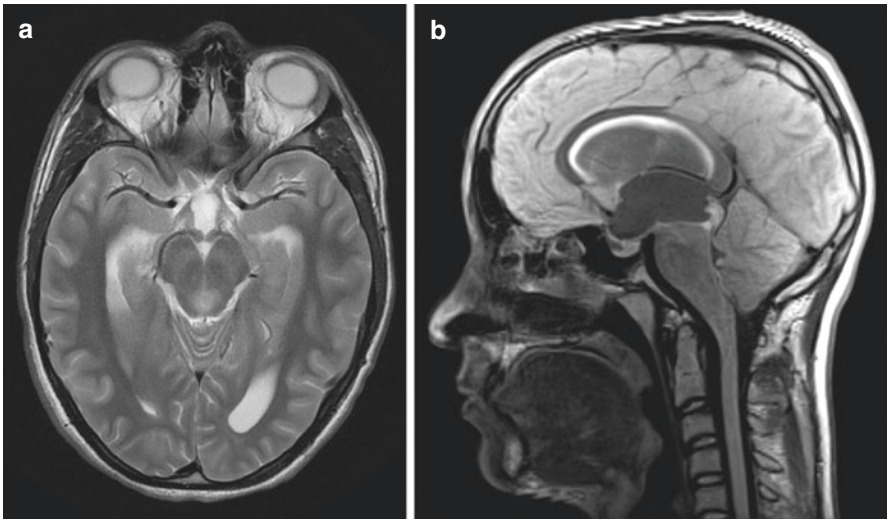

Fig. 22.1 Mesencephalic Brainstem Tumor. (**a**) Axial T2 weighted MRI demonstrating a T2 hyperintense lesion around the aqueduct of Sylvius with enlarged temporal horns and left atrium. (**b**) Sagittal FLAIR MRI demonstrating a large mesencephalic glioma

(Fig. 22.1). Imaging predictors of the need for future surgical intervention due to tumor progression included cystic lesions, size over 2.5–3 cm and/or contrast enhancement [20, 22, 25, 26].

22.3.1.3 Pathology

The majority of mesencephalic brainstem tumors are low grade astrocytomas. A review of the literature conducted by Dağlıoğlu E et al. found in a combined cohort of over 100 patients with mesencephalic brainstem tumors who underwent biopsy, 85% were pilocytic astrocytoma, other low grade astrocytoma or oligodendroglioma with the rare ganglioglioma and the remaining were high grade gliomas [22]. Similar evaluations by Liu et al., Robertson et al. and Ternier et al. found up to 83% of these lesions were pilocytic astrocytomas [20, 22, 27]. BRAF duplication was detected in 25% of these tumors and there were no cases of histone H3K27M mutation [20].

22.3.1.4 Prognosis and Treatment

Surgical interventions for mesencephalic brainstem tumors are typically limited to addressing obstructive triventricular hydrocephalus with either a ventriculoperitoneal shunt or endoscopic third ventriculostomy (ETV) with success rates quoted of 70%-90% with ETV [28–30]. Conservative management is advocated given the

association of these lesions with low grade tumors and their typically indolent course with some studies reporting up to 100% 5 year and 89% 10 year progression free survival in treated tumors [27, 31, 32].

Thresholds for surgical intervention or irradiation remain controversial. Some authors argue larger tumor size and contrast enhancement are significant predictors for progression necessitating surgical or radiotherapeutic treatment [22, 33]. Poussaint et al. reviewed 32 children with a median follow up of 5 years and found the mean tumor size in the group of patients that did not require further surgical intervention or radiotherapy was 1.8 cm in maximal diameter and only 10% had contrast enhancement on their initial MRI scan, while the group of patients requiring subsequent treatment had a mean tumor size of 2.5 cm in maximal diameter on their initial scan and contrast enhancement was present in 76% of patients [25]. Liu et al. similarly reported that lesion size greater than $3cm^2$, contrast enhancement and cystic changes at presentation were risk factors for progression [20]. The importance of these risk factors, however, are still debated given that some authors argue that even with observed progression in low grade tumors the majority of patients remain symptom free [31]. There have been rare reports of potential for malignant progression [21] however the significance of contrast enhancement itself is also controversial with Bognar et al. arguing discordance between biological behavior and contrast uptake of these brainstem lesions [34].

Given the potential for radiographic progression in both high and low grade lesions, conservative treatment recommendations include interval surveillance imaging for the first year in 3–6 month intervals and annually thereafter [35, 36]. The majority of patients with treated obstructive hydrocephalus can remain progression free up to 10 years [33, 37, 38]. In cases of symptomatic tumor progression, irradiation has demonstrated regression or stabilization [35, 37] and surgical biopsy versus subtotal resection with adjuvant radiotherapy have demonstrated control of tumor progression [19, 20]. In very young patients, a trial of chemotherapy is used to stabilize progression in attempts to avoid the side effects of irradiation with weekly vincristine and carboplatin versus thioguanine, procarbazine, lomustine and vincristine (TPCV) regimens showing approximately equal efficacy in treatment of pediatric low grade gliomas [39, 40].

22.3.2 Dorsal Exophytic

Dorsal exophytic brainstem tumors arise from the dorsal medulla, pons or pontomedullary junction and extend into the fourth ventricle and have been reported to comprise 8–22% of brainstem tumors [41]. The most common presenting symptoms are affiliated with hydrocephalus, including failure to thrive, ataxia, papilledema, nausea and vomiting in addition to lower cranial nerve dysfunction with a symptom duration ranging from 2–24 months [41–43]. By virtue of their location and growth pattern, long tract sensorimotor signs are not typically exhibited [44].

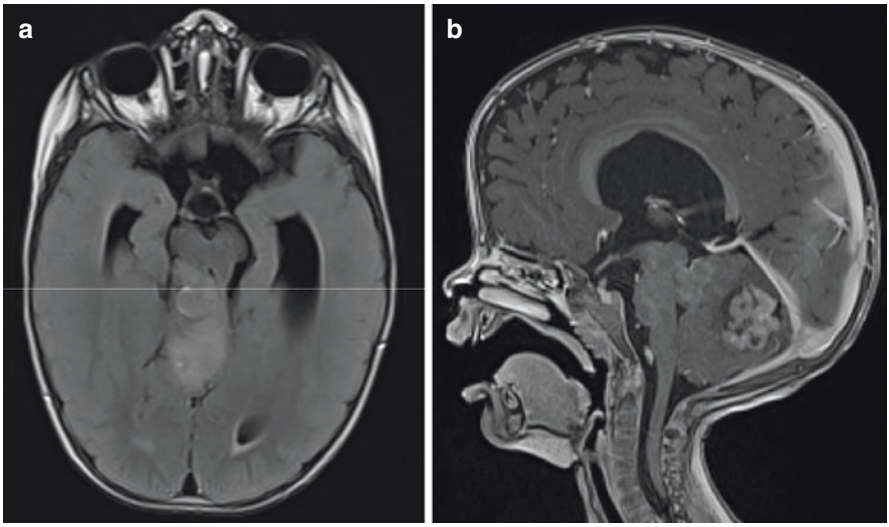

Fig. 22.2 Dorsal Exophytic Brainstem Tumor. (**a**) Axial FLAIR MRI demonstrating high signal extending from right posterior midbrain into the cerebellum. (**b**) Sagittal T1 weighted MRI with contrast enhancement in this exophytic lesion originating from the dorsal pons

22.3.2.1 Radiographic Characteristics

Dorsal exophytic tumors typically demonstrate ventriculomegaly, are isodense and avidly contrast enhance on CT with a growth pattern extending from the dorsal pons or medulla to fill the fourth ventricle and occasionally extend through the cisterna magna [41]. On MRI they tend to be T1 hypo or isointense, T2 hyperintense with high flair signal and contrast enhancement (Fig. 22.2). Caudal extent is limited to the medulla and the ventral extent blends with the dorsal pons or medulla lacking a clear demarcation with lower grade tumors reportedly respecting white matter tracts and pial borders while higher grade pathology violate these barriers.

22.3.2.2 Pathology

The majority of dorsal exophytic tumors are low grade astrocytomas. Khatib et al. found that 92% of their cohort had histopthaology consistent with pilocytic astrocytoma [45] and Stroink et al. reported 90% of dorsal exophytic tumors were low grade astrocytomas [41]. Gangliogliomas, or grade 2 astrocytomas were also present although more rare than their pilocytic counterparts [4, 45, 46]. The prevalence of low grade tumors may explain the longer symptom duration seen prior to diagnosis in this subset of patients [45].

22.3.2.3 Prognosis/Treatment

The overall and progression free survival is better in dorsal exophytic than focal or diffuse brainstem tumors and has been quoted at 100 and 67% [45] likely secondary to the combination of low grade histology and amenability of these lesions to surgical excision [9]. Pollack et al. and Khatib et al. found that 75% and 70% respectively were progression free at 113 and 26 months [4, 45]. Attempted resection is therefore encouraged with the surgical goal of debulking the exophytic component. Subtotal tends to occur over gross total resection given its typically ill defined interface ventrally with variable involvement of lower cranial nerve nuclei and white matter tracts of the pons or medulla.

Routine post operative irradiation is considered only in cases with high grade lesions or rapidly progressing low grade tumors [12]. Repeat resection for regrowth remains an effective option for controlling progression and in cases where this has been performed, malignant transformation or deviation from the initial pathology was not reported [4]. Given obstruction near the foramen of Luscka and Magendie, hydrocephalus may occur pre or post operatively necessitating ventriculoperitoneal shunt insertion or ETV. Chemotherapy options are reserved for younger patients and those rare patients with more aggressive recurrence.

22.3.3 Cervicomedullary

Brainstem tumors localized to the cervicomedullary junction constitute 5–10% of brainstem tumors [3, 12, 47] and have a relatively indolent course with up to 80% reported to present with symptoms for over one year [27]. Clinical presentation is dependent on whether the lesion is centered in the medulla or the cervical spine. When localized in the medulla, patients tend to present with lower cranial neuropathies involving bulbar palsies such as dysphagia, dysarthria, facial palsy, as well as nausea and vomiting not necessarily attributable to hydrocephalus, but to proximity to the area postrema and nucleus soltarius. Tumors arising from the cervical cord exhibit rostral growth limited by white matter tracts such as the pyramidal decussation and inferior cerebellar peduncle resulting in outgrowth towards the obex. Patients with these lesions therefore present with variations of quadriparesis or hemiparesis and long tract signs including myelopathy [48, 49]. More rarely, hiccups, syncope, ataxia apnea and hydrocephalus can also occur [50].

22.3.3.1 Radiographic Characteristics

In general, cervicomedullary lesions exhibit T1 hypointense, T2 hyperintense, with high FLAIR signal and heterogenous or homogenous enhancement on MRI (Fig. 22.3). Depending on histopathology they can be cystic or solid. Morota et al.

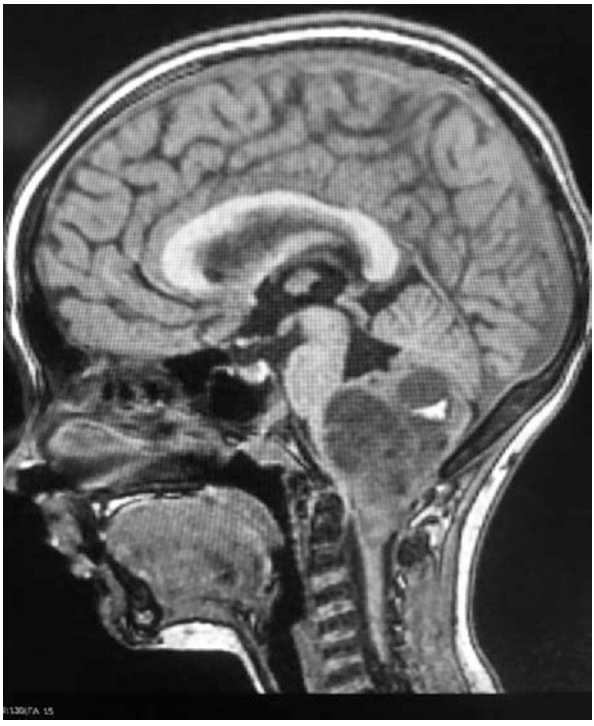

Fig. 22.3 Cervicomedullary Brainstem Tumor. Sagittal T1 weighted MRI demonstrating T1 hypointense cervicomedullary lesion growing posteriorly towards the obex

found through intraoperative stimulation during resection that these tumors tend to push cranial nerve nuclei toward a more ventral location [51]. Histopathologically lower grade lesions may respect the medullary white matter tract barrier created by the pyramidal decussation, inferior cerebellar peduncle and olives, growing instead toward the obex [11, 52, 53]. However, higher grade lesions have been noted to transgress these planes and involve-as opposed to displace-lower cranial nerve nuclei.

22.3.3.2 Pathology

The vast majority of cervicomedullary brainstem tumors are WHO grade I pilocytic or fibrillary astrocytomas, with WHO grade 1 or 2 tumors reported in 84% of patients undergoing surgical biopsy or excision [48, 49, 54]. Other histopathology observed were ganglioglioma, ependymoma, and hemangioblastoma in patients with Von Hippel Lindau. Very rarely are higher grade tumors such as anaplastic astrocytoma reported [48, 54].

22.3.3.3 Prognosis/Treatment

In patients presenting with first time diagnosis of cervicomedullary tumor, prognosis favors long term survival but up to 45% of patients demonstrate recurrence after their initial treatment [48]. The four-year progression-free and total survival rates after surgical excision as initial therapy were 60–70% and 89–100% respectively [48, 49]. for those who had surgery at the time of progression, the progression free and overall survival fell to 41% and 62% respectively, with the only independent variable predicting shorter progression free and overall survival being high histopathologic grade [48].

Surgical biopsy versus excision is recommended with the caveat that subtotal as opposed to gross total resection should be performed if borders with surrounding nuclei and white matter tracts remains unclear intraoperatively. Regardless, the probability of achieving a gross total resection is high with previous reports of successful resection in 75% of cases [48]. Radiotherapy is withheld unless there is demonstrable progression and in patients younger than 7 years where chemotherapeutic options are explored to minimize side effects of irradiation given the expectation of relatively long term survival [11, 48, 50].

22.3.4 Focal

Unlike the prior brainstem categorizations, focal brainstem tumors do not have a particular anatomic predilection aside from rarely occurring in the ventral pons [55]. As a result, presenting symptoms tend to vary widely and include headache, long tract signs, as well as various cranial neuropathies depending on lesion location.

22.3.4.1 Radiographic Characteristics

Focal brainstem tumors tend to have more well defined margins in comparison to their diffuse counterparts. On MRI, they are T1 hypointense T2 and hyperintense with a high FLAIR signal and variably contrast enhancing without a clear tendency to exhibit solid or cystic components (Fig. 22.4). Focal brainstem tumors are commonly less than 2 cm in maximal diameter, taking up less than 50% of the brainstem cross sectional area [35, 55–57].

22.3.4.2 Pathology

Low grade tumors such as pilocytic or fibrillary astrocytoma and less frequently, ganglioglioma are the most common histopathology in focal brainstem tumors [54, 55, 57].

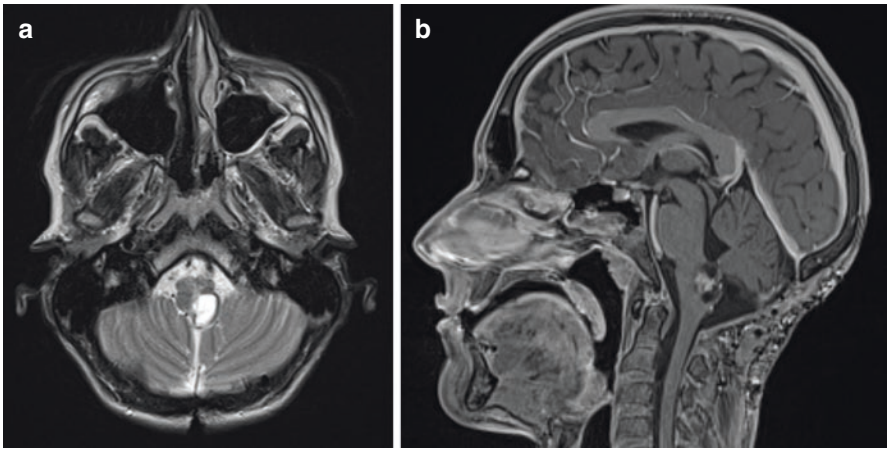

Fig. 22.4 Focal Brainstem Tumor. (**a**) Axial T2 weighted MRI demonstrating a T2 hyperintense lesion isolated to the left posterior medulla with encroachment on the Foramen of Magendie. (**b**) Sagittal T1 weighted MRI with contrast demonstrating heterogenous contrast enhancement of the posterior medullary focal lesion

22.3.4.3 Prognosis and Treatment

In a cohort of patients who underwent surveillance versus radiotherapy or chemotherapy which was the main line of treatment in 66%, clinical outcomes were comparable with a 5 year progression free and overall survival of 70% and 74% respectively [58]. Prognosis tends to be worse for patients younger than 8–10 years, higher pathologic grade, or cervicomedullary site [58, 59]. In a study evaluating patients who underwent surgical resection, however, the 5 and 10 year overall survival was 98 and 90% respectively [55]. Therefore recommendations include attempted surgical excision if the lesion is well circumscribed versus biopsy with plans for resection if the histopathology returns as a truly low grade glioma such as a pilocytic astrocytoma [35, 55, 59].

For unresectable lesions, gamma knife radiotherapy remains a viable option with Yen et al. demonstrating growth stabilization or regression in 80% of treated patients [60].

22.3.5 Diffuse Intrinsic

Diffuse intrinsic tumors mainly occur within the pons and historically were synonymous with diffuse intrinsic pontine glioma (DIPG). They comprise 80% of pediatric brainstem tumors and are locally infiltrative. There is no gender predilection and the average age at diagnosis is 6–7 years [1]. Patients tend to present within one month

of symptom duration with a classic triad of cranial neuropathy with the abducens nerve most commonly affected, ataxia and pyramidal dysfunction [54, 61, 62].

22.3.5.1 Radiographic Characteristics

Characteristic radiographic features of diffuse intrinsic brainstem tumors include T1 iso to hypointense, T2 hyperintense and high FLAIR signal on MRI (Fig. 22.5). They have indistinct borders and may arise from the cerebellar peduncles or extend into the midbrain and encase the basilar. If enhancement is seen, it only constitutes 0–25% of tumor volume and can be accompanied by necrosis [35, 63, 64] but diffusion restriction was only seen in atypical DIPG. Their radiographic characteristics are so stereotyped that historically the diagnosis was based on MRI alone. Dissemination throughout the neuroaxis is not uncommon with one post mortem study demonstrating distant disease in structures such as the frontal lobe [65].

Advanced imaging such as MR spectroscopy and positron Emission tomography (PET) have been implicated in assisting with prognostication. A high choline to N-acetylaspartate ratio has been correlated with decreased overall survival and higher histologic grade [66, 67]. Similarly, patients with tumors exhibiting higher metabolic activity suggested by increased fluorodeoxyglucose uptake on PET has also been associated with shorter overall survival [35, 68, 69].

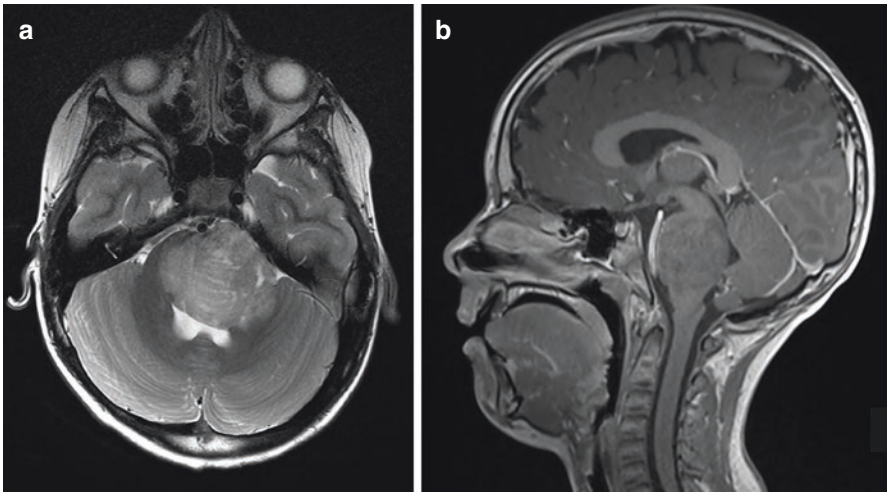

Fig. 22.5 Diffuse Intrinsic Pontine Tumor. (**a**) Axial T2 weighted MRI demonstrating a T2 hyperintense lesion expanding the pons extending into the cerebellar peduncle and beginning to encase the basilar artery. (**b**) Sagittal T1 weighted MRI demonstrating a T1 iso to hypointense lesion expanding the pons

22.3.5.2 Pathology

Historically, DIPG has ranged from WHO grade 2 to 4 but due to their diffuse nature and poor prognosis were universally considered grade 4 lesions. In 2012, several landmark studies isolated a histone 3 K27M mutation (H3K27M) that was identified in 80% of DIPG cases [70–72] resulting in a pathognomonic oncogene that prompted a 2016 WHO supplement reclassifying DIPG as diffuse midline glioma H3K27M mutant WHO grade 4.

Mutation variants from the H3K27M classification include H3.1 (HIST1H3B/C), H3.2 (HIST2H3C) and H3.3 (H3F3A). Identifying mutation variants from the H3K27M have proven important not only for prognostication but also eligibility in clinical trials. Specifically, the H3.1 variant has been found to occur with higher frequency in females and at a younger age [73] while in comparison, patients with the H3.3 variant have been found to be less responsive to radiotherapy, with shorter progression free survival and higher rate of metastatic recurrence [74, 75]. Due to these advances in genetic characterization of such a devastating diagnosis there have been growing calls for biopsying diffuse intrinsic brainstem tumors to not only facilitate further study but also identify patients who would be appropriate for clinical trials addressing relevant molecular targets [61, 63].

22.3.5.3 Prognosis and Treatment

Diffuse intrinsic brainstem tumors have universally portended a poor prognosis since its first description in 1926 [76]. Median progression free survival is commonly quoted around 7 months with overall survival of 9–11 months [1, 62, 77–79]. The only intervention proven to increase overall survival in pediatric patients with DIPG is focal conformational photon radiotherapy with reirradiation once disease progression is observed [80, 81]. The benefit, however, is minimal with disease progression occurring 8–9 months after diagnosis with rapid deterioration after noted progression [35]. Neither cytotoxic nor myeloablative chemotherapy have improved overall survival [82].

Attempts to understand and treat this lethal disease has caused an evolution in thought regarding the role of surgical intervention. Historically discouraged, in 1993 Albright et al. argued against all operative intervention in radiographically diagnosed DIPG citing unacceptable morbidity [83]. However, with the advent of more advanced intraoperative neuronavigation and stereotactic technique, several multi-institutional international studies have demonstrated the safety and efficacy of frame based or frameless stereotactic biopsy through a transcerebellar approach with mortality and largely transient morbidity rates of 0.6% and 7% respectively in studies with the highest quoted incidence [84–88]. Indeed the availability of tissue has driven molecular characterization that in turn have resulted in new therapeutic targets and clinical trials suggesting that surgical biopsy may be the key to ultimately winning the battle against this lethal diagnosis.

22.4 Conclusion

Pediatric brainstem tumors constitute a heterogenous group of lesions with different clinical presentations, histopathologic characteristics, prognosis and treatments. The current classification scheme consists of mesencephalic, dorsal exophytic, cervicomedullary, focal and diffuse intrinsic categories. While mesencephalic, dorsal exophytic, cervicomedullary and focal lesions tend to be associated with low grade histopathology and good long term prognosis, diffuse intrinsic brainstem tumors constitute 80% of brainstem tumors and the overwhelming majority have a dire prognosis with an overall survival of 9–11 months. Recent advances in genetic characterization have resulted in the reclassification of DIPG to diffuse midline glioma H3K27M mutant as well as new molecular targets for clinical trials, but radiotherapy remains standard of care with only recently growing enthusiasm for biopsy. In contrast, mesenecephalic tumors tend to require CSF diversion and can be managed conservatively with surgical intervention or irradiation only in cases of disease progression; dorsal exophytic tumors tend to be treated surgically with extirpation of the exophytic component and treatment of hydrocephalus; cervicomedullary as well as focal lesions may similarly be treated surgically if sufficient demarcation between neoplastic and functional tissue allows excision without causing permanent deficits. Chemotherapeutic options are used for younger patients with disease progression while irradiation has been associated with stabilization or regression in patients with recurrence.

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Chapter 23
Pineal Region Tumors in Pediatric Patients

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Abbreviations

AFP	alpha-fetoprotein
CSF	cerebrospinal fluid
CT	computed tomography
GCT	germ cell tumors
hCG	human chorionic gonadotrophin
ICP	intracranial pressure
LH	luteinizing hormone
MRI	magnetic resonance imaging
NGGCT	non-germinomatous germ cell tumors

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PLAP	placental alkaline phosphatase
PPT	pineal parenchymal tumor
PPTID	pineal parenchymal tumor of intermediate differentiation
PTPR	papillary tumor of the pineal region
WHO	World Health Organization

23.1 Introduction

The pineal region is a deep intracranial space represented by the posterior incisural space containing the quadrigeminal cistern. Tumors present in the pineal region comprise a broad spectrum arising from the pineal gland and surrounding structures. Pediatric patients harbor particular clinical features different from adult patients. Thus, evaluation of pineal region tumors in pediatric patients remains different from adults. Here, we aim to present and discuss the relevant literature concerning the clinical, pathological, treatment modalities, and long-term evaluation of pineal region tumors in pediatric patients.

23.2 Epidemiology

Pediatric pineal region tumors correspond to 2.5% to 8.5% of the intracranial tumors, with higher incidences in Asian countries. In the pediatric population, germ cell tumors (GCTs) are the most common tumors, followed by pineal parenchymal tumors (PPTs). [1–9] Thus, blood and cerebrospinal tumor markers are essential for the patient prognosis, treatment response, and disease monitoring. In this context, increased values of the beta subunit of the human chorionic gonadotropin (hCG) correlate with choriocarcinomas and embryonal carcinomas. Similarly, increased values of Alpha-fetoprotein correlate with yolk sac tumors, embryonal carcinomas, and immature teratomas. Elevated values of Placental Alkaline Phosphatase (PLAP) correspond with probable germinoma diagnosis. Alpha-fetoprotein values over 1000 ng/ml offer a poorer prognosis for the patients [3, 6–9].

Evidence supports that the distribution of pineal region tumors highly varies according to ethnic variables. Thus, in Helsinki, Finland, GCTs are mostly seen in patients in the second decade of life. The most common pineal region tumor in the first ten years of life was the pilocytic astrocytoma, followed by PPTs. In this context, tumor markers and biopsies probably would have less benefit for these patients than other populations [10].

23.3 Clinical Presentation

Children with pineal region tumors tend to present relatively late. The most common symptoms include two big groups. The first group includes symptoms of increased intracranial pressure (ICP) and or hydrocephalus. The second group includes symptoms related to the mass effect of the tumor on surrounding structures.

Most patients present with the first group of symptoms. These patients are usually diagnosed with obstructive hydrocephalus. Obstruction develops due to compression of the cerebral aqueduct. This compression causes obstructive hydrocephalus with symptoms of increased ICP. One of the earliest signs of increased ICP is headaches. They are more common during the night and early morning and often awaken patients from sleep. Sometimes headaches are associated with vomiting, but this rarely gives relief for the patient. Other symptoms of increased ICP explicitly correspond to small children, and they include bulging fontanelle, fast-growing head circumference, and sunset eyes sign. In older children with a rigid skull, hydrocephalus's progression may cause papilledema associated with blurred vision. Other non-specific symptoms, such as memory problems, can also be present.

The second group of symptoms is usually associated with a significant mass of the pineal region. The typical symptom is quadrigeminal plate compression associated with Parinaud's syndrome. This syndrome includes vertical gaze palsy, paralysis of convergence, and light-near dissociation. More than half of patients with pineal region mass have at least one of Parinaud's syndrome components. Further growth of pineal mass can also cause compression of the cerebellum with ataxia and tremor development.

Standing aside, a group of pineal region tumors initially present synchronous lesions. A classic example of such lesions is bifocal germinoma with a bifocal distribution of the tumor in suprasellar and pineal regions. Still unclear if bifocal lesions are primary metastatic disease or simultaneous tumor development [11]. Nevertheless, probably due to more limited space and somehow higher sensitivity of hypothalamic-pituitary axis structures for compression, bifocal germinomas tend to initially present with symptoms related to suprasellar mass. Thereby bifocal germinoma may present with visual disturbance due to the compression of visual pathways and endocrinological symptoms due to hypothalamic-pituitary axis dysfunction. Endocrinological symptoms include delayed growth, precocious puberty, menstrual irregularities, hypogonadism, or diabetes insipidus.

Another example of a primary disseminated pineal tumor is pineoblastoma. This pathology can spread through cerebrospinal fluid (CSF) pathways and cause remote symptoms not related to the primary lesion. These symptoms include spinal cord or optic nerve compression, back pain, and communicating hydrocephalus.

In rare cases, the initial presentation of pineal region tumors may be pineal hemorrhage (apoplexy). This event usually presents a different combination of the following symptoms: a decreased level of consciousness, new acute headache, vomiting, visual disturbances, and meningism.

Thus, summing up, hydrocephalus symptoms are the most common associated with pineal region tumors, followed by symptoms related to the local mass effects like Parinaud's syndrome and cerebellar dysfunction. Less frequently, symptoms of a pineal mass presentation include endocrinological and visual disturbances and symptoms related to pineal hemorrhage like new acute headaches, vomiting, and changing the consciousness level.

23.4 Imaging

Neuroimaging for pineal region tumors consists of two primary imaging modalities: computed tomography (CT) and magnetic resonance imaging (MRI). As most pineal region tumors present with a varying degree of hydrocephalus with related clinical symptoms, the primary images for urgent care set up in most places worldwide are CT scans. This method helps visualize the size of the ventricles and the radiological characteristics of the tumors related to calcification and bleeding within the tumor. On the other hand, the standard method for any brain tumors, including pineal masses, is MRI. Full central nervous system MRI is recommended due to possible leptomeningeal spread of pineal region tumors such as germinomas, pineoblastomas, gliomas, among other malignant tumors.

Additional imaging methods such as MR spectroscopy and 8-F fluorodeoxyglucose positron emission tomography may be required. However, those methods do not add significant advantages to tumor differentiation [12, 13]. The pediatric population differs from adults by different pathology prevalence of pineal region tumors. Figures 23.1, 23.2, and 23.3 represent MRI and CT scan images of different pineal region tumors.

23.4.1 Germ Cell Tumor

GCT, classified as germinomas and non-germinomatous germ cell tumors (NGGCT), are among the most common types in the pediatric population. Radiological characteristics do not allow to reliably distinguish GCTs from NGGCTs as they have very similar features [14]. On CT scans, germinoma usually appears as a homogenous hyperdense mass localized in the midline with peripheral calcification (Fig. 23.1a). On MRI, intracranial germinomas appear hyperintense on T2WI sequence and iso- or hypointense on T1WI sequence. Contrast-enhanced images usually show germinomas as either with homogenous or heterogeneous enhancement whether the tumor contains a cystic component (Fig. 23.1b). A specific feature of GCT on brain imaging is a bifocal presentation in suprasellar and pineal regions. This finding strongly suggests the diagnosis of a GCT tumor. On average, synchronous intracranial germinomas appear up to 30-40% of all primary diagnosed tumors [15–17].

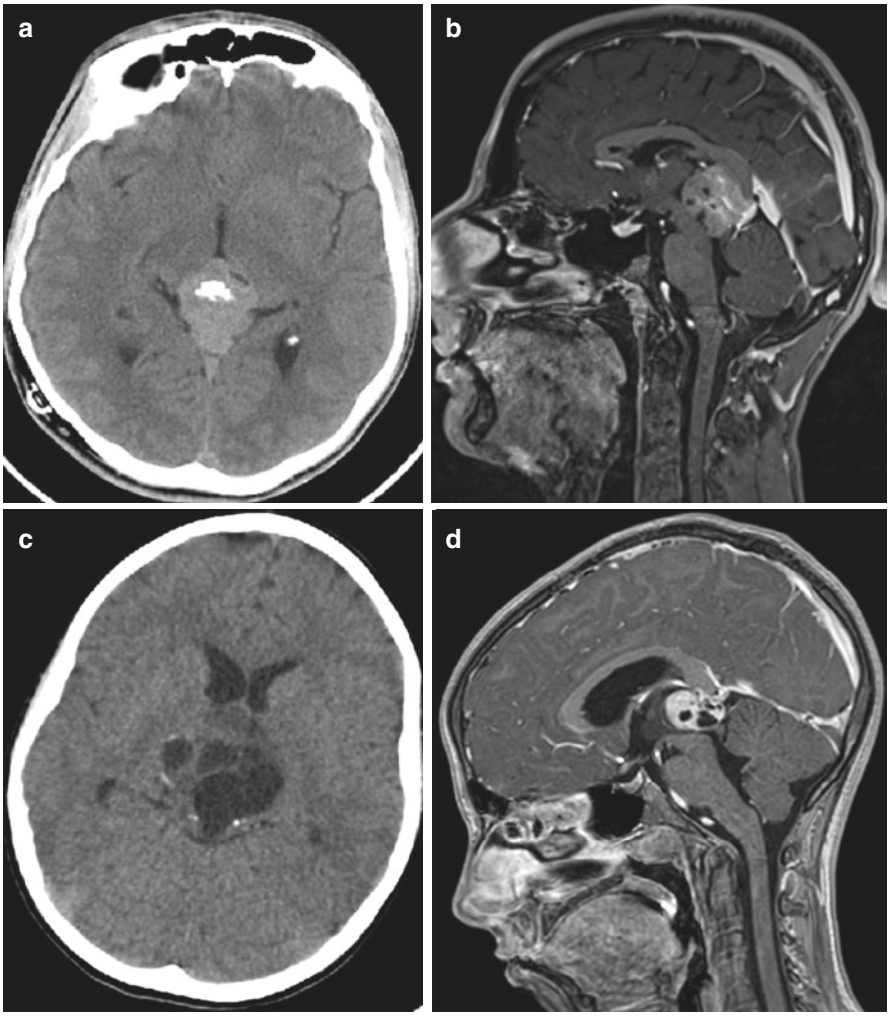

Fig. 23.1 Computed tomography (**a**) and Magnetic resonance imaging (**b**) (T1WI after contrast delivery) of a pineal region germinoma. Computed tomography (**c**) and Magnetic resonance imaging (**d**) (T1WI after contrast delivery) of a pineal region teratoma

23.4.2 Teratoma

Another common type of pineal tumor is a teratoma. On CT, these lesions usually present as multilocular heterogeneous masses. This feature represents the different densities of the cystic components, fat, and calcium elements within the tumor (Fig. 23.1c). Calcification might be present in different tumor areas different from its localized presentation in germinomas. On MRI, teratomas usually appear as

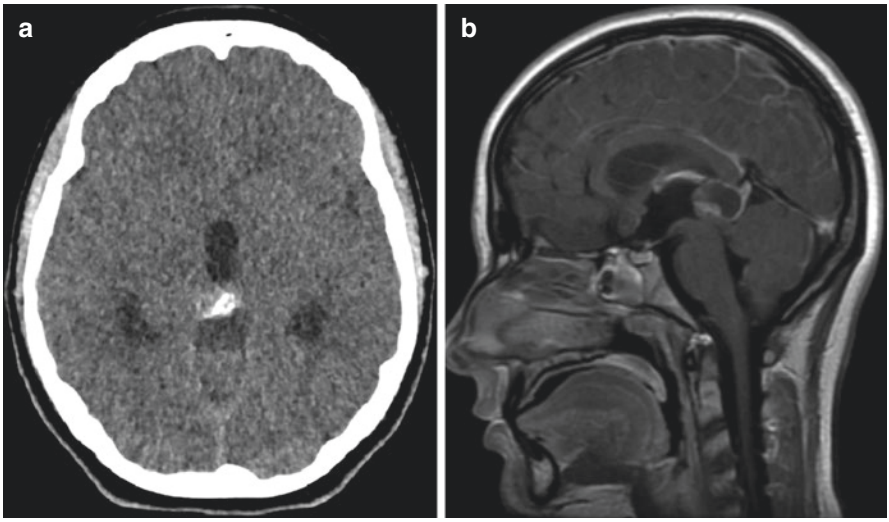

Fig. 23.2 Computed tomography (**a**) and Magnetic resonance imaging (**b**) (T1WI after contrast delivery) of a pineal parenchymal tumor

iso- or hyperintense lesions in T1WI sequence and hypointense on T2WI. Contrast-enhanced images show marked enhancement of the solid component with a lack of contrast diffusion to cystic/lipid components (Fig. 23.1d).

23.4.3 Pineal Parenchymal Tumors

This group of tumors comprises several subgroups such as pineocytomas, pineoblastomas, pineal parenchymal tumors of intermediate differentiation (PPTID), and papillary tumor of the pineal region. On CT scan, pineocytomas usually appear isodense, with cysts and calcifications (Fig. 23.2a) seen in more than 50% of cases [18]. Such cystic components and calcifications make it relatively difficult to differentiate these tumors from benign pineal cysts, especially when the tumor is less than 2-3 cm. On MRI, pineocytomas present as a hypointense mass on T1WI and hyperintense on T2WI. The solid component of the tumor and the cystic wall usually enhances after contrast delivery (Fig. 23.2b). Pineoblastomas usually do not present calcification, and associate with bigger size compare to pineocytomas (> 3 cm) [19, 20]. Due to the bigger size in the presentation, pineoblastomas are more likely to associate with hydrocephalus than pineocytomas.

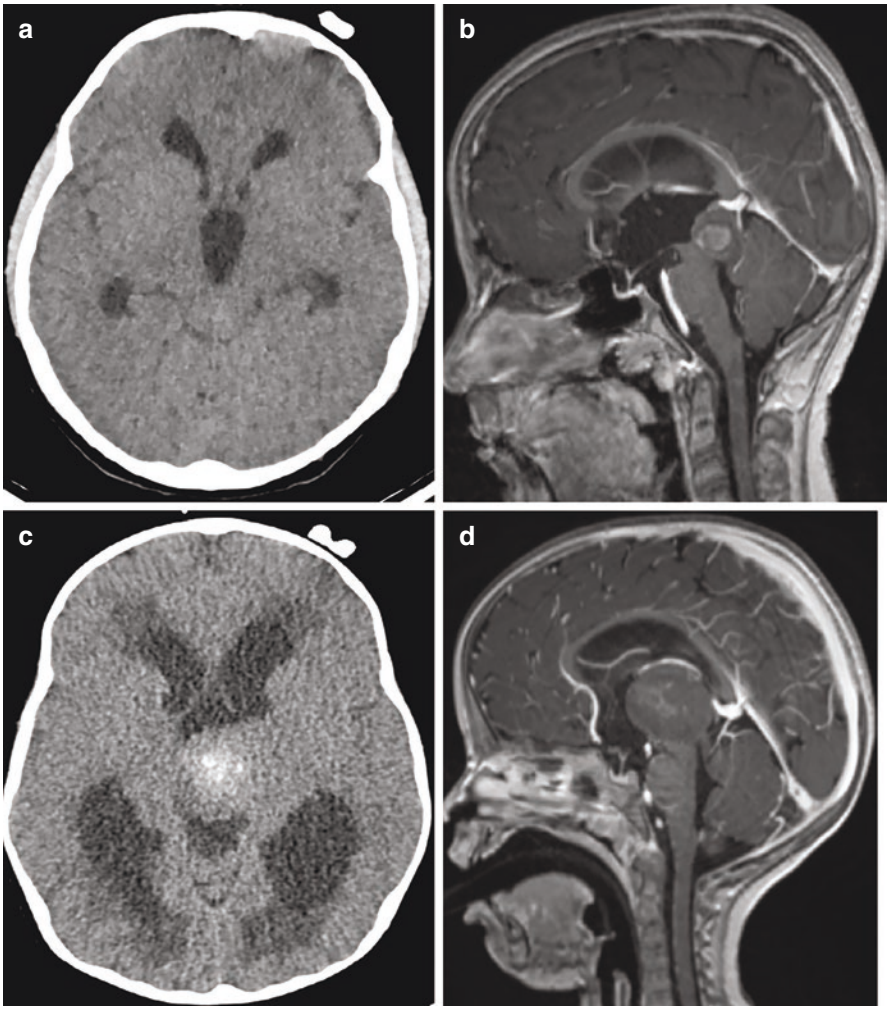

Fig. 23.3 Computed tomography (**a**) and Magnetic resonance imaging (**b**) (T1WI after contrast delivery) of a pineal region pilocytic astrocytoma. Computed tomography (**c**) and Magnetic resonance imaging (**d**) (T1WI after contrast delivery) of a diffuse glioma of the pineal region

23.4.4 Gliomas

Pineal region gliomas include several subgroups related to the degree of malignancy. Pineal gliomas may grow from surrounding structures such as the midbrain, posterior thalamus, third ventricle, cerebral aqueduct, and corpus callosum. Accurate analysis of preoperative images allows correctly identifying the relationships of each particular tumor with the surrounding structures. A detailed description of all glioma subgroups exceeds this chapter's scope. However, diffuse

gliomas minimally differ on imaging, while non-diffuse gliomas are large lesions with cystic components and a low degree of infiltration in the surrounding structures.

In general, radiological features of gliomas are similar to lesions encountered in other parts of the brain. Non-contrast CT scans of non-diffuse gliomas would show hypo- or isodense masses (Fig. 23.3a). The high-grade gliomas can also present initially with intratumoral bleeding, characterized by a hyperdense signal on CT (Fig. 23.3c). On MRI, non-diffuse gliomas would be seen as iso- or hypointense structures compared to the adjacent brain on T1WI and hyperintense on T2WI (Fig. 23.3b). Contrast enhancement may vary from homogenous to heterogeneous aspects in diffuse gliomas (Fig. 23.3d).

23.4.5 Tectal Tumors

This group of tumors is almost exclusively identified in the pediatric population [21]. With widespread neuroimaging techniques, a tectal glioma, in the absence of hydrocephalus, is commonly revealed as an incidental finding [22]. Nevertheless, a tumor progression can cause obstructive hydrocephalus development similar to other lesions of the pineal region. These lesions can also extend to the pulvinar region of the thalamus, visualized on neuroimaging. This type of tumor rarely enhances after contrast delivery. Since tectal glioma might cause chronic hydrocephalus, MRI modalities to evaluate the CSF flow such as sagittal T2-FSE/TSE, 3D-SPACE/CISS play an essential role in planning proper treatment. On the other hand, even such advanced imaging methods may mislead, showing in rare cases a pseudo-flow through an entire third ventricle floor [23].

23.4.6 Aqueductal Tumors

Aqueductal tumors are rare, recently described entities [24, 25]. Previously aqueductal tumors were grouped with tectal and periaqueductal tumors [26]. The importance of recognizing these entities remains therapeutic, which may differ from other tumors pineal region tumors. Thus, any surgical approach not along the aqueductal axis will cause unnecessary damage to the tectum pushed above by the tumor and preserved intact in most cases (Fig. 23.4a, and b). According to the origin of the aqueductal tumors, tumor progression can cause specific radiological findings such as elevation of the tectal plate and tegmental impression [24].

23.5 Molecular Findings and Tumor Microenvironment

The pineal region harbors numerous pathologies, as mentioned above. Among the PPTs, the WHO grade I pineocytomas are benign lesions, while PPTIDs are WHO grade II-III tumors with higher mitotic activity and variably aggressive growth. Similar clinical behavior characterizes papillary tumors of the pineal region (PTPR), a rare lesion thought to arise from specialized ependymocytes of the subcommissural organ of the posterior third ventricle. Pineoblastomas are malignant, grade IV lesions. Like primitive neuroectodermal tumors, PBs are characterized by Homer-Wright rosettes, primitive embryonal cells, increased number of mitoses, and diffuse areas of necrosis.

A recent comprehensive analysis of pineal parenchymal tumors' methylation profiles revealed a broader genetic landscape of those lesions. PPTs include PB-GRP1A, PB-GRP1B, and PB-GRP2, which were associated with different miRNA processing abnormalities such as mutations in DGCR8, DICER1, and DROSHA genes [27]. Homozygous deletions of DROSHA were reported earlier in pineoblastoma together with copy number gains of myomegalin [28]. In general, pineoblastoma belonging to those classes have lower global miRNA levels and occur in older children and adults [27]. Endonuclease DICER (coded by DICER1 gene) is affected in DICER1 syndrome, an autosomal dominant syndrome where the loss of two alleles of this gene leads to tumor development. DICER1 syndrome may include pineoblastoma, multinodular goiter, pleuropulmonary blastoma, cystic nephroma, Sertoli–Leydig cell tumor, Hodgkin lymphoma, and Wilms tumor [29, 30]. Two distinct subgroups of pineoblastoma were also identified: Pin-RB, associated with germline or sporadic RB1 mutations, and PB-MYC, with amplification of the MYC gene. Both affect younger, predominantly male children. Pin-RB tumors with germline or sporadic RB1 mutations have virtually indistinct methylation profiles. Those tumors often exhibit gain of 1q arm and chromosome 16 loss, which is characteristic of retinoblastoma. They also exhibit similar clinical behavior. Therefore, RB1 mutation syndrome is sometimes called trilateral retinoblastoma syndrome. [31] PB-MYC pineoblastomas are similar to medulloblastomas with MYC amplification and also tend to occur in young boys and cause rapid deterioration and death [27].

Pineal parenchyma tumors of intermediate differentiation have different biology from pineoblastomas [27]. They are characterized by KBTBD4 in-frame insertions and lack DICER or DROSHA mutations. Of note, similar KBTBD4 mutations are present in some (Group 3 and 4) medulloblastomas [32]. However mutations in ATRX [33] and histone H3.3 (H3F3A H3K27M) genes were also identified in those tumors [34]. Benign pinealocytomas express genes ordinarily responsible for melatonin synthesis (HIOMT) and phototransduction (OPN4, RGS16) [35]. They are biologically similar to normal pineal parenchyma concerning methylation profile

[27]. Patients with those tumors present elevated melatonin levels before tumor removal; however, this finding rarely corresponds to any functional disturbances [36, 37]. The differentiation between PTPRs from ependymomas or PPTIDs may become challenging. However, some molecular and genetic features may be useful—all PTPRs show chromosome 10 loss, express genes associated with the subcommissural organ of the third ventricle (CALCA, FERD3L, SPDEF), and have a unique methylation pattern [38].

The pineal region is also disproportionally affected by GCTs. This phenomenon is not well understood, but germ cell interactions with diencephalic structures seem to be the cause [39, 40]. It is useful to understand germ cells' biology first as GCTs highjack their properties to propagate themselves. The primordial germ cells first differentiate in the epiblast about a week after fertilization and migrate through the extraembryonic mesoderm to the allantois. After maturation there, they travel to the genital ridge of the mesonephros about ten days after fertilization [41]. The same molecular pathway—SDF-1/CXCR4 axis—is utilized by those tumors when spreading and metastasizing [42]. Global methylation of CpG islands on DNA goes through rapid changes after fertilization. DNA in sperm cells is slightly more methylated than in an ovum. The methylation process falls rapidly, reaching the lowest levels in the blastula phase. Afterward, the methylation in the whole embryo rises rapidly to allow for specialization ad differentiation of cells for an individual's lifetime. However, primordial germ cells demethylate their CpG islands to enter the sex-specific methylation process during gametes development [41]. GCTs lie within that methylation spectrum. Thus, germinomas are closer to the primordial germ cells with low DNA methylation levels and express various genes. NGGCTs resemble the embryonic tissue with higher specialization, higher methylation, and a lower total number of genes expressed [43]. Therefore, it is unsurprising to find germinomas highly infiltrated by B and T lymphocytes (a feature evident even in classical histopathology) [44]. This feature causes a robust immune response that probably inhibits tumor spread. Therefore activation of the PD-1/PD-1 L axis in those tumors may associate a poorer prognosis [45, 46].

Gliomas are also frequently encountered in the pineal region [47]. A breakthrough in understanding glioma biology was discovering a role played by isocitrate dehydrogenase mutation in some of those tumors. The majority of those mutations are site specific (IDH1 R132H) and modify the enzyme function so that 2-hydroxyglutarate (2-HG) replaces the production of α-ketoglutarate. This process leads to numerous intracellular changes, including global DNA and histones hypermethylation and hypoxia-induced factor activation [48, 49]. Therefore, those tumors are slow-growing lesions with scarce but adequate immune infiltration. Moreover, IDH mutation predicts response to procarbazine, lomustine, vincristine chemotherapy in low-grade gliomas. It is also associated with methylation of the MGMT promoter, which is predictive for response to temozolomide treatment in high-grade gliomas [50, 51]. IDH-wild type tumors tend to be characterized by a poor prognosis, necrosis, neoangiogenesis, and fatty but futile infiltration by immune cells [49, 52]. The pineal region contains BRAF-mutated gliomas as well. Some reports describe molecular alterations of BRAF in about 30% of pediatric pineal region

gliomas [53]. BRAF V600 mutations were associated with a poor prognosis and KIA1549-BRAF fusions with a more favorable prognosis [54, 55]. Those alterations also affect the glioma microenvironment by activating the NF-KB pathway and tumor-associated futile inflammation linked to the CCL2 [56, 57]. Finally, one would expect that the pineal region, lying in the midline, should harbor numerous H3.3 K27M mutated gliomas [58, 59]. However, in a study with 45 tectal gliomas, no H3.3 K27 mutant was identified [53]. Those tumors have a uniformly poor prognosis and show a striking lack of immune cell infiltration or response [60].

In conclusion, recent years have brought a better understanding of pineal region neoplasms biology. Those findings have not yet translated into meaningful improvement of the patient perspective. Hopefully, this will change dramatically with ongoing clinical trials like immune checkpoint inhibitors for GCTs, [61] DRD2 antagonist in H3.3 K27 mutant glioma, [62] and vemurafenib or MEK/ERK inhibitors for BRAF-mutated glioma [63, 64].

23.6 Tumor Biomarkers

The biological diversity of pineal region tumors dictates different therapeutical strategies. Some of those lesions are radiosensitive, some are potential targets for novel chemotherapeutics, and some require surgical resection. Thus, precise tumor identity is essential, aiming for the best therapeutic modality [65]. Biomarkers of GCTs are crucial in this strategy [65, 66].

Alpha-fetoprotein (AFP), a Yolk sack product, seems to function analogously to albumin in the fetus. Moreover, it has a proposed role as a hormone-binding molecule, hormone itself, immune suppressor, cell cycle regulation, and apoptosis regulation [67]. Some AFP may be present in adults with reference levels of 0-6 ng/ml, and it physiologically raises dynamically during pregnancy. Like aneuploidies, some fetal abnormalities are associated with decreased AFP levels, while others, such as neural tube defects, are associated with decreased maternal AFP levels during pregnancy [67]. Moreover, individuals with ataxia-telangiectasia syndrome have increased AFP values [68]. AFP also increases in hepatocellular carcinoma. However, AFP is not a highly specific disease marker, as elevated AFP levels appear in liver cirrhosis and hepatitis [69]. Pineal region neoplasms that produce an increase of AFP levels in serum and CSF are yolk sac tumor, [70] embryonal carcinoma, [71] immature teratoma, [72] and mixed gem cell tumors with those components [3]. It is unclear whether measuring AFP concentration in CSF is in any way superior to that in serum. However, it is worth noting that serum AFP concentration is reliable in detecting GCTs with yolk sac components regardless of their location and metastatic status [73]. According to the International Germ Cell Consensus Classification, AFP concentrations are useful to stratify patients with GCTs to intermediate or high-risk groups [74]. Therefore, elevated AFP levels impel to consider aggressive treatment combining resection, chemo- and radiotherapy from a clinical perspective [3, 75].

hCG is a hormone produced by syncytiotrophoblast and later placenta contributing to physiological changes during pregnancy. hCG contains two subunits, α, and β. The former is also part of the luteinizing hormone (LH), follicle-stimulating hormone, and thyroid-stimulating hormone. LH and hCG have a common receptor, and therefore ectopic hCG production can result in pseudo precocious puberty [76, 77]. Pineal region tumors that can produce hCG are germinomas, choriocarcinomas, embryonal carcinomas [71, 77] and mixed GCT with those components [3, 77]. Choriocarcinomas secrete hCG consistently different from germinomas, associated with elevated serum hCG levels in about 50% of cases. Germinomas that secrete hCG represent germinoma with syncytiotrophoblastic giant cells [78]. The preoperative serum concentration of hCG above 15 mIU/ml [78] and preoperative CSF hCG concentration above 1000 ng/ml [79] were observed in recurrent germinomas. Therefore, therapeutic decisions based solely on hCG detection in serum or CSF are challenging.

PLAP is normally expressed in syncytiotrophoblast and appears to participate in immunoglobulin transport to the fetus. Germ cells express a Placental Alkaline Phosphatase-like enzyme that is highly homologous to PLAP, usually detected in PLAP assay. Importantly, smoking is also associated with elevated PLAP serum levels [80]. Elevated PLAP levels in CSF appeared to correspond with a GCT containing a germinoma component. Thus, a strategy of neoadjuvant treatment based on CSF PLAP levels was proposed [81]. However, some evidence also demonstrated that embryonal carcinomas and choriocarcinomas could cause a rise in serum PLAP concentrations in GCT patients [80, 82].

Unfortunately, other pineal region tumors, lack specific, clinically tested biomarkers [83]. Serum micro-RNA concentrations undergo investigation as potential biomarkers of glioma, [84] meningioma, [85] and GCTs [86]. While current biomarkers are essential for the decision-making process, it should be kept in mind that a significant number of GCT patients harbor mixed components [3]. Therefore, the non-germinoma component can recur after primary radiotherapy [77, 81].

23.7 Treatment

Different factors have to be considered when selecting the management strategies of pineal region tumors, such as the clinical status and comorbidities of the patients, the presence of hydrocephalus, the presence of serum-CSF markers, among others.

23.7.1 Surgical Indications

The presence of malignant germ cell markers represents the only circumstance that could make a tissue diagnosis unneeded, allowing to proceed directly with chemotherapy and radiotherapy. However, second-look surgery may be required for the removal of residual tumors after a partial response [16, 87–89].

Differently, when malignant germ cell markers are negative, the knowledge of the specific histologic subtype of the lesions is paramount (as the pineal region harbors very different tumors) for the correct selection of the optimal management strategies [6, 89–92].

The histologic diagnosis may be accomplished by either biopsy (stereotactic or endoscopic) or an open surgical approach, depending on the clinical status of the patient, the extension of the tumor, and the experience of the surgeon [6, 90–92].

The direct removal of the lesion through an open surgical approach may achieve a more precise histologic diagnosis due to the more extensive tissue sampling. The peculiar heterogeneity of pineal tumors' cell populations makes this particularly relevant [6, 89–92]. Moreover, the gross-total lesion removal may be curative for benign tumors (Fig. 23.4). Together with appropriate adjuvant therapies, it may contribute to reach favorable long-term outcomes in patients with malign pineal tumors [6, 89–92]. Finally, when obstructive hydrocephalus is present, the direct and radical removal of the lesion, with or without the opening of the posterior third ventricle, may allow a satisfactory and immediate restoration of the CSF pathways by relieving the compression of the third ventricle outflow tract and aqueduct, thus avoiding the need of a shunt procedure in many cases [6, 89–92].

On the other hand, the biopsy of pineal tumors is advisable when the clinical status of the patient and or the extension of the lesion make an open surgical approach risky. Indeed, stereotactic and endoscopic biopsies of pineal lesions are generally well-tolerated. Moreover, the endoscopic approach may allow performing a third ventriculostomy. However, both stereotactic and endoscopic biopsies may be associated with a risk of intra-operative bleeding. Besides, the reported diagnostic accuracy for endoscopic and stereotactic biopsies is lower than that of open surgical approaches, as a biopsy taken from one area could not show all tumor features [6, 91–93].

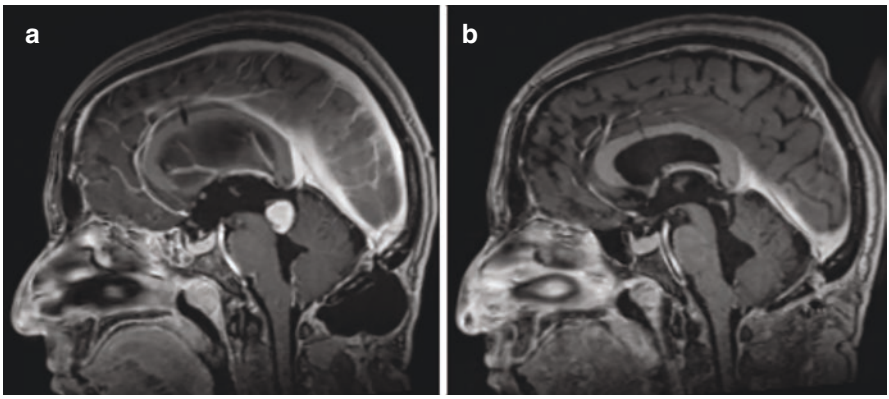

Fig. 23.4 (**a**) Pre- and (**b**) postoperative magnetic resonance imaging (T1WI after contrast delivery) of an aqueductal WHO grade II ependymoma

23.7.2 Hydrocephalus Management

Most patients with pineal region tumors present symptoms related to obstructive hydrocephalus. Various techniques may be applied to re-establish an adequate CSF flow, depending on the patient's clinical status and the experience of the surgeon [6, 90–92]. The direct and radical removal of the lesion, with or without the opening of the posterior third ventricle, may allow a satisfactory and immediate restoration of the CSF pathways by relieving the compression of the third ventricle outflow tract and aqueduct, thus avoiding the need of a shunt procedure in many cases [6, 90–92].

An endoscopic third ventriculostomy, i.e., the third ventricle floor opening to the prepontine cistern, represents a minimally invasive, well-validated, and frequently adopted technique to decrease the intracranial pressure and restore CSF flow gradually. Moreover, the endoscopic approach permits to perform a biopsy of the lesion [6, 91–93]. This could be helpful for the selection of the best treatment protocol of the lesion. However, it is worth noting that the reported diagnostic accuracy for endoscopic biopsies is about 50-78.6% as a biopsy taken from one area could not show all tumor features [6, 91–93].

External ventricular drainage may be adopted to relieve the intracranial pressure pre-operatively, but it is associated with a higher risk of infectious complications than endoscopic third ventriculostomy. Nonetheless, an external temporary ventricular drainage could be adopted to an a priori permanent ventriculoperitoneal shunt. Indeed, this last treatment option, often used in the past, could determine a peritoneal seeding of malignant cells. Besides, the placement of a shunt could cause ventricular collapse resulting in a potential tumor enlargement, thus making the surgical approach more complex and reducing the rate of gross total tumor resection [6, 90–92].

For the reasons mentioned above, the endoscopic third ventriculostomy should be preferred to ventriculoperitoneal shunt also for the management of post-operative hydrocephalus [6, 90–92].

Radiotherapy and-or chemotherapy may considerably shrink certain GCTs in a few weeks, thus resolving concomitant hydrocephalus without surgery. In these circumstances, steroid therapy may be optional for mitigating the hydrocephalus-related symptoms while adjuvant therapy reduces the lesion size.

23.7.3 Radiotherapy

Radiotherapy represents a cornerstone of the treatment of most pineal tumors. However, the concerns regarding the recognized late long-term effects of craniospinal irradiation employed in children with GCTs and pineoblastomas (such as auditory and visual impairment, endocrine and neurocognitive dysfunction, and secondary malignancies) have raised a growing interest in developing management protocols that could permit a reduction of both radiotherapy dose and field [94, 95].

Regarding germinomas, radiotherapy is associated with satisfactory outcomes (curative rates of 90-100%) but may adversely affect the patients' functional outcome [96–100]. As a consequence, the whole central nervous system radiation (≈30-60 Gy), which represented once the standard radiation therapy field and was generally followed by a 50 Gy boost to the primary tumor site, is being progressively replaced by smaller radiation fields and doses for localized disease [98, 99, 101–103]. Indeed, there was evidence that a lower dose of 21-25 Gy could be well tolerated without reducing the risk for spinal relapses [98, 99, 101–103]. Moreover, studies favored the replacement of whole central nervous system radiation with whole-brain radiotherapy, as similar recurrence rates were reported in patients who received spinal irradiation and in those who did not [98, 99, 101–103]. Subsequently, several authors showed that whole-brain radiotherapy could be safely and effectively replaced by whole ventricle field radiation for localized disease [98, 99, 101–103]. Even if associated with inductive chemotherapy, radiation fields smaller than whole ventricle may be associated with higher rates of spinal failures [98, 99, 101–103]. However, neoadjuvant or pre-irradiation chemotherapy may allow decreasing radiotherapy doses and volumes, with lower risks of long-term radiotherapy-related adverse effects [89].

NGGCTs have shown a worse sensitivity to radiation than germinomas, with a reported 5-year survival rate ranging from 10 to 27% to 60% [3, 104]. Hence, radiation therapy is usually associated with other treatment modalities in these tumors and-or applied for craniospinal irradiation in metastatic disease. Moreover, precise radiation dosages and fields remain unclear [89].

Radiation therapy, radiosurgery, as well as chemotherapy may be used as adjuvant treatments for partially resected teratomas, as the maximal surgical removal still represents the gold standard management for such tumors [89, 105, 106].

Regarding tumors of the pineal parenchyma, more precisely, pineoblastomas, radiotherapy may be used as adjuvant treatment combined with chemotherapy. Some authors have advised against the use of radiation therapy in children younger than three years of age to prevent the potential significant long-term effects on the developing brain. However, this was often associated with poor outcomes (death for disease progression within 4-13 months of diagnosis) [107]. For patients older than three years of age, the association of surgery, chemotherapy, and radiotherapy determined a 5-year progression-free survival of 92.9% [108]. We recommend a protocol of 36 Gy craniospinal radiation with an additional 25 Gy boost of radiation on the tumoral bed, divided into a daily dose of 1.8 Gy [109].

For PPTIDs, we recommended radiation therapy in case of partial resections, small recurrences at the follow-up, and pleomorphic variants with pineoblastoma features, or very high proliferation index and high mitotic activity as well [110]. Prophylactic spinal irradiation is controversial when there is no radiologic evidence of spinal seeding [110].

Regarding pineal region astrocytomas, lesion biopsy followed by local irradiation may determine long-term survival [111].

23.7.4 Chemotherapy

Various studies reported high response rates of GCTs to multiple-agent chemotherapy [112–115]. In 1994, Allen et al. observed a 100% response rate of germinomas to single-agent therapy with carboplatin in 10 patients [116].

The results of the First International Central Nervous System Germ Cell Tumor Study showed high response rates among both germinomas (84%) and NGGCTs (78%) using multiple-agent chemotherapy (several cycles of carboplatin, etoposide, and bleomycin *plus* cyclophosphamide in case of incomplete response) [16]. In 2001, the Japanese Pediatric Brain Tumor Study Group observed similar complete response rates among germinomas (83.6%) and germinomas with syncytiotrophoblastic giant cells using multiple-agent chemotherapy (etoposide with carboplatin or cisplatin). In contrast, patients with NGGCT presented no or limited responses [88].

Nonetheless, high rates of recurrence were registered by both studies during the subsequent follow-up without radiotherapy [16, 88]. The first study reported a recurrence rate of 51%, between 8 and 49 months, after a complete response to neoadjuvant chemotherapy. Most recurrences received a combination of RT and chemotherapy. The 5-year survival rates were statistically different in the germinoma (84%) and the NGGCT (62%) groups [16]. The Japanese study in patients with germinomas with a complete initial response reported A 50% recurrence rate within 1.5 years [88].

Various studies have shown high response rates of NGGCTs after multiple-agent chemotherapy [16, 87, 88]. Moreover, chemotherapy may also help reduce the high vascularity of some malignant NGGCTs. Second-look surgery for residual tumor after neoadjuvant chemotherapy is usually employed before further treatment [16, 87, 88]. Residual lesions after initial chemotherapies are often resistant to radiation, such as teratoma or necrotic tissue [16, 87, 88].

A paradoxical growth of mature teratomas (growing teratoma syndrome) may be observed during or after neoadjuvant chemotherapy [117, 118]. Chemotherapy may also reduce the possibility of peritoneal spread of tumor cells in patients who underwent a CSF shunt for malignant GCTs [16, 87, 88]. The combination of chemotherapy and radiotherapy may reduce the relative doses, thus potentially improving cure rates and reducing the corresponding side effects, including pituitary dysfunction [88, 119].

Regarding tumors of the pineal parenchyma, more precisely, pineoblastomas, chemotherapy may be used as adjuvant treatment in combination with radiotherapy. Some authors have advised against the use of radiation therapy in children younger than three years of age to prevent the potential significant long-term effects on the developing brain. However, this was often associated with poor outcomes (death for disease progression within 4-13 months of diagnosis) [107]. For patients older than three years of age the association of surgery, chemotherapy, and radiotherapy determined a 5-year progression-free survival of 92.9% [108].

Various chemotherapeutic agents have been used, such as cyclophosphamide, vincristine, cisplatin, and etoposide [120, 121]. The use of high-dose chemotherapy

with autologous stem-cell rescue in addition to radiotherapy in patients with newly diagnosed pineoblastomas determined encouraging results, with actuarial 4-year progression-free and overall survivals of 69% and 71%, respectively [121].

In our experience, proper multidisciplinary management of pineoblastomas, which associates gross total microsurgical resection of the lesion and an adjuvant therapy based on accurate craniospinal adjuvant radiotherapy with a boost of radiation on the tumoral bed, and when needed, an adequate but aggressive medulloblastoma-like chemotherapy, may improve the overall survival of these malignant lesions [109].

23.8 Long Term Outcomes

The specific histologic subtype represents the single most predictive factor of the outcome, as the pineal region harbors very different tumors.

The prognosis is usually excellent for germinomas, with 5-, 10- and 20-year survival rate of 93.7%, 92.7%, and 80.6%, respectively [3, 89, 98, 99]. Denyer et al., in one of the more extensive multicenter analysis of treatment outcomes for intracranial GCTs, recently confirmed that radiotherapy alone is associated with better survival outcomes than biopsy and resection, but no change in survival when compared to chemotherapy alone [89].

The reported 10-year overall survival rate for NGGCTs ranges from 70 to 80% with the current treatment modalities, and the worst survival outcomes have been associated with intracranial choriocarcinomas [3, 122]. The addition of chemotherapy in NGGCTs patients who underwent removal prolonged the survival, differently from radiotherapy [89].

Matsutani et al. reported 10-year overall survival rates in mature and malignant teratomas of 92.9% and 70.7%, respectively [3]. The reported 5-year overall survival rate for teratomas with malignant elements range from 68 to 70.7% [3, 101].

To summarize, the reported overall 5-year survival rate for all intracranial GCTs is over 75%, and tends to be better in germinomas and mature teratomas than in NGGCTs [105, 123].

Regarding tumors of the pineal parenchyma, pineocytomas present an excellent long-term prognosis after resection [124].

For pineoblastomas, the association of surgery, chemotherapy, and radiotherapy determined a 5-year progression-free survival of 92.9% [108]. We recently reported favorable long-term outcomes in three patients with pineoblastoma, thanks to accurate multidisciplinary management (gross-total resection, radiotherapy, and chemotherapy). One patient died >14 years after surgery, and the other two patients are still in good condition without disease recurrence more than 12 years after surgery [109].

The 5-year survival rate for WHO grade II PPTIDs is 74%, and 34% for WHO grade III [125–127]. We registered good long-term outcomes in a series of 15 patients with PPTIDs (5-year and 10-year survival rates of 92% and 71%,

respectively) thanks to a treatment protocol based on maximal safe surgical removal and radiotherapy in case of partial resections, small recurrences at the follow-up, and pleomorphic variants with pineoblastoma features, or very high proliferation index and high mitotic activity as well [110].

Astrocytomas of the quadrigeminal plate present an indolent progression in most cases, and lesion biopsy followed by local irradiation may determine long-term survival [111].

23.9 Future Perspectives

Microsurgical and endoscopic techniques should be further refined. New minimally invasive techniques should be developed to allow a safer gross-total resection of the lesions when needed while avoiding postoperative complications.

The creation of more accurate diagnostic and therapeutic algorithms and advancements in radiochemotherapy delivery modalities could help obtain optimal long-term outcomes of the pineal region tumors while decreasing the potential side effects of the different therapies. In this regard, multi-variate meta-analyses of the different pineal tumors, evaluating the patients' clinical status and comorbidities, the grade of their tumors, the employed treatments, and long-term outcomes could be helpful to optimize management algorithms [89].

The improvement of imaging studies and serum and CSF markers, together with the development of deep-learning algorithms, could permit a more precise differentiation of the various histological subtypes, thus allowing a better selection of the subsequent management.

Besides, the advancement in genetic tests could be helpful for tumor diagnosis, as well as for predicting the cancer risk.

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Chapter 24
Paediatric Brain Tumours: Rare Variants

Jia Xu Lim, Liming Qiu, Sharon Y. Y. Low, and Wan Tew Seow

24.1 Introduction

Oncological diseases that affect the paediatric central nervous system (CNS) are diverse and challenging. Rarer variants of these conditions, despite being numerous, only make up a small proportion and hence may be encountered sparingly throughout a clinician's career. As these lesions are rare and hence generally poorly understood, treatment should be undertaken via a multidisciplinary approach, considering the patient's age, presentation, neurological status, and extent of disease at diagnosis. Overall, there remains a great need to collaborate and pool knowledge to further advance knowledge to provide the best possible care for our patients [1].

In this book chapter, the authors describe two forms of embryonal tumours (AT/RT and EMTR), choroid plexus tumours, and desmoplastic infantile tumours (DIG and DIA) in this chapter and focused on their definition, diagnosis, pathogenesis, management principles, and touch on the current controversies and latest advances.

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24.2 Atypical Teratoid/Rhabdoid Tumour (AT/RT)

24.2.1 Definition

Embryonal tumours of the CNS are malignant lesions arising from foetal cells of the brain [2]. Atypical teratoid/rhabdoid tumour (AT/RT) is a malignant central nervous system (CNS) embryonal tumour composed predominantly of poorly differentiated elements. These lesions frequently include rhabdoid cells, with inactivation of SMARCB1 (INI1) or SMARCA4 (BRG1). If SMARCB1 and SMARCA4 status cannot be confirmed, the tumour is classified as CNS embryonal tumour with rhabdoid features. Other forms of CNS embryonal tumours include medulloblastoma, ETMR, and others (previously known as primitive neuroectodermal tumour) [3–7].

24.2.2 Epidemiology

AT/RT makes up <5% of all paediatric brain tumours, however, it represents up to 20% of those less than 3 years old [3, 4, 6–9]. It is very rare in the adult population with only 86 reported cases [10]. It has been hypothesized that the true incidence may be underestimated due to similarities in radiological and histological appearances with other CNS neoplasms [7, 9]. AT/RT affects the male population more often than the female population at a ratio of 2.1: 1.6 [7, 9]. It also has a slight supratentorial predominance compared to infratentorial location [7] and 20% presents with disseminated disease, seeding the cerebrospinal fluid pathways [7].

24.2.3 Histological and Molecular Classification

AT/RT corresponds histologically to WHO grade IV [2]. Recent insights have led to an international consensus on AT/RT classified into three distinct molecular subgroups [11]: ATRT-TYR (tyrosinase), ATRT-SHH (sonic hedgehog), and ATRT-MYC, Fig. 24.1 summarises these findings. ATRT-TYR has overexpression of tyrosinase in most cases, which is not present in other ATRT subgroups. Tyrosinase is a protein that assists in melanin synthesis and neural tube development [12]. Overall, the melanosomal pathway, tyrosine metabolism and epithelial proliferation is enriched in ATRT-TYR. The ATRT-SHH subgroup overexpresses both sonic hedgehog and Notch pathway members, and ATRT-MYC overexpresses MYC oncogene. This subgrouping has implications in clinical presentation, prognosis, and targeted therapeutic options.

ATRT-TYR patients are the youngest amongst the subgroups with a median age of diagnosis of 12 months and are mostly infratentorial, unlike the other subgroups.

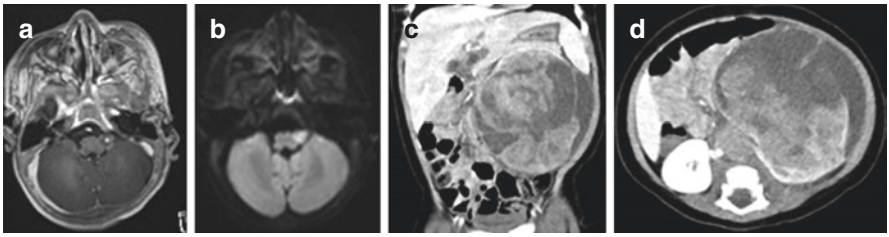

Fig. 24.1 Imaging of Rhabdoid Tumour Predisposition Syndrome. (Patient example from our institution, Neurosurgical Service, KK Women's and Children's Hospital). MRI brain images demonstrating a small lesion at the left medulla with heterogeneous enhancement and restricted diffusion associated with a large heterogeneous left renal tumour seen on CT imaging. (**a**) Axial T1W + C image; (**b**) Axial DWI; (**c** and **d**) Axial and coronal images of contrasted CT of the abdomen. (*MRI: magnetic resonance imaging; CT: computed tomography; T1W + C: T1 weighted with contrast; DWI: diffusion weighted image)*

Table 24.1 Molecular Subtyping of AT/RT {adapted from [10]} Summary of the 3 molecular subtypes of AT/RT and their epidemiological and oncogenic associations

Molecular subtyping	ATRT-TYR	ATRT-SHH	ATRT-MYC
Median age (mths)	12	20	27
Gender distribution (Male: Female)	57:43	55:45	52:48
Tumour location	Supratentorial: 25% Infratentorial: 75% Spine: 0%	Supratentorial: 65% Infratentorial: 35% Spine: 0%	Supratentorial: 50% Infratentorial: 38% Spine: 12%
Major oncogenic pathways, transcriptional features	BMP signalling Melanogenesis (TYR, TYRP, MITF) Mesenchymal genes (OTX2, PDGFRB, BMP4)	Neurogenesis SHH signalling (GLI2, BOC, PTCHD2) NOTCH signalling (ASCL1, CBL, HES1) MYCN	MYC HOX cluster genes

ATRT-SHH is the only subgroup that extends both supra- and infratentorially and is further subdivided into ATRT-SHH-1, with a mainly supratentorial location, and ATRT-SHH-2, with a mainly infratentorial location. Interestingly, ATRT-MYC is the only subgroup with AT/RT arising from the spine. Radiologically, ATRT-TYR has been reported to have bandlike contrast enhancement, while ATRT-SHH has a lower degree of enhancement and ATRT-MYC is associated with strong peritumoural edema [13] (Table 24.1).

Table 24.2 Diagnosis and Surveillance of RTPS (*US: ultrasound; MRI: magnetic resonance imaging)*. Summary of diagnostic criteria and recommended radiological surveillance modalities for patients with RTPS

Diagnosis of RTPS
Patient with both of the following: • Rhabdoid tumour and/or a family history of rhabdoid tumour and/or multiple SMARCA4- or SMARCB1- deficient tumours (synchronous or metachronous) • Identification of a germline pathogenic variant in SMARCA4 or SMARCB1 by molecular genetic testing
Surveillance of RTPS
SMARCB1-related RTPS • Less than 1 year old: Monthly US head, 2–3 monthly US abdomen and pelvis OR 2–3 monthly MRI head, abdominal and pelvis • 1 to 4–5 years old: 3 monthly MRI brain, spine and whole body AND 3 monthly US/MRI abdomen and pelvis The missense variant of SMARCB1-related RTPS is deemed to have very low risk and hence screening is not required. SMARCA4-related RTPS has no surveillance guidelines due to insufficient data.

24.2.4 Associated Conditions/ Syndromes

24.2.4.1 Rhabdoid Tumour Predisposition Syndrome

Rhabdoid tumour predisposition syndrome (RTPS) is an autosomal dominant condition characterised by markedly increased risk of developing rhabdoid tumours. These tumours can be intracranial (AT/RT), extracranial extrarenal (head and neck, paravertebral muscles, liver, bladder, mediastinum, retroperitoneum, heart, pelvis), or renal [14, 15] (Fig. 24.1).

Affected patients usually present within the first year of life with synchronous tumours with aggressive behaviour. close surveillance for these patients is recommended under four years of age with regular monthly to three monthly physical examination, head, abdominal and pelvic ultrasound, or brain, spine and whole-body MRI, depending on the age. The diagnostic criteria and surveillance guidelines are outlined in Table 24.2 [14–16]. Recommended treatment of this condition requires a multidisciplinary approach that usually includes surgery, radiation, and chemotherapy.

24.2.5 Natural History and Prognosis

Due to its rarity, the natural history of RTPS is poorly studied. Prognosis after surgical resection, adjuvant chemotherapy and radiotherapy remains dismal with a median survival of 16.8 months and median event free survival of 10 months [7]. Other studies report a 53% progression free survival and 70% overall survival at 2 years [17], and 22% overall survival rate and 13% event free survival at 3 years [8]. As the AT/RT subgrouping has only been recently established, prognostic

studies based on this new classification are still underway. ASCL 1 protein expression has been associated with better outcome and is highly expressed in ATRT-SHH [18], potentially signifying better prognosis in this subgroup of patients.

Other good prognostic factors include age > 3 years on diagnosis [9, 19], non-disseminated disease on diagnosis [20–22], non-RTPS AT/RT, supratentorial location of tumour [23], gross total resection with surgery [19, 24].

24.2.6 Clinical Presentation and Diagnosis

Due to its malignant nature and rapid progression, AT/RT patients typically have metastatic disease at initial presentation. Clinical features may vary, and neurological symptoms are location-dependent—that is, supratentorial or infratentorial. These can include non-specific symptoms and signs of raised intracranial pressure such as lethargy or vomiting, or focal neurological deficits attributable to its cortical location. AT/RT diagnosis is suspected and made based on the following modalities: radiological, cerebrospinal fluid (CSF), and histopathological assessment.

24.2.7 Radiological Features [25, 26]

As previously described, AT/RT occurs in the supratentorial region more often, usually in the hemispheres and less commonly in the suprasellar cistern, ventricles, and pineal region. These lesions correspond to ATRT-MYC and ATRT-SHH subtypes. Infratentorially, it mostly occurs in the cerebellar hemispheres and sometimes occur in the fourth ventricle, cerebellopontine angle, and brainstem. These are most frequently the ATRT-TYR subtype.

AT/RT are often heterogeneous tumours that are hypercellular that may have concurrent haemorrhage, necrosis, cysts and, or calcifications. Imaging of such conditions should include the entire neural axis due to the high incidence of dissemination on presentation. (Fig. 24.2) Important differential diagnoses for AT/RT are outlined in Table 24.3. The CSF is routinely investigated to assess for dissemination along CSF pathways. Following that, CT of the thorax, abdomen and pelvis is also required to assess the patient for other extra-CNS manifestations of rhabdoid tumours.

24.2.8 Management

At this point in time, there is a paucity of large-scale, multi-centre randomised studies to guide optimal treatment. Also, there is no international consensus on standard therapeutic approaches [27, 28]. Treatment considerations include patient's age,

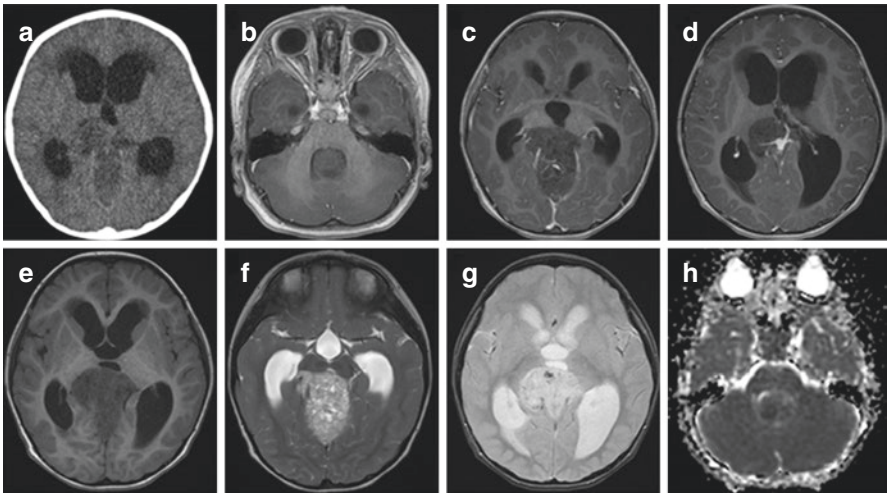

Fig. 24.2 Neuroimaging of AT/RT. (Patient example from our own institution, Neurosurgical Service, KK Women's and Children's Hospital). Brain imaging demonstrating a large heterogeneously lesion extending from 4th up to 3rd ventricle and supracerebellar region, and posteriorly into the quadrigeminal cistern. It demonstrates minimal heterogeneous enhancement with internal cystic changes and calcifications and areas of restricted diffusion. Obstructive hydrocephalus is also observed. (**a**) Axial CT image; (**b–d**) Axial T1 + C at the level of 4th ventricle, 3rd ventricle and ventricular atrium respectively; (**e**) Axial T1W image; (**f**) T2W image; (**g**) Axial GRE image; (**h**) Axial ADC image. (*CT: computed tomography; T1W + C: T1 weighted with contrast; GRE: gradient echo; ADC: apparent diffusion coefficient*)

Table 24.3 Radiological differential diagnoses for AT/RT. Summary of differential diagnoses for AT/RT based on radiological features in the supratentorial and infratentorial regions of the brain

Radiological differential diagnosis of AT/RT
• Supratentorial
Other CNS embryonal tumours: *C19MC-altered ETMR*
RELA-fusion ependymoma
Teratoma
Malignant astrocytoma
• Infratentorial
Medulloblastoma

tumour location, and extent of disease dissemination. Maximal safe resection along with adjuvant chemotherapy with or without radiation is the current treatment paradigm. Research efforts are still ongoing for targeted therapies.

24.2.8.1 Surgery

Maximal safe resection with surgery along with histological and biological diagnosis are the aims of surgery. Despite multiple smaller studies demonstrating a correlation between extent of resection and survival outcomes, in a meta-analysis

published, the extent of surgery was not found to be significantly related to recurrence free and overall survival [28]. Nevertheless, relook surgery after induction chemotherapy, should there be resectable remnants, is recommended in some treatment protocols, both published before and after that meta-analysis [29].

24.2.8.2 Chemotherapy

Conventional dose chemotherapy treatment for AT/RT has been met with conflicting reports with most demonstrating poor progression free survival at 1 year. High dose chemotherapy showed an improvement in survival despite attempting to spare craniospinal irradiation, both in younger and older children. The Head Start II protocol [30], St. Jude Children Research Hospital [9], and the Canadian Paediatric Brain Tumour Consortium [24] have all published on various forms of this chemotherapy regimen. Recently, the Children's Oncology Group [31] published their protocol of postoperative adjuvant chemotherapy using two courses of multiagent chemotherapy followed by three courses of high dose chemotherapy, stem cell rescue and involved field radiation therapy (depending on patient's age and disease location and extent). Comparing with the historical cohort, this cohort demonstrated improved outcomes of 37% event free survival and 43% overall survival at 4 years.

Intrathecal chemotherapy is an interesting concept that was explored in the prophylactic and therapeutic management of metastatic AT/RT. Once again, conflicting reports of survival and outcomes have been reported. A meta-analysis performed in 2016 revealed a higher median overall survival but no significant difference the median recurrence free survival and concluded that intrathecal chemotherapy may be useful as part of a multimodality treatment for disseminated disease [28].

24.2.8.3 Radiotherapy

Presently, there are no clear guidelines for the use of radiation therapy in AT/RT due to, once again, conflicting, and inconclusive reports of the efficacy of radiation therapy. The questions of whether or not to give radiation, when to give radiation and what form of radiation (photon or proton), and to where (focal, cranial, or craniospinal) has not been resolved. The current principles for this form of therapy has been to avoid or delay radiation as much as possible, especially if the patients are young and do not have disseminated disease. In the recently published protocol from the Children's Oncology Group [31], the authors noted that "high dose chemotherapy and local radiation therapy alone may be adequate to achieve disease control in older patients with nonmetastatic disease" and that they "strongly recommended that it follow consolidation in future trials" due to the finding that timing of radiation did not affect survival for patients who continued to receive protocol therapy beyond induction. The EU-RHAB registry, however, reports that radiotherapy significantly increases the mean survival time and 3 year overall survival in infants with tolerable acute side effects [32].

24.2.9 Controversies and Current Advances

Many believe that advances in AT/RT treatment lie in subgroup-specific targeted molecular therapy. Epigenetic inhibitors (EZH2 and histone deacetylase inhibitors), targeted and multi-kinase inhibitors (CDK and TKI inhibitors) and growth and lineage specific pathway inhibitors (ICG-IR, BMP pathway inhibitor) are being studied for its effects. For ATRT-SHH subgroup, the enhancer of zeste homolog 2 (EZH2) inhibitors are potentially useful, with in vitro studies showing that ATRT-SHH-1 cell lines are more sensitive to EZH2 inhibitors [33]. ATRT-MYC, being associated with extracranial rhabdoid tumours, potentially has a therapeutic target with tyrosine kinase inhibitors suppressing rhabdoid tumour cell growth in vitro and against a xenograft model in vivo [34].

24.3 Embryonal Tumour with Multi-layered Rosettes, C19MC-Altered

24.3.1 Definition

The embryonal tumour with multi-layered rosettes (ETMR) is an aggressive CNS embryonal tumour with multi-layered rosettes and alterations (including amplification and fusions) in C19MC locus at 19q13.42 [2].

Should the copy number at the 19q13 C19MC locus show no alteration or is not tested, the lesion is classified as an ETMR, not otherwise specified (NOS) [1]. The diagnosis of ETMR was put forward in 2010 and unifies the various diagnosis of embryonal tumours with abundant neuropils and true rosettes, ependymoblastomas and medulloepitheliomas [35–37].

24.3.2 Epidemiology

The median age of diagnosis of this condition is 31.1 months with a female predisposition. These tumours are also mostly supratentorial (two-thirds) and is commonly disseminated at presentation (18%) [37].

24.3.3 Histological and Molecular Classification

EMTR corresponds histologically to WHO grade IV [1]. LIN28A is an encoded protein involved in stem cell pluripotency, metabolism and tumourigenesis. Strong immunoexpression of this protein is a sensitive and specific diagnostic tool of ETMR [38, 39].

24.3.4 Natural History and Prognosis

ETMRs are reputed to have a dismal prognosis with a median survival of around 12 months [36, 39]. At this point in time, there are no known associated conditions or genetic predisposition syndromes.

24.3.5 Clinical Presentation and Radiological Features [25, 40]

The most common presentation is that of raised intracranial pressure associated with headaches, nausea, and vomiting, as well as focal neurological deficits based on its location. EMTRs are observed to be rapidly growing, large, heterogeneously enhancing tumours with a mixed solid-cystic appearance, containing calcification, internal haemorrhage, cysts, and necrosis. The radiological features are summarised in Table 24.4 and demonstrated in Fig. 24.3.

24.3.6 Management

Due to varied histologic labels and the relatively recent discovery of the molecular diagnostic marker, there is limited data on treatment and outcomes. A multidisciplinary approach is strongly recommended. Treatment principles include aggressive treatment with maximal safe resection, followed by high dose chemotherapy [41], such as the PNET-HR protocol [42], and various forms of radiation therapy, including prophylactic conventional craniospinal radiotherapy and proton therapy [43]. As the majority of ETMR patients are below the age of 4 years old, the benefits and long-term toxicities to neurocognitive development and growth needs to be considered when giving radiation therapy.

Table 24.4 Differential diagnosis of ETMR. List of possible differential diagnoses for ETMR based on radiological findings

Radiological differential diagnosis of ETMR
Other CNS embryonal tumours: *AT/RT*
RELA-fusion ependymoma
Teratoma
Malignant astrocytoma, glioblastoma
CNS neuroblastoma, glioneuroblastoma

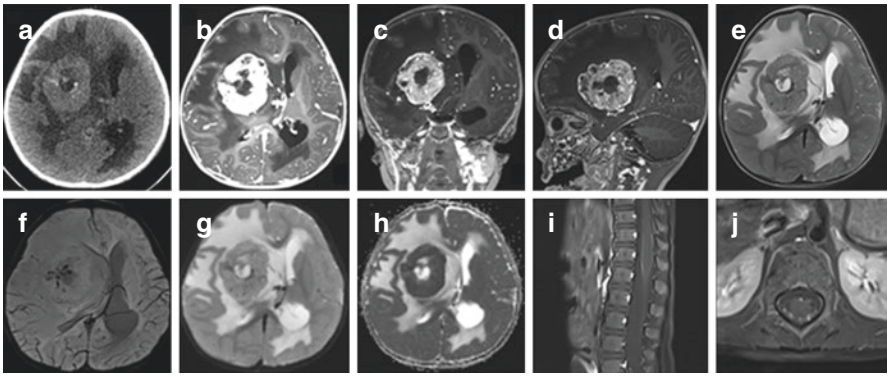

Fig. 24.3 CT and MRI brain of ETMR. (Patient example from our institution, Neurosurgical Service, KK Women's and Children's Hospital). Neuroimaging demonstrating a moderately large heterogeneously enhancing lesion arising from the right external capsule with internal haemorrhage and restricted diffusion. Representative spine image of the same patient demonstrating a leptomeningeal enhancement suspicious of a drop metastasis. (**a**) Axial CT image; (**b–d**): Axial, coronal and sagittal T1 + C; (**e**): Axial T2W image; (**f**) Axial GRE image; (**g–h**) Axial DWI and ADC images; (**i–j**) Sagittal and axial T1W + C whole spine. (*CT: computed tomography; MRI: magnetic resonance imaging; EMTR: embryonal tumour with multi-layered rosettes; T1W + C: T1 weighted with contrast; GRE: gradient echo; DWI: diffusion weighted image; ADC: apparent diffusion coefficient*)

24.3.7 Controversies and Current Advances

A recent study that found ETMRs with C19MC not frequently amplified had germline mutations in DICER1 or other microRNA-related aberrations such as the miR-17~92 microRNA (miRNA) cluster. Loss of DICER 1 function led to R-loop associated chromosomal instability and hence, targeting R-loops with topoisomerase and PARP inhibitors might be an effective strategy for ETMR [44]. Other studies showed potential efficacy with bromodomain inhibitor JQ1 [45], mTOR pathway inhibitors [46] and PLK1 inhibitors [47].

24.4 Choroid Plexus Tumours

24.4.1 Definition

Choroid plexus tumours are neoplasms arising from the choroid plexus epithelium and can be divided into choroid plexus papillomas (CPP), atypical choroid plexus papillomas (aCPP), and choroid plexus carcinomas (CPC) [2]. CPP is a benign ventricular papillary neoplasm derived from choroid plexus epithelium, with very low

or absent mitotic activity. The aCPP is a choroid plexus papilloma that has increased mitotic activity but does not fulfil the criteria for choroid plexus carcinoma. CPC is a frankly malignant epithelial neoplasm demonstrating at least four of the five histological features: frequent mitoses, increased cellular density, nuclear pleomorphism, blurring of the papillary pattern with poorly structured sheets of tumour cells, and necrotic areas [48]. CPC can sometimes mimic other CNS embryonal tumours. Preserved nuclear expression of SMARCB1 and SMARCA4 in almost all tumours helps in differentiating it from AT/RT, and a negative LIN28A separates it from ETMR.

24.4.2 Epidemiology

Choroid plexus tumours are rare, accounting for less than 1% of all brain tumours [49, 50], and 12–20% of brain tumours in patients less than 1 years old [50, 51]. Amongst choroid plexus tumours, CPP is the commonest at 58.2%, while aCPP makes up 7.4% and CPC makes up 34.4% [50–55]. Although choroid plexus tumours can occur at any age, they are more common in the paediatric population. While almost half of CPPs occur in the paediatric age group, half of CPCs occur in patients less than 3 years old [56, 57]. There is a slightly male predisposition for choroid plexus tumours.

24.4.3 Histological and Molecular Classification [2]

CPP and aCPP correspond histologically to WHO grade I and II, respectively and CPC is WHO grade III. CPP are circumscribed cauliflower-like masses located in the ventricles, which may contain cysts and haemorrhages. They are usually well delineated from brain tissues. Microscopically, they resemble normal choroid plexus, albeit containing more crowded, elongated, or stratified cells. Delicate fibrovascular connective tissue fronds are covered with a single layer of uniform cuboidal to columnar epithelial cells with round or oval, basally situated monomorphic nuclei. aCPP display increased mitotic activity of 2 or mitoses per 10 high-power fields. CPC show frank signs of malignancy with at least 4 of 5 features: frequent mitoses, increased cellular density, nuclear pleomorphism, blurring of papillary pattern and necrotic areas. Brain invasion is common. Almost all choroid plexus tumours express cytokeratin and vimentin and most stain positively for CK7 and transthyretin. More aggressive tumours display less S100 positivity and increased Ki-67 index.

24.4.4 Associated Conditions/Syndromes

CPP is associated with in Aicardi syndrome (triad of total/partial agenesis of corpus callosum, chorioretinal lacunae and infantile spasms). Hypomelanosis of Ito have also been associated with CPP, especially in X;17(q12;p13) translocation. About 40% of CPC is associated with LI Fraumeni Syndrome (LFS)/germline TP53 mutation [58]. It is also found in Rhabdoid Tumour Predisposition Syndrome (Please refer to RTPS under AT/RT segment).

24.4.4.1 Li-Fraumeni Syndrome

Li-Fraumeni syndrome is defined as an autosomal dominant disorder characterised by multiple primary neoplasms in children and young adults, with a predominance of soft tissue sarcomas, osteosarcomas, breast cancer, brain tumours and adrenocortical carcinoma. LFS is commonly secondary to a germline mutation in TP53 tumour suppressor gene on chromosome 17p13 [58, 59]. The diagnostic criteria are detailed in Table 24.5.

24.4.5 Natural History and Prognosis

CPPs have a good prognosis when complete resection is achieved, although recurrences and dissemination are possible [64]. aCPP has a relatively benign course, with prognosis more similar to CPP rather than CPC [65]. Male gender and older age are associated with reduced overall survival. In contrast, CPC behaves aggressively with dissemination along CSF pathways in up to 30% of cases [66] and 5-year survival rates of 26–73% [67].

24.4.6 Clinical Presentation

The main presentation of choroid plexus tumours is often secondary to symptoms of hydrocephalus either obstruction of the CSF pathways or from overproduction of CSF. This can manifest in the infant as increasing occipitofrontal circumference, failure to thrive, bulging fontanelles, separated sutures, vomiting, or strabismus. In the older child or adult, they may present with headache, nausea, vomiting, lethargy, blurring of vision, papilloedema, etc. [68]. Due to its malignant nature, CPCs may present in a more subacute manner compared to the relatively benign CPP and aCPP.

Table 24.5 Diagnostic Criteria of Li-Fraumeni and Li-Fraumeni Like Syndrome [60–63]. Summary of clinical features for the diagnosis of Li-Fraumeni and Li-Fraumeni Like Syndromes

Li-Fraumeni syndrome	Clinical criteria [60]	• Onset of sarcoma <45 years old AND • ≥1 first degree relative with any tumour <45 years old AND • 1st or 2nd degree relative with caner <45 years old OR sarcoma at any age
Li-Fraumeni like syndrome (LFL)	LFL-E2 definition [61, 62]	• Sarcoma at any age in the proband AND • Any two of the following within the family – Breast cancer <50 years old – Brain tumour – Leukaemia – Adrenocortical tumour – Melanoma – Prostate cancer – Pancreatic cancer <60 years old – Sarcoma
	LFL-B definition [61]	• Any childhood cancer or sarcoma, brain tumour or adrenocortical carcinoma onset <45 years old in the proband AND • 1st and 2nd degree relative with a cancer typically associated with LFS at any age AND • 1st or 2nd degree relative in the same lineage with any cancer diagnosed at an age of <60 years old
	Chompret criteria [63]	• Tumour belonging to LFS tumour spectrum in the proband <46 years old AND ≥ 1 1st or 2nd degree relative with a LFS tumour <56 years old or with multiple tumours OR • Multiple tumours in the proband, first of which having onset <46 years old AND ≥ 2 belonging to the LFS spectrum OR • Adrenocortical carcinoma or choroid plexus carcinoma in the proband regardless of family history

24.4.7 Radiological Features [25, 69]

CPP and aCPP have similar radiological features. They are intraventricular, well-delineated and lobulated with a frond-like papillary (cauliflower) appearance with homogeneous enhancement and fine speckled internal calcifications. These lesions can be located anywhere in the ventricles where normal choroid plexus is sited, most commonly in the lateral ventricles, followed by the 4th ventricle. CPC are similar in appearance, but they enhance heterogeneously and breach the ventricular ependyma into adjacent brain (Figs. 24.4 and 24.5). Vasogenic edema, necrosis, internal haemorrhage and cystic changes are common. These details and the differential diagnoses are summarised in Table 24.6. Extraventricular choroid plexus tumours found in the cerebellopontine angle and within the parenchyma have also been reported. They are rare and has been speculated to be an embryonic remnant of

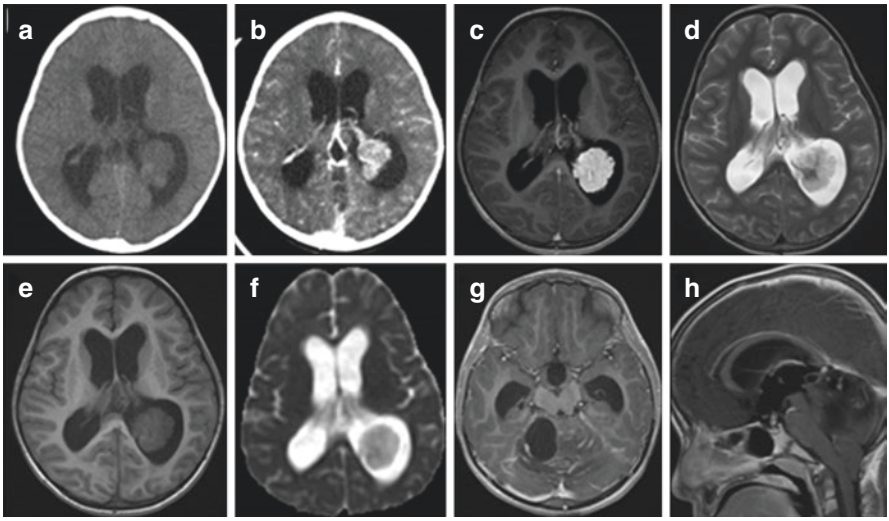

Fig. 24.4 Neuroimaging of a typical Choroid Plexus Papilloma. (Patient example from our own institution, Neurosurgical Service, KK Women's and Children's Hospital). Well-demarcated, intraventricular lesion in the atrium of the left lateral ventricle with a cauliflower appearance seen with intense homogeneous enhancement suggestive of a choroid plexus papilloma. Despite the low-grade nature of this lesion, there is dissemination along the CSF pathways with a solid-cystic lesion in the right cerebellar hemisphere and pituitary stalk, highlighting the importance of imaging of the entire neuroaxis. (**a** and **b**): Axial plain and contrasted CT image; (**c–f**) Axial T1W + C, T2W image, T1W image, ADC image at the level of ventricular atrium respectively; (**g**) Axial T1W + C image at the level of midbrain; (**h**) Sagittal T1W + C image (*CSF: cerebrospinal fluid; CT: computed tomography; T1W + C: T1 weighted with contrast; ADC: apparent diffusion coefficient*)

the choroid plexus. The entire neural axis should be imaged in all choroid plexus tumours due to the possibility of diffuse leptomeningeal dissemination.

24.4.8 Management

The management of choroid plexus tumours includes gross total surgical resection, followed by adjuvant treatment depending on the histological diagnosis. Surveillance can be considered for small, non-obstructive lesions that do not demonstrate high risk features. For CPPs, gross total resection is sufficient with regular radiological follow up to exclude recurrence. aCPPs do not have established treatment guidelines in view of the relative rarity. Recurrent and residual tumours are generally treated with gross resection with adjuvant chemotherapy. CPC treatment is typically treated with maximal safe resection with adjuvant chemotherapy. Radiotherapy is generally only considered in older patients more than three years old in view of the neurocognitive and developmental complications in the younger population.

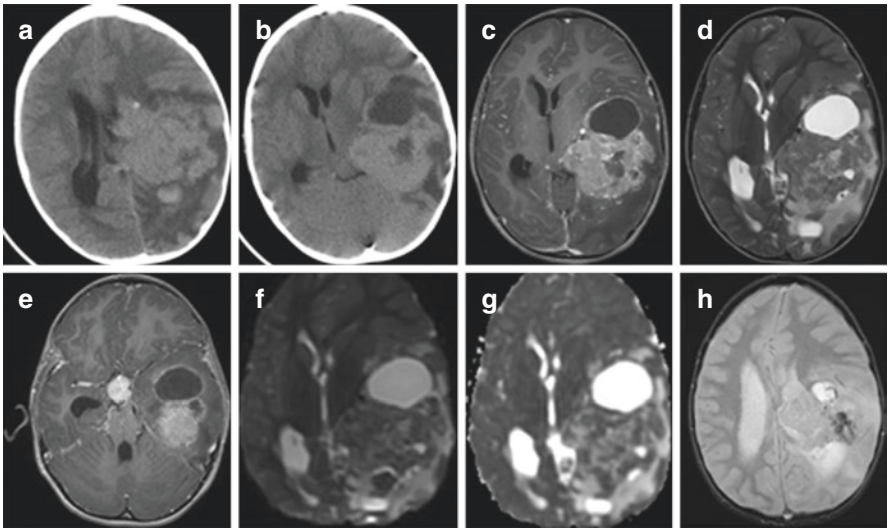

Fig. 24.5 Neuroimaging of Choroid Plexus Carcinoma. (Patient example from our own institution, Neurosurgical Service, KK Women's and Children's Hospital). Large lesion arising from the choroid plexus of the left lateral ventricle with lobulated appearance, cystic changes, and internal calcification with brain invasion. There is also suggestion of dissemination into the suprasellar cistern and hydrocephalus. (**a** and **b**): Axial CT image at the level of ventricular atrium and 3rd ventricle; (**c**) Axial T1W + C image at the level of the 3rd ventricle; (**d**) Axial T2W image; (**e**) T1W + C image at the level of suprasellar cistern; (**f**) Axial DWI; (**g**) Axial ADC image; (**h**) Axial GRE image. (*CT: computed tomography; T1W + C: T1 weighted image with contrast; DWI: diffusion weighted image; ADC: apparent diffusion coefficient; GRE: gradient echo*)

Table 24.6 Differential diagnosis of Choroid Plexus Tumours. Summary of differential diagnoses for choroid plexus tumours based on radiological findings in the paediatric and adult populations

Radiological differential diagnoses of choroid plexus tumours
Paediatric population
• Supratentorial
Other choroid plexus tumours: papilloma, atypical papilloma, carcinoma
Choroid plexus hyperplasia: bilateral and diffusely enlarging
• Infratentorial
Medulloblastoma
Atypical teratoid/rhabdoid tumour
Ependymoma
Adult population
Choroid plexus xanthogranuloma: bilateral multiloculated cyst within enhancing choroid plexus glomus in middle to elderly patients
Choroid plexus metastasis

According to the Head Start protocol [67], which included children under 10 years old with CPC, 3- and 5- year progression free survivals are 58% and 38% and overall survivals are 83% and 62%. These patients were treated with maximal safe resection and subsequent intensive induction chemotherapy. A relook surgery

was performed if there were any residual tumour left at this point. Patient then underwent consolidation with myeloablative chemotherapy and autologous haematopoietic cell rescue. Craniospinal irradiation is delivered only for patients older than six years and has evidence of residual tumour after induction chemotherapy. This protocol potentially produces long term remission with avoidance of radiation therapy.

24.4.8.1 Surveillance

There are no clear guidelines for the surveillance of non-surgically managed choroid plexus tumours. In our institution, small lesions that are non-obstructive of the CSF pathways, that do not demonstrate features suggestive of an aCPP or CPC, are routinely monitored with regular clinical monitoring and annual neuroimaging. Progressive ventriculomegaly, increase in tumour size, and change in tumour characteristics that are suggestive of aCPP and CPC are some indications for intervention.

24.4.8.2 Surgery

Surgery for choroid plexus tumours can be challenging due to its vascular nature and the amount of blood loss that can be incurred intraoperatively. This is especially the case in CPCs. A surgical strategy of early identification of vascular supply and coagulation of tumour surface helps to mitigate this risk [70]. Gross total resection in CPCs confers survival benefit with 2-year survival of up to 72% and 5-year survival of up to 65% [68].

These tumours often affect the very young, with corresponding low total blood volumes. Reports of massive intraoperative blood loss of 182% of estimated blood volume [68] and postoperative death due to metabolic complications from intraoperative blood loss [67] have been made. Various strategies such as preoperative embolization of the anterior and posterior choroidal arteries [57, 71] in choroid plexus tumours and neoadjuvant chemotherapy for CPCs have been attempted, in addition to aggressive replacement of blood volume, and it has been shown to reduce intraoperative blood loss and increase the extent of resection. Re-look surgery in CPCs can be considered, either early, after the patient recovered from the first surgery for further resection, for residual tumour after completion of induction chemotherapy, or after demonstrating radiological progression of residual tumour. There is limited literature comparing each option.

24.4.8.3 Preoperative Embolization

Preoperative embolization has been used to augment the resection as previously described in the chapter. This technique is purported to improved resection and reduced intraoperative blood loss [71], however, other authors have mentioned that

this is not within their treatment protocol due to the risk of complications [65]. Nevertheless, this option can be considered when encountering a choroid plexus tumour that is likely a carcinoma, especially when the patient is being treated in an experienced high volume neurointerventional centre.

24.4.8.4 Chemotherapy and Radiotherapy

As described previously, neoadjuvant chemotherapy has been attempted to improve extent of resection and reduce blood loss. This is done with a regime of 2 to 5 cycles of ICE (ifosfamide, carboplatin, etoposide) [68, 70]. With regards to adjuvant chemotherapy, the Head Start protocol [67] involves an induction therapy of intravenous vincristine, cisplatin, cyclophosphamide, and etoposide, with or without high dose methotrexate, or oral etoposide and temozolomide, depending on the regimen. Consolidation therapy consists of carboplatin, thiotepa and etoposide followed by autologous haematopoietic cell rescue. The Comprehensive Cancer Centre-Central Nervous System Tumours Unit (CCC-CNS) uses a combination of either vincristine or ifosfamide and cisplatin or carboplatin [68].

24.4.9 Radiation Therapy

At the time of this writing, adjuvant radiation therapy is controversial in the treatment of CPCs. CCC-CNS gives craniospinal irradiation only for patients above 3 years old [68] while the Head Start protocol has a cut off age of 6 years old [67]. Adjuvant radiation therapy has been used differently with multiple institutional practice published and no clear consensus or guidelines. For institutions that advocate radiation, there is a disparity with regards to the age cut-off of patients included for this treatment (3 years old by CCC-CNS [68]; 6 years old by Head Start [67]). Other authors have contested even the use of adjuvant radiation claiming that there is no survival benefit with adjuvant radiation therapy regardless of extent of resection. There is also a less aggressive phenotype of CPC described in tumours with low total structural variations and absence of TP53 dysfunction which confers a 5-year survival of 82% without radiation therapy [72].

24.5 Desmoplastic Infantile Astrocytoma and Ganglioglioma

24.5.1 Definition

Desmoplastic infantile tumours (DIT) are benign glioneuronal tumours composed of a prominent desmoplastic stroma with a neuroepithelial population. They include desmoplastic infantile astrocytoma and ganglioglioma (DIA and DIG). DIA

involves neoplastic astrocytes while DIG involves astrocytes together with a variable mature neuronal component, sometimes with aggregates of poorly differentiated cells [73]. There is an even more rare form of DITs that presents at above the age of 5 [74]. These tumours will not be addressed within this chapter.

24.5.2 Epidemiology

DIA and DIGs are rare paediatric neoplasms, representing 0.3% [74] and 0.4% [75] of brain tumours, respectively. They occur supratentorially in the vast majority of the cases, involving the cortical regions [76]. This is most common in the frontal and parietal regions with temporal and occipital being less likely. Rarely, suprasellar DIA with leptomeningeal have been reported [77, 78]. Based on large institutional series, DIGs affect boys more than girls and diagnosis is more commonly obtained in the first 2 years, typically less than 18 months [75], although there have been reports of older children and young adults with the diagnosis [73]. Unlike DIGs, DIAs affects both genders equally [74].

24.5.3 Histological and Molecular Classification

DIA and DIG correspond to WHO grade 1 [2]. Macroscopically, they are large tumours, often involving more than one lobe, containing large cyst fluid and a solid component superficially and involves leptomeninges and superficial cortex primarily. Histologically, DIA/DIGs have spindle cells in a desmoplastic stroma, large astrocytes with glassy cytoplasm and a variable amount of undifferentiated neuronal or ganglion cells. The presence of ganglion cell component within the tumour distinguishes DIG from DIA [79, 80]. Despite the suggestion of histologically aggressive features such as mitotic figures, cellular pleomorphism and atypia, outcome remains good with good surgical resection [80–83].

24.5.4 Natural History and Prognosis

DIA/DIG demonstrate good long-term prognosis with regards to survival, recurrence, and progression of residual tumour, especially with gross total resection. CSF seeding and malignant transformation [83–86] are noted to be rare and only described in isolated reports.

24.5.5 Clinical Presentation and Radiological Features

DIA and DIG presents with clinical features suggestive of raised intracranial pressure in a subacute fashion. It has been reported that these patients tend to present slightly quicker in the infant population, around 3 to 6 months duration, in contrast with the 6 to 9 months duration in the older child [81]. Imaging of DIA and DIGs usually reveal a large heterogeneous solid-cystic lesion, peripherally located in the supratentorial compartment. The solid component is commonly dural-based, while the cystic component is typically seen in the deeper portion of the tumour [25, 87, 88] (Table 24.7 and Fig. 24.6).

24.5.6 Management

Surgery is the mainstay of treatment with chemotherapeutics reserved for recurrent or residual tumours demonstrating growth when surgery is not feasible [80, 89]. Radiation has not been shown to be clearly beneficial in these group of patients [77]. Surveillance is generally not recommended as most of these tumours present at a large size with significant mass effect. Gross total resection with surgery demonstrates long term survival without recurrence [87, 90] in both DIA and DIG, at median follow up of 15.1 years [79] and 8.7 years [75] respectively. Residual tumour has been noted to either remain stable or demonstrate slow progression. Isolated reports of tumour regression have been noted. Resection of DIG may not be straightforward due to its vascularity, lack of a clear brain-tumour interface and the tendency to infiltrate eloquent regions. Staged resection is one of the surgical strategies proposed [75]. Chemotherapy are usually reserved for cases where there is disease progression, and surgery is not a safe option. Radiotherapy is a last resort option for chemotherapy-resistant patients [88].

Table 24.7 Differential diagnosis of DIA and DIG. Summary of differential diagnoses for DIA and DIG based on radiological findings in the paediatric and adult populations

Radiological differential diagnosis of DIA and DIG
Infant
Teratoma: much more heterogeneous than DIA/DIG and may extend extracranially
Primitive neuroectodermal tumour
Both lesions are usually not as large as DIA/DIG and their solid component does not abut the dura
Older children and adults
RELA-fusion ependymoma: often contains calcifications and internal haemorrhage

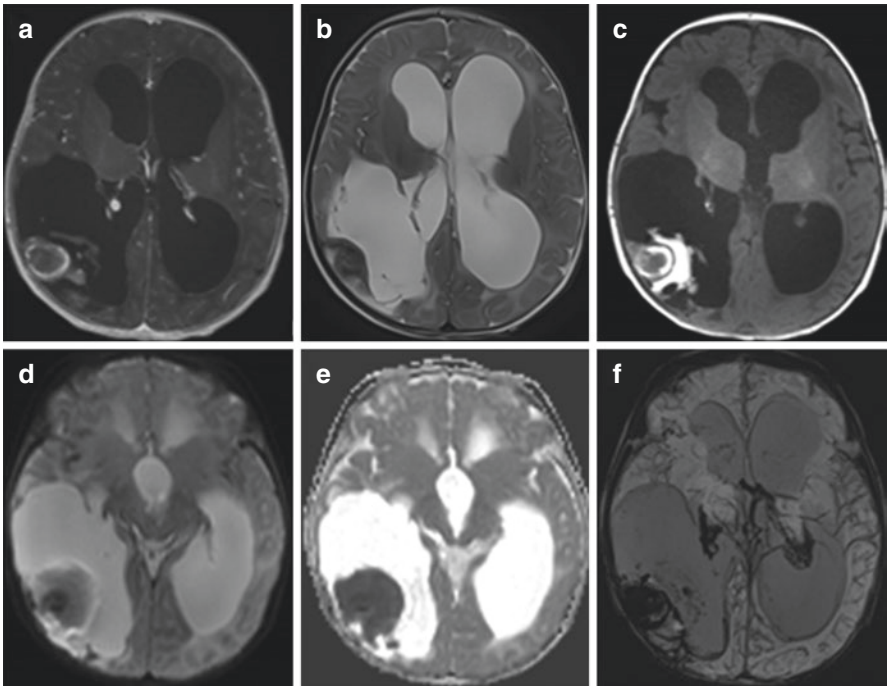

Fig. 24.6 Neuroimaging of Desmoplastic Infantile Astrocytoma. (Patient example from our institution, Neurosurgical Service, KK Women's and Children's Hospital). Large, solid-cystic lesion with the solid component based on the parietal dura and cystic component deep and communicating with the right lateral ventricle. The lesion demonstrates a patchy enhancement of the solid component, partial cystic wall enhancement, and internal haemorrhage. There is no restricted diffusion. (**a**) Axial T1W + C image; (**b**) Axial T2W image; (**c**) Axial T1W image; (**d**) Axial DWI; (**e**) Axial ADC image; (**f**) Axial SWI. (*T1W + C: T1 weighted image with contrast; DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient; SWI: susceptibility weighted imaging*)

24.5.7 Controversies and Current Advances

BRAF V600E [91–94] and V600D mutations [95–97], MYCN amplifications and EGFR amplifications [98] have been found in DIG/DIA. BRAF mutations have been reported by several case series to be present in up to 50% of DIG/DIA. Although it does not seem to directly correlate with prognosis, it represents a potential target for targeted therapy for recurrent or non-resectable tumours and deserves further investigating [96, 99].

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Chapter 25
Spinal Tumors

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25.1 Introduction

Spinal axis tumors (SAT) comprise 0.5–5% of all central nervous system (CNS) neoplasms in children, and are less frequent than in adults [1, 2]. SATs are typically classified based on their location relative to the dura mater, as intradural or extradural. Intradural SATs are further classified as intramedullary or extramedullary [3]. In children, intradural tumors occur in a similar or higher frequency in comparison to extradural tumors, in contrast to adults, in whom two-thirds are extradural [4, 5], but the overall incidence of spinal tumors is lower in children [6]. In terms of histology, astrocytoma and ependymoma are the most common histological types, accounting for 60% and 15–30% of all primary intramedullary SATs respectively [1]. Metastatic spinal cord lesions manifest in approximately 3% of children with a systematic malignancy [7]. Desousa and colleagues, in their series, observed that, at the time of diagnosis, 75% of children with SAT were aged 10 years or under, and 50% were under five years [4]. The mean age of patients is approximately 8 years at diagnosis [5]. SATs have been associated with genetic syndromes, including types 1 and 2 neurofibromatosis (NF), tuberous sclerosis, Turcot's syndrome and others, which should be looked for when a child is diagnosed with a SAT, and *vice versa*. In particular, patients with spinal hemangioblastoma should be assessed for Von Hippel-Lindau (VHL) disease [8].

The majority of SATs in children (70%) are located at the cervical or thoracic level, or involve both of these levels [5]. Holocord extension is observed in 10% of children with intramedullary SATs. Males and females are affected in the same

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frequency, without sex predilection in any specific tumor [9]. New techniques in microscopic neurosurgery and overall tumor management have improved the quality of life and survival rates of children with SATs [8].

25.2 Clinical Features

The majority of SATs show slow progression, and symptoms may occur only after months, or even years. Symptoms are initially usually atypical and mild, with the result that the final diagnosis will often be confirmed with a delay of 6 to 9 months after the onset of symptoms [8, 9]. An exception are high-grade SATs, which develop severe myelopathy, with a rapidly deteriorating clinical picture [2, 8, 10]. The most common symptoms and signs associated with SATs in children include back pain (40–60%), weakness and motor deficits (50–80%), urinary dysfunction (30%), alterations in deep tendon reflexes (55–80%), sensory deficits (40%), and gait disturbance in the case of intramedullary tumors (60–80%) [2, 4, 8–10]. Urinary and gait disturbances will usually occur after the onset of motor and sensory impairment, and are suggestive of SAT extension and increased severity [10]. Bladder and bowel incontinence may be difficult to diagnosis in infants. A palpable mass in the spinal region may be present in approximately 10% of children with SAT [5], and spinal deformities, such as kyphosis or scoliosis, in 5%; scoliosis may occur in one-third of children with intramedullary tumors [5, 10]. Asymptomatic presentation is not uncommon, and approximately 8% of children with SAT will be diagnosed during examination for other diseases [5]. The tumor level (cervical, thoracic, lumbar) is probably not associated with the duration of the symptoms [2]. A high level of suspicion for SAT is indicated when a child complains of progressively worsening back pain with no recent history of trauma or intense athletic activity, especially when the pain is more intense during the night or wakes the child [8]. In around 10% of children with SAT, the neoplasm is part of a genetic syndrome, and SAT should therefore be added to the differential diagnosis of back pain in this category of patients [5].

25.2.1 Hydrocephalus in Patients with Primary SATs

The onset of hydrocephalus (HC) in patients with a spinal neoplasm is rare, although in one case series, the frequency was 15% [11]. The prevalence of HC with SAT is higher in children than in adults, and it is estimated that 90% of these cases concern children. The frequency appears to be higher in children aged under six years, with no sex predilection. In children with primary intradural SAT and HC the neoplasm is usually intramedullary (90%), and located in the cervical (30%), thoracic (16%), or cervicothoracic region (26%). In most of these cases, the tumor type is astrocytoma (about 60%), followed by ependymoma (10%), and a high grade astrocytoma

is a possible risk factor for the occurrence of HC [12]. The pathophysiology of HC in such cases is difficult to interpret, although subarachnoid blockage of cerebrospinal fluid (CSF) pathways from disseminated tumor cells or neoplastic inflammation of the leptomeninges appears to be the mechanism. Other factors may be brain pulsation (the hydrodynamic theory) and alterations in CSF viscosity [12–14]. The presentation of HC following the diagnosis of a malignant SAT is related to intracranial dissemination, and is associated with higher mortality (30%) [12]. As excision of the tumor resolves the HC in only 25% of patients, a shunt will need to be placed in most patients to reduce intracranial pressure [15].

25.3 Diagnosis-Imaging

Magnetic resonance imaging (MRI) is the examination of choice for diagnosis of SATs [16]. The appearance on MRI may be suggestive of tumor histological type, and imaging features are related to the tumor type and grade. Intramedullary lesions usually show cord expansion on MR imaging, and cysts or syringomyelia may be observed. In general, homogeneous enhancement of a spinal neoplasm is observed in lower grade tumors, while ependymomas are enhanced more rapidly and intensively than astrocytomas [2, 17, 18]. Ependymomas more often appear with sharp borders, while astrocytomas are infiltrative [8]. As Baleriaux and colleagues point out, extended perifocal edema should be differentiated from malignant infiltration [18].

Other common imaging features in ependymomas are the “cap sign” and a bleeding tendency (high signal in T-1 weighted images). Cap sign is a hypointense rim in T-2 weighted images, and it represents a collection of hemosiderin. It is usually observed in tumor poles. Tumor type may also be implied from the level of the lesion in the spine, with astrocytomas being located more frequently in the thoracic region and ependymomas in the cervical region.

A common imaging feature observed in primary SATs, and mainly in ependymomas, is the presence of cysts located inside the tumor (intratumoral cysts) or beside the tumor (polar-satellite cysts) [1, 18]. The content of intratumoral cysts has a high protein concentration, in contrast to satellite cysts, the content of which is similar to CSF, and thus gives a similar signal (low signal in T1-weighted sequences and high signal in T2-weighted sequences) [18].

The presence of a syrinx is another feature observed in SATs. The term hydromyelia refers to a cavity, containing CSF, located in the central canal. The wall of this cavity is covered with ependymal cells. Syringomyelia refers to a parenchymatic cavity that occurs as a result of ependymal wall dissection and leak of CSF from the central canal into the spinal parenchyma, the wall of which is thus not covered by ependymal cells [19, 20]. In everyday clinical practice and imaging, it is challenging to distinguish between these two entities, which in many cases coexist. The spinal syrinx may therefore simply be called “hydrosyringomyelia” or “syringohydromyelia”. On MRI, these lesions may display a cystic component with a high

signal in T2-weighted images (CSF component), and low signal in T1-weighted images. The presence of a syrinx is not pathognomonic of SATs, and most syringes are congenital, and associated with various syndromes (e.g., type I or II Chiari, Dandy-Walker malformation, etc.). They may also occur as a result of a trauma or an inflammatory process. Whenever a syrinx is discovered, however, contrast enhancement imaging should be conducted to rule out possible spinal neoplasia [17, 19, 20].

Approximately 95% of intramedullary tumors are primary, and metastatic lesions are rare. On MRI, intramedullary metastatic lesions manifest as eccentrically located nodules with multiple patterns of enhancement. In a spinal neoplasm, the presence of an enhancement rim ("rim sign") and of ill-defined enhancement in the tumor margin ("flame sign") are nearly diagnostic of a metastatic lesion [17, 18]. Metastatic epidural lesions of the spine in children are predominantly from Ewing's sarcoma (ES) and neuroblastoma, and they can cause significant compression in the spinal cord [21].

Computed tomography (CT) is rarely utilized in the diagnosis of childhood SATs, because of the high dose of radiation used in this imaging procedure, and the limited ability of CT to illustrate CNS structures. Spinal CT is usually performed in children only as an emergency (when the patient develops severe myelopathy). Typical CT findings of SATs are vertebral erosion, widening of the spinal canal and calcifications [10, 16]. CT myelography is rarely used for children with spinal tumors.

Apart from SATs, spinal lesions can occur in children as a part of an inflammatory disease or of other non-neoplastic conditions. Bacterial and viral inflammations, transverse myelitis, congenital malformations (e.g., meningomyelocoele, diastematomyelia), and vascular malformations, such as arteriovenous malformations (AVM) and cavernomas should be included in the differential diagnosis.

An imaging feature that may help in their differential diagnosis from tumors is that inflammatory processes show no significant alterations in spinal cord dimensions at the site of the lesion [8].

25.4 Differential Diagnosis

25.4.1 Intradural Intramedullary Tumors

25.4.1.1 Astrocytoma

In children, astrocytomas comprise 60% of all intramedullary SATs, making them the most common primary spinal neoplasia. They are intradural,intramedullary tumors that originate from malignant transformation of astrocytes, and are thus neoplasms of CNS glia [8, 22]. According to the World Health Organization (WHO), astrocytomas are classified as low grade (grades I, II) and high grade (grades III, IV). Alternative terms for the astrocytoma gradings are: pilocytic astrocytoma for

grade I, diffuse or fibrillary astrocytoma for grade II, anaplastic astrocytoma for grade III, and glioblastoma (GBM) for grade IV (previously called glioblastoma-multiforme). Approximately 80% of spinal astrocytomas are low grade, with grade II being the predominant type (50%). High-grade spinal astrocytomas comprise 10–20%, and are related to poor survival, although cases with better prognosis have been described (Fig. 25.1) [22, 23]. An essential aspect of high-grade spinal astrocytomas is the multiple degrees of malignancy that are often observed within the same tumor. In such cases, the tumor grading can be challenging, and some pathologists consider this type to be intermediate grade II-III astrocytomas [22]. High-grade astrocytomas can develop as a result of malignant transformation of a previously low-grade astrocytoma, which requires a prolonged latent phase [24, 25].

The mean age of children with spinal astrocytoma is 5 years, and there is no sex predilection [9]. The cervical spinal cord is predominantly affected, followed by the thoracic spine, or both these levels may be affected [26, 27]. Early onset symptoms in low-grade spinal neoplasms include worsening back pain at rest, and sensory and motor deficit. Myelopathy symptoms, such as urinary and gait disturbance, may present throughout the disease progress, and require urgent treatment [2, 8]. In high-grade astrocytomas, the mean duration from onset of symptoms to diagnosis is

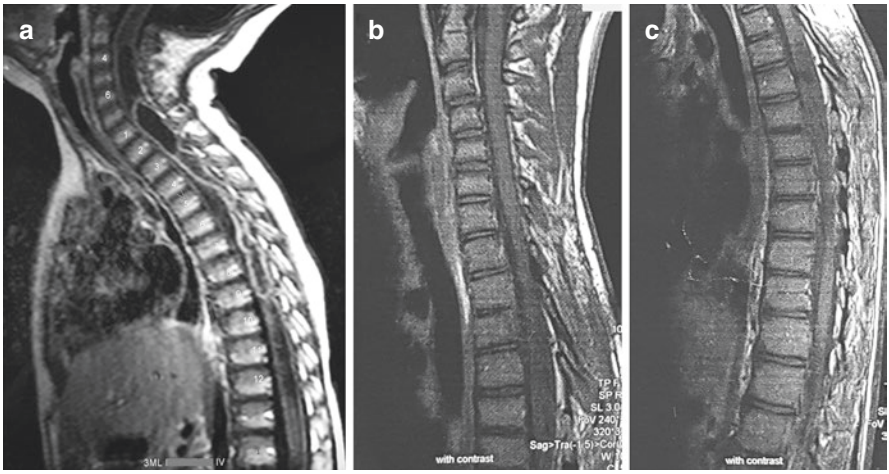


Fig. 25.1 A previous healthy 14-month-old boy presented with gait imbalance. MRI of the spinal cord revealed an enhancing intramedullary mass extending from C2 to T12 most probably a diffuse astrocytoma (**a**). The patient underwent a two-stage surgical procedure. First, laminotomy extending from C3 to T4 was performed, followed by tumor resection; then, laminotomy from T5 to T11 and further tumor removal. During both procedures, because of the semi-solid nature of the lesion, gross macroscopic total excision was conducted via a 2.5 cm midline myelotomy in the exposed length of the spinal cord each time. Histopathological examination of the lesion was consisted with high-grade glioma. The patient had an uneventful postoperative course. On follow-up examination 14 years later, no tumor recurrence was observed and the patient was in excellent neurological status, with complete sphincter control (**b, c**)

approximately 7 weeks, significantly shorter than for lower grades, due to the infiltrative nature and rapid growth [2, 8, 27].

The classification of astrocytoma according to the WHO is defined by the histological features of the tumor. The presence of cystic areas and Rosenthal-fibers is suggestive of WHO grade I (pilocytic astrocytoma), while mild cellular atypia without further malignancy findings is observed in WHO grade II (diffuse astrocytoma). WHO grade III (anaplastic astrocytoma) is characterized by features such as increased cellular atypia and the presence of anaplastic cells. Finally, the appearance of multiple anaplastic cells, cellular necrosis, and microvascular proliferation characterize WHO grade IV (GBM) [28, 29]. In terms of immunochemistry, expression of glial-fibrillary-acidic-protein (GFAP) is probably related to the grade of astrocytoma, with lower grades having greater expression [30].

In MRI imaging, astrocytomas appear as eccentrically located lesions with ill-defined borders. In T1-weighted images, they are iso- to hypointense, and in T2 weighted images they are usually hyperintense. The pattern of enhancement is usually heterogeneous. Enhancement of the solid nodule is observed in pilocytic astrocytomas, and areas of cystic degeneration are not uncommon. Other imaging features, such as cysts and syringes may be observed, but hemorrhage is rare in low-grade astrocytomas [3, 8, 17]. Diffusion tensor imaging (DTI) can demonstrate the infiltration of neoplastic cells into spinal tracts in high-grade astrocytomas, which is useful in the pre-operative planning [31]. In general, the ability of MRI to determine the grade is limited in spinal astrocytomas. The presence of leptomeningeal spread is a typical feature of malignancy, and is a risk factor for the onset of HC [8, 12, 32].

Surgery is the first-line treatment for spinal astrocytomas, but as they have ill-defined borders, with a tendency for microscopic infiltration, the macroscopic and microscopic borders of the tumor may not correspond. Gross total resection (GTR) of the tumor is rarely achieved, and in about 50% of the patients, tumor recurrence should be expected, even after GTR [22, 26]. In the series of Nicole Townsend and colleagues, the GTR rate was 10%, and in the remainder of cases, subtotal resection (STR) or biopsy of the tumor was achieved. As is to be expected, GTR is associated with a higher risk of postoperative neurological impairment than STR. Current data on the efficacy of chemotherapy and radiotherapy in children with spinal astrocytoma are limited. For low-grade astrocytoma, adjuvant therapy with carboplatin, vincristine, procarbazine, and cyclophosphamide may be effective, but its use is probably limited for high-grade astrocytoma. Temozolomide, a chemotherapeutic agent used for brain GBM may also be utilized for spinal GBM [9, 26].

The prognosis of children with spinal astrocytoma is related to the tumor grade. Overall survival is poor in high-grade astrocytoma, being less than six months [8]. In the series of in Townsend and colleagues, the mortality of intramedullary astrocytoma was 40%, with a progressive four-years tumor-free survival of 60%. The mortality in children with low-grade spinal astrocytoma is 25%. The extent of tumor resection and duration of radiation treatment are not associated with survival in high-grade spinal astrocytoma [26, 33]. These reports illustrate the advantage of

STR over GTR for high-grade astrocytoma, in terms of mortality and post-operative morbidity and quality of life [9, 26, 33].

25.4.1.2 Ependymoma

Ependymoma is the second most common intramedullary tumor in children, and childhood ependymoma comprises 13–30% of all CNS ependymomas. Spinal ependymomas arise from cells of the ependyma that covers the central canal [34, 35]. Type 2 NF is related to spinal ependymoma [34–36]. Children presenting with spinal ependymoma are usually older than children with astrocytoma, between 12–14 years [8, 9, 28, 34, 36]. Ependymomas are considered intramedullary tumors, with the exception of myxopapillary ependymoma, which typically has an intradural-extramedullary location. Extra-CNS ependymomas have also been described, with the most common location being the sacrococcygeal region [37].

WHO classifies ependymomas into three grades of malignancy, but data on the prognostic value of grading these tumors are conflicting [38, 39]. Macroscopically, ependymomas appear as soft, usually well-defined, encapsulated tumors, with a central location in the spinal cord, as they arise from cells of the central canal. Intramedullary ependymomas are usually located in the cervical spine, while myxopapillary ependymomas are located in the filum-terminale/conus-medullaris area. The typical microscopic features of ependymomas are ependymal rosettes and perivascular pseudo-rosettes [8]. Anaplastic features, such as increased mitosis, necrosis, and microvascular proliferation are suggestive of grade III ependymoma [17]. Recently, DNA methylation status has been considered as critical for the pathogenesis of ependymoma.

Initial clinical manifestations of spinal ependymoma include vertebral-back pain in 50% of the children, weakness and gait difficulties (30%), and sensory disturbance (20%), as described in the series of Lonjon and colleagues. Motor dysfunction, kyphosis/scoliosis, and bladder dysfunction were progressively developed up until diagnosis in 80%, 25%, and 10%, respectively, of the children with spinal ependymoma. One child had a cyst that extended into the fourth ventricle and obstructed CSF flow, and as a result, this child developed hydrocephalus. The duration from early-onset symptoms to diagnosis in this series was from 5 to 84 months. The disease progress develops slowly in low-grade ependymomas, while in high-grade tumors, the progress is faster [36].

On MRI imaging, ependymomas appear as well-defined lesion with a central location in the spinal cord. The signal of the lesion is iso- to hypointense in T1-weighted images and hyperintense in T2-weighted images. They show symmetrical enhancement, more homogeneous than astrocytomas [10]. They tend to show hemorrhagic areas that are hyperintense in T1-weighted images, and deposits of hemosiderin, the “cap-sign”, may be observed in the tumor poles as a hypointense ring in T2-weighted images. Rostral cysts are a common imaging feature, and syrinx formation may be present in 65% [17].

GTR is considered the first-line treatment for spinal ependymomas and should be attempted in all patients, preserving normal spinal parenchyma. Intraoperative monitoring is a useful tool for the surgeon to assess the extent of allowable tumor resection. STR or simple biopsy is usually performed for tumors with ill-defined borders or in those cases where GTR is considered to be of high risk. In the case of anaplastic ependymoma, the main aim of treatment is spinal cord decompression, and the extent of resection should be decided on with preservation of the patient's post-operative neurological status in mind [8, 9]. GTR is not always achieved, and in many cases, the extent of resection is subtotal, or just a biopsy sample. In the series of Kutluk and colleagues the rate of GTR for childhood spinal ependymoma was approximately 50%, and in the series of Lonjon and colleagues, 70%, but their definition of GTR was different. The reported GTR rate for spinal ependymoma is significantly greater than for astrocytoma [9, 36].

Adjuvant radiotherapy and chemotherapy for spinal ependymoma are controversial. In general, radiation treatment for low-grade ependymomas after GTR is not recommended [36], and the efficacy of chemotherapy is questioned [9]. Prognostic factors for survival are the grade, the extent of resection and the child's age. The prognosis is more favorable in children aged under 3 years and over 10 years [36]. In adult ependymomas an increased risk has been reported of a second malignancy during the follow-up period [2], which should be considered possible in children, also.

25.4.1.3 Ganglioglioma

Gangliogliomas (GGs) are rare, representing 0.5–1% of all CNS neoplasms. Histologically they contain mixed populations of neoplastic ganglionic (neuronal) cells and glial cells, usually astrocytes [40]. Some authors have reported that spinal GGs are the second most common intramedullary SAT in children, comprising 15% of these cases [41, 42]. The mean age of patients with spinal GG is around six years at diagnosis, with most patients being under 19 years [43], and with no sex predilection. The cervical spinal cord is predominantly affected [2].

WHO classifies GGs into benign (grade I) and malignant, or anaplastic (grade III). Some authors have proposed an intermediate grade, based on histological features, but currently, criteria for grade II have yet to be officially recognized by WHO [44]. Anaplastic GGs (AGGs) (grade III) account for 4–5% of all GGs and are related to poor survival (approximately 29 months). AGGs occur mainly as de-novo lesions, although it is estimated that10% result from malignant transformation of a benign GG [45]. AGGs of the spinal cord are exceedingly rare, and only a handful of cases have been reported.

GGs of the spinal cord tend to show slow growth, with the duration of symptoms ranging from 1 month to 5 years. Due to this slow growth, they usually occupy many spinal levels, and holocord extension is more frequent than in other SATs [16, 42]. In the series of Lang and colleagues, approximately 80% of patients had back pain and radiculopathy, 10% only radiculopathy, 10% only weakness, and 3% had

pain and paresthesiae [43]. NF is not generally considered to be related to GG, although Sawin and colleagues described a case of spinal GG in a patient with type 2 NF [46].

The differential diagnosis of GGs from other glial tumors is challenging, and various criteria have been proposed to confirm GG [41]. Histologically, the neoplastic cells may express chromogranin and neuronic specific enolase, while the glial element may be positive for GFAP [41]. Anaplastic features are observed in grade III GGs, but differentiation from high-grade astrocytoma may be difficult, especially when the specimen is obtained from areas rich in glial component. In such a case, the presence of eosinophil granular bodies (EGB) and bi-nucleated synaptophysin ganglion cells is suggestive of AGG [47].

GTR is the first-line treatment for spinal GGs, and STR is only performed when the tumor borders cannot be distinguished from normal spinal parenchyma, in order to preserve neurological function. In the series of Lang and colleagues, GTR was performed in almost all cases, but they observed a higher recurrence in comparison to supratentorial GGs. Adjuvant chemotherapy and radiotherapy are not recommended for low-grade GGs after GTR. The possible role of adjuvant therapy is in tumor relapse, in patients with STR, or in patients with AGGs [2, 43]. The prognosis of patients with spinal GGs is probably less favorable than that of those with cerebral GGs. After tumor excision, the 5-year survival rate was 89% in the Lang's series, while the event-free survival was 50% for low-grade, and approximately 20% for high-grade spinal GGs [43].

25.4.1.4 Hemangioblastoma

Hemangioblastomas are benign (grade 1) tumors that are exceedingly rare in childhood, with an incidence of lower than 1/1,000,000. Hemangioblastoma is strongly associated with VHL disease, which is diagnosed in 65% of cases in children, or it can be sporadic. Epidemiological data on pediatric hemangioblastomas is provided by the series of Cheng and colleagues. They are most commonly located in the cerebellum (40%), followed by the spinal location (intramedullary, 30%). An association with VHL is observed in 75% of children with spinal hemangioblastoma. The mean age at presentation of spinal hemangioblastoma in children is approximately 12 years, and the cervical and thoracic spine are predominantly affected. The tumor is usually located in the dorsal spine, and thus the patients usually present sensory deficits. These tumors should be excised as masses, and GTR with excision of the mural nodule is the optimal method. Intraoperative bleeding can be fatal and preoperative embolization is recommended when the risk of bleeding is high. Stereotactic radiosurgery is an alternative method of treatment. The prognosis is usually favorable, but there is a risk of recurrence in the case of underlying VHL, and all the children should be monitored [8, 48].

25.4.2 Other Intramedullary Tumors

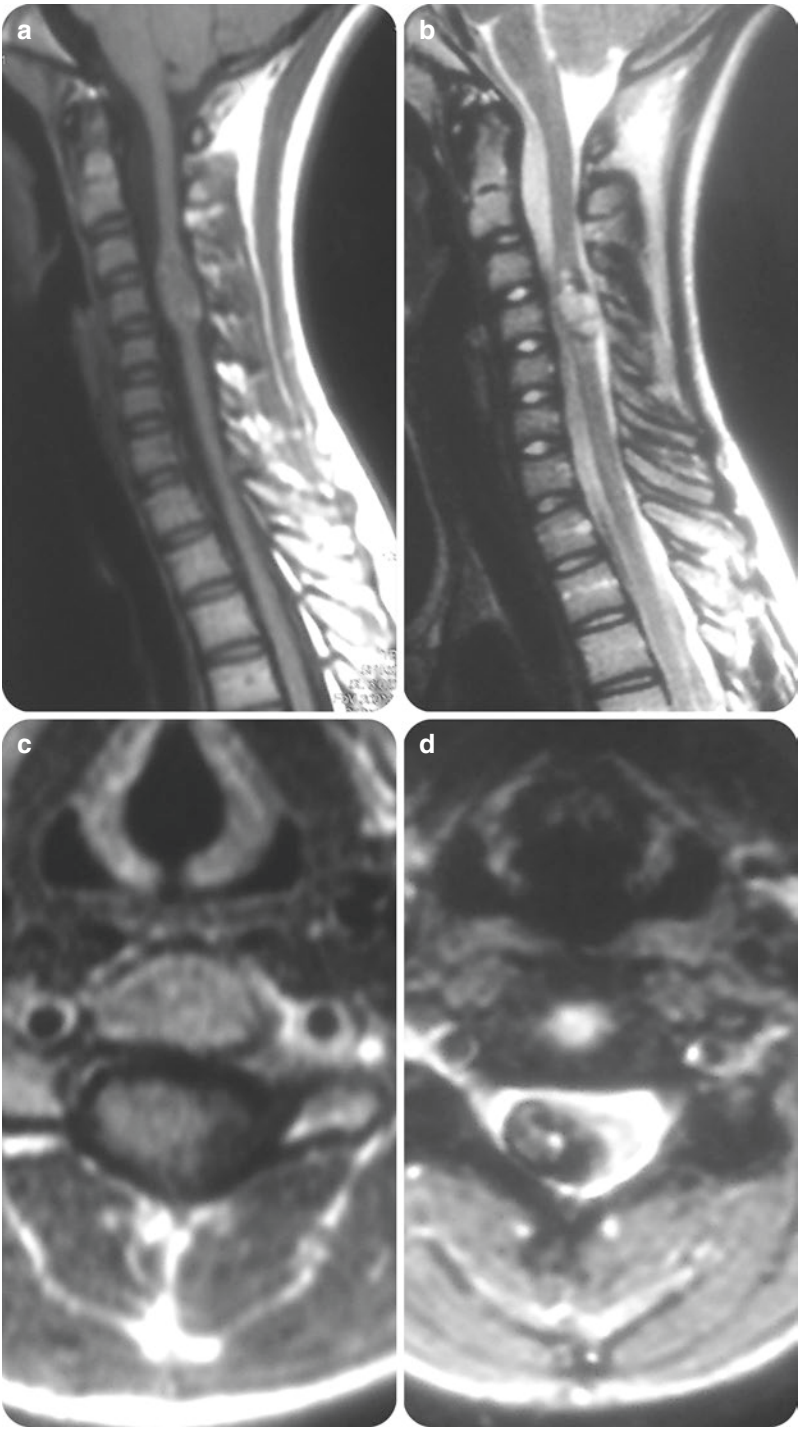
Spinal cord lipoma is a rare entity, and it is usually associated with spinal dysraphism. Nondysraphic cases have been also reported, but are exceedingly rare [49]. The thoracic spinal cord is the most common localization of lipomas. Usually there is no clear plane of cleavage between the lipoma and neural structures, and thus decompression with limited tumor resection is the goal of surgery, followed by long-term monitoring. Repeat surgical intervention may be needed if additional neurological dysfunction develops. Intramedullary cavernous angioma is a very rare malformation, especially in children. Hemorrhage may have devastating clinical consequences and surgical excision is the treatment of choice (Fig. 25.2).

25.5 Intradural Extramedullary Tumors

25.5.1 Dermoid and Epidermoid Tumors

In children, in contrast to adults, intradural extramedullary tumors comprise nearly 1/3 of all SAT tumors. Dermoid and epidermoid tumors are usually congenital, arising during neural tube formation, when the neuroectoderm does not become normally separated from the ectoderm. Epidermoids are cystic lesions lined by squamous epithelium, while dermoids are lined by squamous epithelium and other skin elements, such as hair follicles and glands. Currently, epidermoid and dermoid cysts tend to be classified as the same entity, because of their shared development mechanism, clinical features and management. These tumors may also be acquired, developing after spinal surgery from dropped skin elements. Dermoid tumors are most commonly located in the spinal cord (mainly intradural location), while epidermoids are usually intracranial. These tumors account for approximately 10% of all spinal tumors in children. The lumbosacral region is affected predominantly (90% of the cases), and spinal dysraphism is observed in most cases [1, 16]. These tumors may be asymptomatic or they may present with back pain and sensory deficits. Motor deficits, and urinary and gait disturbances are indications for surgical excision. The progression of symptoms is probably related to growth of the cyst from accumulation of keratin debris. In many cases, these tumors are accompanied by dermal sinuses, and thus the patients are at high risk of developing bacterial

Fig. 25.2 Intramedullary cavernous hemangioma in a 13-year-old girl with to right hemiparesis. Magnetic resonance imaging (MRI) shows a cervical intramedullary lesion resembling cavernous hemangioma (**a**. Sagittal T1, **b**. Sagittal T2, **c**. Axial T1 and **d**. Axial T2-weighted image). Laminectomy with gross-total resection was performed. Histological examination revealed a tumor of mixed pathology of cavernous hemangioma, arteriovenous malformation and capillary hemangioma, with immunohistochemical positivity for CD34, WT-1, GFAP. Postoperatively the patient showed improvement


a
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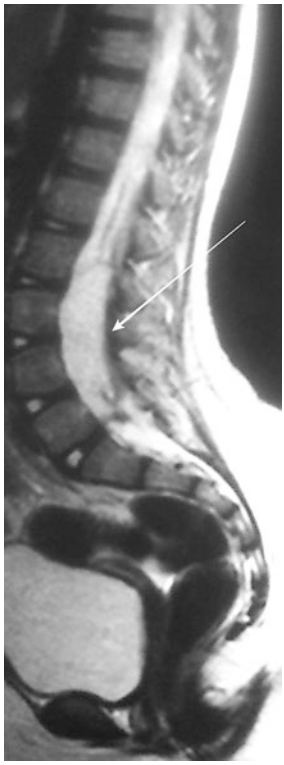

Fig. 25.3 Spinal dermoid cyst. Magnetic resonance imaging (MRI), sagittal T2-weighted image showing a dermoid cyst (arrow) extending from L2 to S1. A dermal sinus was also present. The lesion was totally excised

meningitis (Fig. 25.3) [50]. Dermal sinuses are another indication for surgery. GTR is the optimal treatment, and the recurrence rate is low [1, 16, 51].

25.5.2 Meningioma

Meningioma typically occurs in adults, and is exceedingly rare in childhood, with less than 100 cases reported to date [52]. Spinal meningioma in children is strongly associated with type 2 NF; in the series of Wang and colleagues, 40% of children with spinal meningioma were finally diagnosed with type 2 NF [53]. The mean age of the patients was 11 years, with a male predilection, and the mean symptom duration was 9.7 months [52]. The clinical manifestations resemble those of other spinal tumors, with back pain and progressive motor and sphincter dysfunction and sensory deficit. They are located predominantly in the cervical and thoracic spine and are typically intradural-extramedullary, but extradural location is not uncommon. Meningiomas exhibit homogeneous enhancement in contrast-MRI. GTR is the treatment of choice, even for ventrally located tumors [54]; if GTR cannot be performed, STR is associated with a 90% probability of tumor relapse [1, 53].

25.5.3 Schwannoma/Neurofibroma

Spinal schwannomas/neurofibromas in children constitute nearly 4% of all spinal tumors, and schwannomas are strongly associated with type 2 NF. Spinal schwannomas are well-defined and encapsulated lesions that are completely separated from the neural roots. They exert pressure on the sensory roots, but may be asymptomatic for many years, with symptoms mainly occuring in the 5th decade of life. In children, the mean age of patients with schwannoma is 16 years, with no sex predilection. They present initially with back pain, and as the tumor enlarges, myelopathy develops, with motor deficits and urinary/gait disturbances. Total excision of the tumor, with full preservation of neural roots, is the optimal treatment, although some authors suggest that neural root excision should be performed to reduce the recurrence rate. Adjuvant chemo/radiotherapy is utilized for recurrent tumors [1, 16, 55].

Neurofibromas are tumors containing schwann cells, fibroblasts, and mast cells. In contrast to schwannomas, they are not encapsulated, and they may encroach on the whole cross-section of the neural root [56]. These tumors are related to type 1 NF, and about 2% of patients with type 1 NF have spinal neurofibromas, often multiple. They are usually asymptomatic until adolescence, but they tend to erode the surrounding vertebrae, ending up with causing severe kyphosis/scoliosis. Surgical excision is performed only for large and symptomatic neurofibromas. GTR is practically impossible without root sacrifice, because of the lack of a clear excision plane. STR with imaging observation of tumor growth is an alternative treatment method [52, 53].

25.6 Atypical Teratoid Rhabdoid Tumors (AT/RT)

AT/RT is a relatively uncommon, highly malignant embryonal tumor of the CNS, which mainly affects children aged younger than 4 years. It is usually located in the cerebellum (60%) and supratentorial structures, and only a few cases of spinal location have been reported. Loss of function in the *SMARCB1* suppressor gene, located in the 22q11.23 chromosome has been detected in patients with AT/RT. Microscopically, various different cell populations are observed, including rhabdoid cells, epithelial cells of mesenchymal origin, and cells that resemble other embryonal neoplasms. The differential diagnosis from other, less malignant embryonal neoplasms can be challenging or even impossible. AT/RT is usually located intradural-extramedullary in the spinal cord, with longitudinal extension in the subdural space that may involve multiple spinal segments, and leptomeningeal infiltration is common. Hydrocephalus, usually due to intracranial dissemination, may be present, and AT/RT is the most common cause of hydrocephalus from extramedullary spinal tumors in children. At the time of AT/RT diagnosis, approximately 60% of the children will have metastatic lesions [12, 57, 58].

Tumor resection is attempted in almost all cases, to decompress the spine and to collect a biopsy sample. GTR is related to a longer progression-free survival, but no significant difference is observed in overall survival. Adjuvant chemotherapy and radiotherapy protocols are utilized, including high dose chemotherapy with thiotepa and craniospinal irradiation, but the prognosis of AT/RT is extremely poor, and mean survival is less than 20 months [56–58].

25.7 Primary Neuroectodermal Tumors (PNET)

PNETs represent a group of malignant tumors, histologically characterized by small, generally poorly differentiated cells with large nuclei and little cytoplasm. The t(11;22)(q24;q12) translocation is specific for the ES/pPNET tumor family. The term PNET was introduced to describe all non-medulloblastoma embryonal tumors, but it was removed from the 2016-WHO classification of CNS tumors. Spinal PNETs represent about 1% of all spinal tumors [59], and predominantly affect children and young adults, with a mean age at presentation of 20–25 years, and male predilection. They are usually located in the cauda equina, and they manifest with pain, paresthesiae and progressive myelopathy. On MRI, they appear with low signal in T1-weighted images and high signal in T2-weighted images, with little to no enhancement. GTR is achieved in approximately 35% of patients. Adjuvant chemo- and radiotherapy have been utilized, but their influence on overall survival is uncertain. The overall survival of patients with spinal PNET is not favorable, with an estimated mean survival of less than 2 years [59, 60].

25.8 Extradural Tumors

Extradural tumors comprise approximately one-third of SATs in children. They are classified into tumors of the epidural space and bone tumors of the spinal column. Various degrees of malignancy are observed in this tumor category. Common pediatric tumors of the spine include neuroblastoma, ES, osteoid osteoma (osteoblastoma), osteosarcoma, rhabdomyosarcoma, aneurysmal bone cyst (ABC), germ cell tumors, lymphomas, and leukemias. Metastatic lesions of the spine are usually located extradurally. The clinical manifestations of extradural neoplasms include back pain and radiculopathy initially, with myelopathy occuring later in the disease progress from compression of the spinal cord. Scoliosis is not uncommon, and is caused by the lytic effects of these neoplasms on the vertebrae. Many of these tumors are benign and slow-growing, with no significant symptoms, and they may be completely asymptomatic. MRI is utilized for the assessment of spinal cord compression, and CT is a useful tool for investigating the bone lesions caused by these neoplasms. The management varies, but in general, surgical intervention is performed for all tumors, benign or malignant, that produce pressure effects and

significantly affect the quality of life. In addition, surgery is applied in the case of malignant tumors, to prevent dissemination and to prolong overall and event-free survival. GTR should be attempted, when possible, because it is related to more favorable survival. Chemotherapy is of crucial significance in the treatment of leukemias and lymphomas affecting the spinal column. Chemotherapy and radiotherapy constitute additional measures to reduce the recurrence rate and prolong survival in malignant tumors [1, 16, 61].

25.9 Osteoid Osteoma/Osteoblastoma

Osteoid osteomas and osteoblastomas are usually benign tumors. They arise from osteoblasts and produce osteoid, and share similar histological features, their differences being in size, with osteoid osteomas being mainly less than 1 cm and osteoblastomas over 2 cm. Approximately 10% of these tumors are located in the spine, with osteoblastomas having a greater predilection for this site (30–40%). The cervical spine is predominantly affected. The mean age of patients is reported to be 13 years. Back pain, usually nocturnal, occurs in almost all symptomatic patients, alleviated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and about one fourth develop scoliosis. CT is sensitive in detecting these lesions, and radionuclide imaging is the most effective for visualizing osteoid osteoma. Indications for surgical removal are persistence of intense back pain despite NSAIDs administration, fast-growing tumor size, and, in osteoblastoma, suspicion of malignancy. Total resection is the optimal treatment, with fusion when large parts of the vertebrae need to be removed. The recurrence rate is approximately 10% after GTR and almost 100% after STR. The efficacy of adjuvant radiotherapy is questioned, with authors suggesting reoperation in the case of tumor recurrence [1, 16, 62, 63].

25.10 Neuroblastoma

Neuroblastomas (NB) account for 10% of childhood cancers and are the type of solid tumor most frequently located extracranially. This neoplasm arises from progenitor cells of the sympathetic CNS, and usually progenitors are found in the adrenal medulla (50% of cases) and the sympathetic chain (20–30% of cases). Spinal cord compression from neuroblastoma is not uncommon and is considered the most common cause of spinal compression as a pediatric emergency. The optimal treatment of neuroblastoma with spinal compression is complicated, and various different protocols have been developed.

The treatment algorithm is guided by the risk of tumor recurrence and the patient's neurological status. The recurrence risk is estimated using the International Neuroblastoma Staging System (INSS), which takes into consideration the patient's age, the histological features of the tumor, *N-myc* amplification and DNA ploidy,

giving a classification as low, intermediate, and high risk for recurrence. The preferred treatment in low risk cases is surgical resection, with chemotherapy in the case of recurrence. For the intermediate risk cases, the treatment protocol includes multiagent chemotherapy and surgical resection. The therapy in high risk neuroblastoma is multimodal and is performed in four stages, induction, consolidation, maintenance, and the stage of biologic agents. In the case of significant compression with neurological deficit, the decision for surgical decompression before chemotherapy depends on the degree of neurological impairment at the time of clinical evaluation. It should be noted that NB excision is associated with severe postoperative morbidity in patients with spinal cord compression, and the presence of severe neurological deficit is related to poor mean survival [64–66].

25.11 Aneurysmal Bone Cysts

Aneurysmal bone cysts (ABC) are benign blood-filled cavities that occur predominantly in children and young adults. They are considered non-neoplastic lesions and can be primary (70%), or secondary to other bone tumors (30%). Although benign, they tend to cause erosion of the surrounding bones. The spinal location accounts for 15% of all ABC cases in childhood, with the thoracic and cervical spine being mainly affected (95%). The mean age of children with spinal ABC is 11 years. Back pain due to bone erosion, pathological fracture in a vertebra and radiculopathy are common symptoms. Vertebral collapse is a common imaging feature. The mean duration from the onset of symptoms to diagnosis in children is usually about one year. When diagnosed, surgical removal is suggested, with total resection of the lesion, because remnants of the cyst may lead to tumor recurrence. The prognosis is very favorable after successful excision of the lesion [67, 68].

25.12 Ewing's Sarcoma

ES is composed of small round cells and is considered to be a malignant peripheral primitive neuroectodermal tumor (PNET). Its pathogenesis is strongly related to t (11,22) (q24, q12) translocation. The spinal cord is usually involved secondarily by ES, by metastasis from long bone. Primary spinal ES accounts for 10% of all ES. The mean age of presentation is 15–20 years, with a slight male predilection. The lumbosacral spine is most commonly affected, with location in the posterior elements. The optimal treatment is controversial, as many patients already have systematic disease at the time of presentation. Radiotherapy is utilized for local control of the disease. Tumor resection is performed in localized disease, but with a high recurrence rate, due to the adhesive nature of the neoplasm to the normal bone [69].

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Part V
Trauma

Chapter 26
Abusive Head Trauma

Georgios Alexiou, Georgios Kafritsas, and Neofytos Prodromou

26.1 Introduction

Abusive head trauma (AHT) or non accidental head trauma or shaken baby syndrome is a traumatic brain injury caused by abuse of infants or children. John Caffey, an American radiologist, reported in 1946 six children with fractures of the long bones, chronic subdural hematoma and additional, in two cases, retinal hemorrhages [1]. Approximately 30 years latter Caffey coined the term "whiplash shaken infant syndrome". This mechanism of rotational acceleration/deceleration explained why there were frequently no externally visible signs of injury and of the retinal hemorrhages. In 2009 the American Academy of Pediatrics recommended the use of the term AHT based on the understanding of pathologic mechanisms that apart from shaking may involve blunt impact or a combination of shaking and blunt impact [2]. AHT is the most common cause of fatal traumatic brain injuries in children younger than 2 years [3]. Incidence of AHT is reported to be 14–40/100,000 children under the age of 1 year [4]. The highest incidence of fatal AHT is found in male infants between 1 and 2 months of age [5]. The outcome varies from complete or partial recovery to serious brain injury and subsequent disability or even death.

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26.1.1 Risk Factors

The main attributes that indicate abuse of a child are usually related to the parents or the caregivers. If they present with a problematic behavior or an abusive history, as well as, low economic income, low educational level, low child's birth weight and maternal Native American race, the chances of abusive behaviors are high [6]. Also, if parents or the caregivers are not experienced with child's care provision or they are young and even single-parent families, the possibility increases. Most frequent the perpetrators are fathers and stepfathers between the ages of 18 and 44 years old [7]. AHT is mostly an immediate consequence of anger or impatience of the care provider to a crying child. It is common for a child to cry or scream for prolonged interval due to colic or feeding requirements. Other triggers include disobedience, domestic arguments, toilet training difficulties and feeding problems [8]. An important issue is that one third of infants with AHT had been seen by physicians after AHT and the diagnosis was not recognized. The missed diagnosis had as a consequence to experience medical complications the 40.7% of children, whereas some deaths could have been prevented [9].

26.2 Clinical Presentation

The most difficult part of abusive head injury is the diagnosis and constitutes a medical, forensic, and social challenge. Early diagnosis is important for ideal treatment. The majority of caregivers attempt to hide the cause of trauma and often report a fall from a heigh, fall from stairs or trauma inflicted by another child. Feldman et al. reported that all unintentional injuries were a result of motor vehicle accident or other documented major trauma [10]. Low height falls, in most of the cases cause minor injuries, thus if the child presents with more severe injuries this should raise suspicions. The estimated risk of death from falls under 1.5 m in vertical height in children under the age of 5 is <0.48 per 1 million per year [11]. The presenting symptoms can range from death, severe head injury, minor head trauma to unsuspected findings or other nonspecific symptoms. In about half of cases there is an acute presentation and common symptoms are those of intracranial hypertension, bulging fontanel, epilepsy, drowsiness, apneas, reduced muscle tone and shock. Brainstem injury resulting from flexion-extension movements can cause acute respiratory failure and brain edema that led almost always to death. Less common are fractures in long bones or ribs [5]. Furthermore, there might be nonspecific symptoms and signs, such as vomiting, apnea, poor feeding or swelling of the scalp. Kelly et al. after reviewing the records of 345 children, that were referred to a child protection team over a 20-year period, found that in children under 2 years of age features of particular interest for AHT were absence of history of trauma (90%), no evidence of head trauma (90%), complex skull fractures with intracranial injury (79%), subdural hemorrhage (89%) and hypoxic ischemic injury (97%) [12].

26.3 Physical and Laboratory Evaluation

At first, a detailed history of the injury circumstances should be obtained. Important questions are if any witnesses to the event were there, delay in requesting medical care and if the alleged event justifies the injuries [13]. Apart from that, clinicians should obtain past medical history and consider child's age, growth and developmental status. Assessments of child abuse involve a multidisciplinary approach. Regarding physical examination, a complete examination should be performed, and physicians should suspect AHT when there is an infant with bruises on the head or body and intra-oral lesions, mainly a torn labial frenum. Severe intracranial injury after a short fall is exceedingly rare. Detailed neurologic evaluation as well as laboratory testing with measurement of hepatic and pancreatic enzymes should ensue. Furthermore, in case of intracranial hematoma platelets and clotting mechanism evaluation should be performed. Glutaric aciduria type 1 (GA1) is a rare metabolic disorder caused by glutaryl-CoA-dehydrogenase enzyme deficiency. This disorder causes cerebral atrophy and expansion of CSF spaces, both of which predispose to subdural hematoma. In case of fractures the levels of vitamin D and parathyroid hormone should be evaluated to rule out rickets. DNA-based sequencing of *COL1A1* and *COL1A2* in case of suspected osteogenesis imperfecta should be performed [13]. Periorbital and eyelid ecchymosis or subconjunctival hemorrhage can be found. Fundoscopic examination is of paramount importance to evaluate the retina and rule out presence of hemorrhages, which can be found in up to 85% of cases [14].

26.4 Imaging Findings

The imaging and laboratory workup must rule out medical diseases that can mimic AHT [15]. Imaging is of paramount importance for the correct diagnosis of AHT, because in many patients there are no external marks of injury [16]. Furthermore, it is important to diagnose the injury as soon as possible for timely treatment and complications avoidance. However, no single injury is pathognomonic for AHT. Skeletal survey should be performed for fracture diagnosis. In children less than 3 years fractures from AHT are 100 times more common than from a metabolic disorder such as rickets and 20 times more common than osteogenesis imperfecta [17]. Multiple unexplained fractures in different stages of healing are highly specific for AHT. Although posterior rib fractures traditionally were considered highly specific for abuse, recent evidence found no association of rib fracture location and likelihood of abuse [18]. For an acutely ill child unenhanced CT is usually utilized. Brain and cervical, thoracic and lumbar MRI usually ensues when possible. If the child is in stable condition MRI is more appropriate than CT to investigate for some additional injuries that have been missed in first stage, like spine injuries. Imaging findings of unintentionally short falls usually are linear skull fracture, associated epidural hematomas, focal contusion, and seldom small focal

post-traumatic subarachnoid hemorrhage [15]. Furthermore, intraparenchymal hemorrhage and skull fractures can be equal observed in inflicted and noninflicted traumatic brain injury. Nevertheless, fractures tend to be complex in AHT [19]. Subdural hematoma (SDH), contusion and diffuse axonal injury may be seen in AHT. In a series of 66 children, younger than 36 months old, that presented with SDH, chronic or mixed acute and chronic SDH were detected only in AHT children. Of notice, no children with unintentionally injured had SDH [10]. Interhemispheric subdural hematoma is not specific for AHT [20]. The mechanism of acceleration/deceleration in AHT results in stretching and tearing of bridging cortical veins causing SDH. Choudhary et al. investigated by MR venography children diagnosed with AHT. Sixty-nine percent of children had compression of cortical veins and sinuses from subdural hemorrhage or edema. Direct trauma to the cortical bridging veins, described as lollipop sign, was found in 44% of cases [21]. Brain edema in AHT may be due to trauma or hypoxemia caused by apnea from brain-stem injury. Furthermore, findings suggesting previous injuries might be seen such as extra-axial hematomas [22].

Although cervical spine injuries have been considered as a rare event in AHT, recent MR studies revealed significant findings [23]. Infants, contrary to older children are much more likely to experience ligamentous injuries. These injuries do not usually produce instability and may be missed from CT. Injury to the nuchal, atlanto-occipital and atlanto-axial ligaments were demonstrated in 78% of children with AHT and in 46% of the children with accidental trauma. The incidence of spinal SDH in the AHT group was 66% compared to 2% among the accidentally injured group. A high correlation between occipitocervical ligamentous injuries with evidence of brain ischemia can be found in AHT [23].

26.5 Treatment

Physicians are required to report to child protective services any case with reasonable suspicion of AHT. At presentation supportive care, monitoring of vital signs and management of immediate complications are important. A child who does not cry or does not react normal to painful stimuli may suffer severe injury. Anticonvulsants should be started to prevent seizures, which are a very common complication. The treatment and surgical intervention of non-accidental head injury is the same like the injuries that occur by other type of mechanisms. For epidural and subdural hematomas craniotomy in infants is the same as for older children, but extra care should be given to minimize blood loss. In case of brain oedema a hinge-craniotomy technique is worthwhile given that decompressive craniectomy and subsequent cranioplasty is associated with increased complication rates [24].

26.6 Prognosis

Morbidity and mortality from an abusive head trauma vary. There can be mild mental retardation to severe cognitive abnormalities, motor and sensory disabilities, visual and hearing problems, attention disturbances, delayed growth and feeding problems. Also hemiplegia, quadriplegia, hydrocephaly and microcephaly can appear. Death can also be immediate or can appear later. Manfield et al. reported that five years after AHT 81.8% of children had a moderate or severe disability. At acute discharge the disability was lower (64.5%). The main impairments that were detected were behavioral problems (53%), vision disturbances (44%), fine motor difficulties (26%), motor problems (26%), communication difficulties (24%) and 16% had epilepsy [22]. Although clinicians are mandated by law to report child abuse, only 20% of reported cases are substantiated following investigation. The main reasons are absence of available evidence and injuries attributed to accidents or associated to a medical condition [7]. The outcome of pediatric subdural hematoma associated with AHT is worse with a 20% mortality rate and a 50% rate of neurological morbidity [25].

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Chapter 27
Pediatric Skull Fracture

Mohammad Jamous and Amer Al-Omari

27.1 Introduction

The anatomy of the pediatric skull is challenging, this complexity stems from the variable nature and changing appearances of sutures over the normal developmental period. Sutures are a type of fibrous joint that occurs only in the skull. Synchondroses, which are also found in the skull, are a type of hyaline cartilage joint. Normal developmental sutures are seen in all infants and toddlers and in some older children but not in adults, and they are likely to be misdiagnosed as fractures particularly asymmetric sutures, which are not uncommon [1].

The distinction between normal sutural anatomy and fractures is critical, this differentiation is even more difficult in the pediatric population, in whom numerous sutures have a variable appearance. Some basic rules can be applied to help differentiate fractures from sutures. Fractures have sharp, non-sclerotic borders and may bifurcate. They may cause diastasis of the sutures, often cross the sutures themselves, and increase in diameter as they approach a suture. Indirect signs such as overlying soft-tissue injuries, including hematomas, can be useful [2]. In contrast, sutures join other sutures rather than cross them. They do not cause diastasis of other sutures and remain relatively uniform in diameter. Sutures have a "zigzag" or interdigitating pattern with sclerotic borders.

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27.2 Imaging

Pediatric closed head injury (CHI) is a common condition in the emergency department. Skull fractures are the most common abnormal findings encountered after CHI. Computed tomography (CT) scan of the brain is the diagnostic test of choice to evaluate for skull fractures and intracranial injuries. The decision to perform a CT scan is a complex one, especially for infants and toddlers. Some advocate that any child younger than 3 months with a nontrivial injury should receive a head CT, because of the high incidence of intracranial injury in this subgroup with a normal initial physical examination [3].

Skull X-ray are routinely obtained in all cases of head injuries at admission or as outdoor patients, in a search for linear skull fracture on the assumption that a skull fracture predisposes the patient to the development of an intracranial mass lesion.

Ultrasound is an imaging modality that could be used to evaluate for the presence of skull fractures, which are strongly associated with intracranial injuries. There is good evidence to support the use of bedside ultrasonography to detect long-bone skeletal fractures [4, 5]. Bedside ultrasonography can be used by pediatric emergency medicine physicians to detect skull fractures in children with acute CHI, but it needs well experienced sonographer, and it could be performed on minor head trauma [6].

27.3 Types of Skull Fracture

27.3.1 Linear Skull Fracture

Linear skull fracture can be non-displaced fractures as seen in Fig. 27.1 or displaced fractures as seen in Fig. 27.2, with displaced fractures there is higher risk of brain injury or underlying bleeding also in younger patients less than 3 years old it could be complicated later with growing skull fracture.

Isolated linear skull fracture in pediatric age group is not uncommon seen in the emergency department, some studies [7, 8] discussed the need of hospitalization or discharge home from emergency as the rate of life-threatening complication or an underlying brain injury is extremely low and find it unnecessary to monitor patients with an isolated linear skull fracture post minor head trauma.

Growing skull fracture—also known as post traumatic leptomeningeal cyst—is a rare late complication of linear skull fracture in less than 0.05% to 1.6% of cases but is a significant complication and almost occurs exclusively in children younger than 3 years [9, 10].

Xue-song Liu et al. [11] divided the progression of growing skull fracture into three stages, the first stage is the prephase which start from the time of injury to the time just before enlargement of the fracture where all patients treated by craniotomy with duroplasty and in this stage the complications are few and neurological deficit

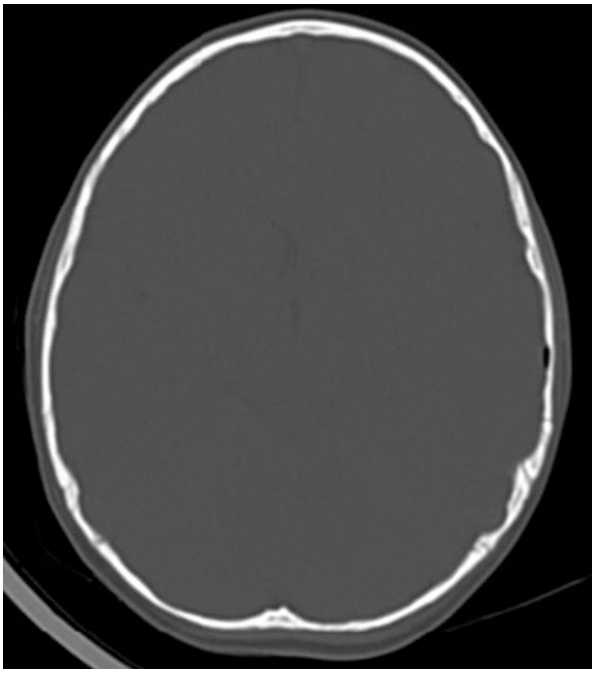

Fig. 27.1 Left temporal linear non-displaced skull fracture with underlying small pneumocephalus

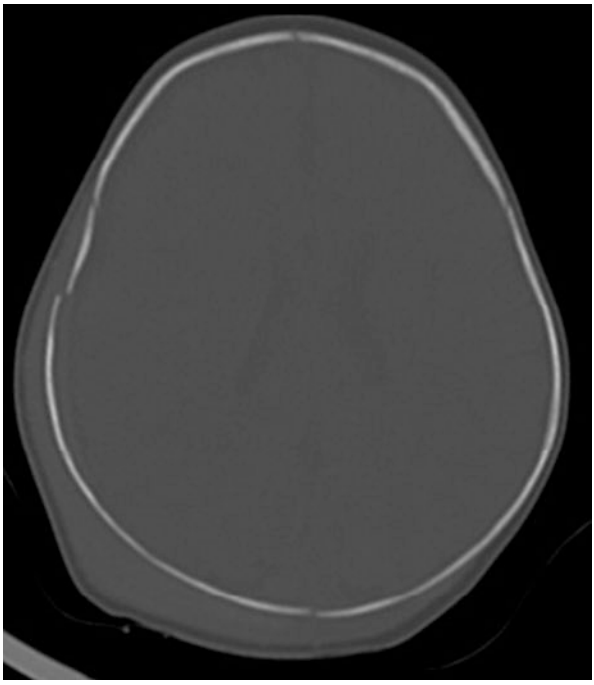

Fig. 27.2 Right parietal linear displaced skull fracture

did not occur, therefore it is the best period for treatment. The second stage is the early phase which starts from the beginning of fracture enlargement to 2 months after the beginning of enlargement, in this stage the skull defect is small and the neurological deficit is mild, half of them underwent craniotomy and the other half underwent cranioplasty with autologous bone and all of them had duroplasty. The third stage is the late stage and it starts 2 months after the initial enlargement, during this stage, the bone defect becomes larger, and skull deformity and neurological disorder become severe if left untreated, all patients in this stage underwent cranioplasty using alloplastic material with duroplasty.

27.3.2 Depressed Skull Fracture

Depressed skull fractures (DSFs) account for 7–10% of children admitted to hospital with a head injury and 15–25% of children with skull fractures [12–14]. DSFs can lead to significant complications when they are associated with dural tears, penetration of the brain parenchyma by a foreign object or bone fragment, and the presence of underlying brain injury or intracranial hematoma. Post-traumatic epilepsy and infection are among the most important complications. Although management of compound DSFs is surgical, some authors favor a conservative approach to simple DSFs [15, 16].

Simple depressed skull fracture: most common in frontal and parietal bones, there was no difference in outcome (seizures, neurological dysfunction, or cosmetic appearance) in surgical versus non-surgical treatment. Although surgery is indicated in case of definitive evidence of dural penetration, focal neurological deficit related to the fracture, or cosmetic. In younger children, remodeling of the skull as a result of brain growth tends to smooth out the deformity. Mortality rate is 1% [17].

Compound depressed skull fracture as seen in Fig. 27.3: it is rare in younger patients and associated with a higher incidence of dural and cortical laceration than are simple DSFs and has a higher mortality rate 3%. The incidence of coexisting intracranial lesions increased when the fractured bone is deeper than 1 cm [17].

27.3.3 Ping-pong Skull Fracture

It is a depressed skull fracture that happens in newborns and infants due to the high plasticity of the skull bone at this age group as seen in Figs. 27.4 and 27.5, it is generally related to obstetrical maneuvers during difficult deliveries, or trauma.

The treatment for this fracture is controversial and vary in the same hospital, some prefer conservative treatment as this fracture might go back to normal and elevate themself spontaneously without any active management, some authors used an outer manipulation technique for elevation of the fracture but this technique needs an experience and further fracture might happen during manipulation, others

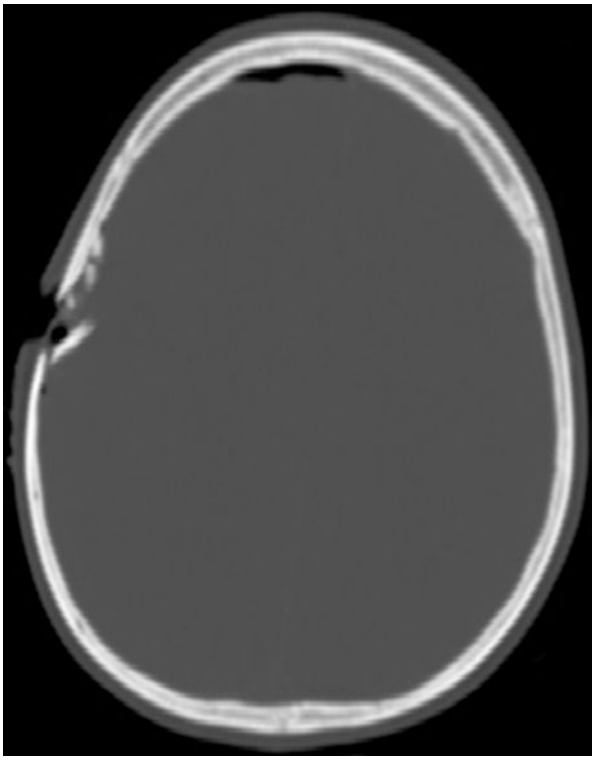

Fig. 27.3 Right parietal comminuted depressed skull fracture with underlying bone fragments and sign of dural tear as there is right subdural pneumocephalus

[18] used breast milk extractor to elevate it, and surgical techniques there is wide different techniques used from normal opening and craniotomy to using burr hole and an elevation of the bone through the burr hole or even using percutaneous microscrew elevation [19].

27.3.4 Basilar Skull Fracture

The frequency of basilar skull fracture as seen in Fig. 27.6 varies from 5% to 14% in children with head injuries [20]. The clinical signs of a skull base fracture include retroauricular and/or periorbital bruising, hemotympanum, cerebrospinal fluid (CSF) otorrhea and rhinorrhea.

Around 25% of patients who had CSF leak develop meningitis, which is associated with a 10% mortality rate [21], The median time between injury and onset of meningitis is reported to be 11 days [22].

Ulla Perheentupa et al. [23] reviewed 63 pediatric patients with basilar skull fracture and found that road traffic accidents were the main etiology of fracture followed by falling down, also he noticed that the temporal bone is the most common fractured bone.

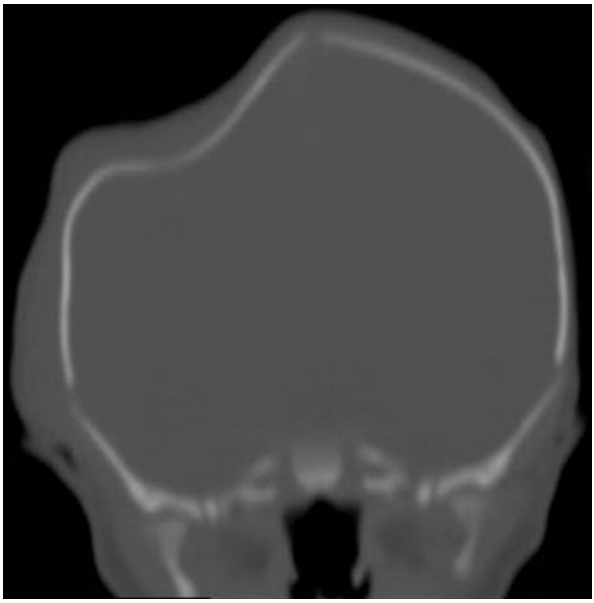

Fig. 27.4 Right parietal depressed skull fracture in neonate, ping pong skull fracture

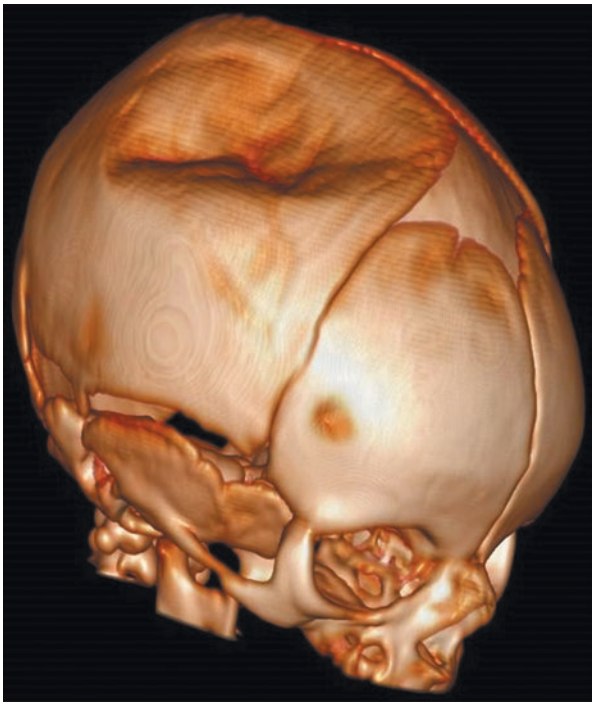

Fig. 27.5 3D reconstruction CT brain for neonate with right parietal ping pong fracture

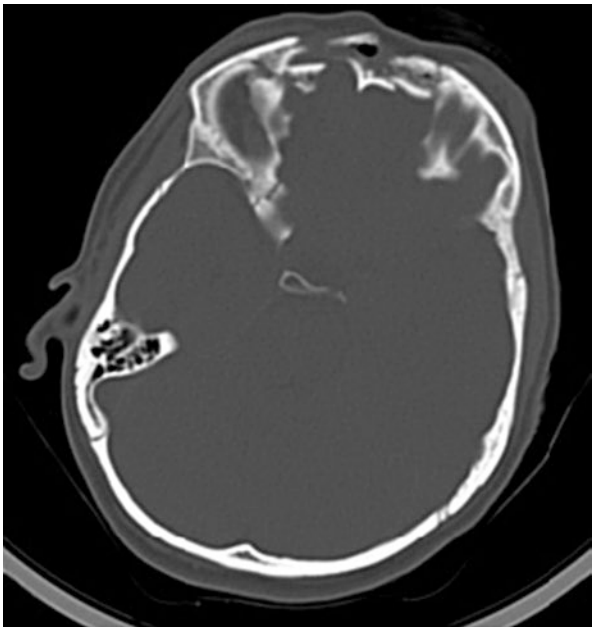

Fig. 27.6 Frontal base of skull fracture

CT brain with thin cuts over the base of the skull is recommended for all suspected cases, CT angiography is needed in case of suspected vascular injury due to fracture, and in case of CSF leak; CT cisternography may be required.

Most cases of CSF leak post trauma will resolve spontaneously within the first two weeks, if the leak is persistent it means there is a fistula developed or large dura tear that needs to be treated surgically, either by CSF conversion via lumbar drain or base of skull repair surgery or combination of both. If CSF leak left untreated it could lead to meningitis and its complications or hydrocephalus. In all cases of CSF leak prophylactic antibiotics like cephalosporins are recommended.

Basilar skull fracture may have intracranial involvement, in a series of 96 children with brain injuries by Jagannathan et al., 68% had subarachnoid hematoma, 46% contusion, 23% subdural hematoma and 5% epidural hematoma [24].

Most cases are treated conservatively, surgical treatment is indicated in cases of persistent CSF leak, severely displaced fracture, or sinus involvement.

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Chapter 28
Epidural Hematoma

Andreas Zigouris

28.1 Introduction

A general classification of traumatic brain injuries (TBI) in children includes skull fractures, hematomas and traumatic axonal injury (DAI) [1]. TBI is a major cause of death and disability in children. The majority of TBI is of mild severity. Epidural space contains a small amount of lymphatic fluid and has small thickness due to tight adherence of dura mater in the inner table of skull. Some authors described epidural as "virtual" space [2]. Epidural hematoma (EDH) results from accumulation of blood in the epidural space from vessels that ruptured due to external shear forces or directly after a skull fracture. Blood can lead rapidly to detachment of dura from inner table and to formation of various size hematomas. Patient's clinical condition is usually subtle and nonspecific so the diagnosis can be quite challenging. Emergency surgery must be undertaken whenever it is necessary, especially considering the rapid and fatal progression of this traumatic lesion [1, 3].

28.2 Epidemiology

In children EDH represents 2–3% of all head injuries. EDH is more common in children aged between 6 and 10 years and only rarely can be found in infants [4, 5]. The lower incidence of EDH in children compared to adults is due to the tighter adherence of the dura to the inner table of skull. Only posterior fossa EDH can be found more frequently in children and is often related to laceration of the dural venous sinuses. In children aged between 0 and 5 years there is no gender predilection in EDH occurrence. However, in children older than 5 years EDH is twice more

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common in males. Boys have a tendency to risky play activities and have an increased risk of TBI near puberty. Girls are at a lower risk of TBI after the age of 10 [6]. Furthermore, head injuries in children are most common during summer, when children spend more time outdoors. Younger children and high-velocity trauma are associated with higher risk for secondary brain injury, a condition responsible for higher morbidity and mortality rates [7].

EDH is usually caused by traffic accidents (passenger, pedestrian and bicycle driver), falls, sport activities and assault [4]. Pasaoglu et al. and Ersahin et al. found that falls were the most common mechanism of injury in more than 60% of the pediatric cases studied [8, 9]. Stair falls and falls from furniture also are important causes [10]. Paiva et al. reported that almost 60% of the EDHs were related to accidents inside the home [11]. Duthie et al. and Umerani et al. reported assault as a cause of EDH in 9.0 and 6.9%, respectively [12, 13]. Among infants the history of a trivial fall from a chair or low bench is typical and only 30% is due to fall from a height greater than 1 m [5]. Motor vehicle accidents as a cause of EDH are of low frequency in infants compared with older children [14].

The more common birth injuries to the neonatal brain include extracranial hemorrhage (caput succedaneum, subgalea hemorrhage, or cephalohematoma), skull fracture, and intracranial hemorrhage. EDH is a rare form of neonatal birth injury accounting for 2% of newborn intracranial hemorrhage and is related to the newborn's position during labor and delivery [15, 16]. Among neonates Takagi et al. found EDH in only 2 out of 134 autopsied patients and a review by Merry et al. reported only 1 neonate among 417 patients with EDH [17]. This rare event may be explained by the tight dural adherence at the level of the sutures, especially coronal, the absence of middle meningeal artery groove which makes the middle meningeal artery less susceptible to injury, the poor development of the dural vessels in neonates and the elasticity of the skull at this age [16, 18]. Newborns with greater risk for birth-related injuries include those above the 90th percentile for weight. The rate of birth injury is higher in infants weighing more than 4500 g.

Posterior fossa EDH in children is rare but is associated with better prognosis than adults [10, 19, 20]. EDH consists 25–40% of all posterior fossa pediatric traumatic lesions [19, 20]. It accounts for 5% of TBI in children and 1.2–12.9% of all pediatric EDHs with a mean age of 6.2 years [10, 19]. A history of fall is found in more than 60% of patients and motor vehicle accidents are responsible for 10% of posterior fossa EDH [10, 19, 21]. Subacute and chronic EDH in the posterior fossa have been reported, but the vast majority are acute with mild and often atypical symptoms [22].

28.3 Symptomatology

The clinical course of a pediatric EDH may be lethal and thus requires high clinical suspicion. EDH in children may present after mild or moderate injury, symptoms may not be typical and the course is more insidious compared to adults. Children

may have an EDH after a relatively mild head trauma and 38% of them are alert with normal vital signs at diagnosis [23]. The cardinal symptom is the altered state of consciousness. Infants present most frequent with drowsiness and vomiting (Fig. 28.1). More than half of children with EDH presented with headache and persistent vomiting. McKissock et al. noted that vomiting was a more frequent symptom in children in comparison with adults [24]. Cook et al. reported that among 100 patients with EDH and GCS of 14 or 15, 40% had nausea or vomiting but no focal neurological signs [25]. Severe neurological signs such hemiparesis or ipsilateral pupil dilatation is observed in less than 20% of patients. The well-known lucid interval can be seen in less than 30% of children and early seizures are reported in 10% of EDH cases [4, 8].

In posterior fossa EDHs symptoms are atypical and there is a risk for rapid and fatal deterioration. Berker et al. and Sencer et al. reported that for posterior fossa EDH progressive headache, nausea, vomiting, and altered level of consciousness are the most common clinical findings. Red flags are symptoms related to cerebellar or/and brainstem compression [10, 20]. Lucid interval is not classically observed and is more often when posterior fossa EDH is associated with supratentorial lesions [19].

The majority of infants (68%) appear normal. Drowsiness, vomiting and irritability are common symptoms [5]. About 60% of infants have a true lucid interval that is longer in duration compared to older children due to better tolerance of raised intracranial pressure (ICP) and in some cases, due to clot decompression through the skull fracture into the co-existing cephalhematoma. Main source of bleeding is diploe and less frequently disruption of a branch of the middle meningeal artery. Histological examination of the infantile bones revealed increased diploic vascularization. Mallet and Boumahni have classified the clinical symptoms observed in infantile EDH into three categories: 1) neurological symptoms, 2) visible signs on the head (bulging fontanelle, increased head circumference), 3) no specific symptoms of acute neonatal distress [26]. Pyramidal signs, seizures and hypotonia occurred more frequently in infants (61%) than in older children (41%). The size and extent of an EDH in infants was related to the frequency of anemia observed preoperatively, which is not an unusual occurrence [9, 24]. EDH and scalp hematoma are sufficient enough to cause anemia and even shock as the total blood volume is less in infants [5, 27]. Rarely, the breakdown of hemoglobin retained in the tissues may result in hyperbilirubinemia and jaundice [28]. EDH in newborn and infants could be associated with cephalohematoma, which is a subperiosteal collection of blood secondary to the rupture of blood vessels between the skull and the periosteum. It occurs in about 1% of live births and is usually observed over the parietal bone [28]. Cephalohematoma is seen most often in male patients after a prolonged, difficult, forceps-assisted delivery or after the application of excessive suction with a vacuum extractor [27, 28]. In less than 20% of cases may be associated with linear skull fracture. This lesion can be recognized as a palpably firm, tense mass that resolves over weeks to months, may calcify and become incorporated in periosteal new bone [16].

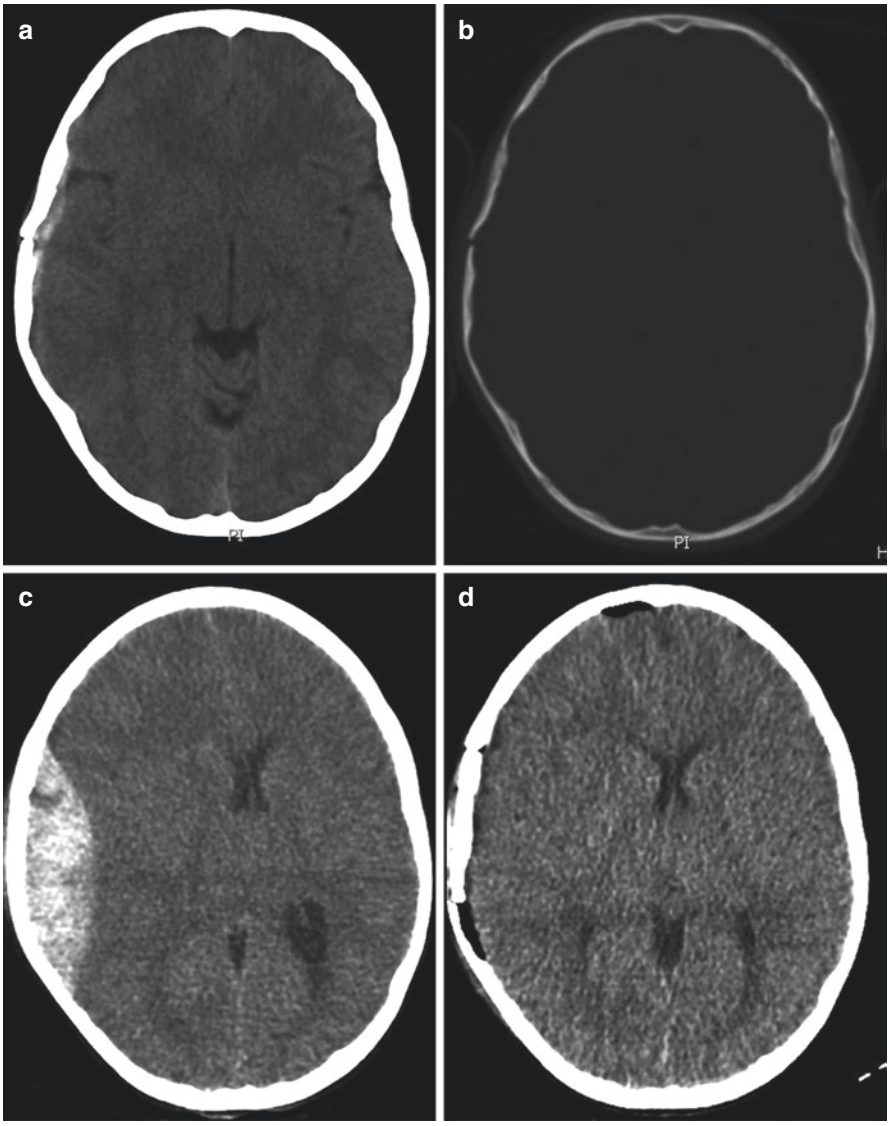

Fig. 28.1 (**a**). A 6-year old boy presented in the emergency department after a fall. Brain CT revealed a small temporoparietal EDH and an overlying linear skull fracture (**b**). The patient presented alert with normal vital signs. (**c**) Three hours later because of altered level of consciousness and vomiting a repeat CT scan was performed and revealed an increase of EDH thickness and midline shift. The patient was operated on via a temporoparietal craniotomy. (**d**) Postoperative CT scan. The patient had a full recovery

The clinical course between children and adults has certain differences due to increased tolerance of pediatric skull (elastance and compliance) in cases of increased intracranial pressure after head injury. The greater compressibility of the child's brain coupled with the greater pliability of the young skull, enable better transmission of the energy generated by an impact. In children, the pressure–volume curve is shifted to the left, implying that children tolerate acute increases in intracranial volume poorly. Based on Monro-Kellie doctrine open fontanelles, greater water content of the brain parenchyma, lower brain/cerebrospinal fluid (CSF) ratio, different head/body ratio, the compensatory mechanisms for blood loss, unfused cranial sutures and large subarachnoid spaces can delay overcoming of critical point and lead to more gradual course of neurological decline [29]. Great care is important in a shunted child because of the risk of rapid hematoma grow.

The most common location of an EDH is the temporoparietal region followed by frontal region. Absence of skull fracture in children with EDH is not unusual. In case of an infantile EDH the vast majority (90%) had an associated skull fracture [5]. The infant's skull is thinner, softer, and more deformable when fractured, but heals quickly due to accelerated bone growth. The source of bleeding is often venous from diploic space after skull fracture [4, 8]. Infants after evacuation of hematoma had as bleeding points bone margins or dural surface because of greater vascularity of these structures in this age group. The posterior fossa EDH results either from a diastatic fracture of the squamous portion of the occipital bone or a tear in the transverse sinus, noting that a fracture is detected in more than 85% of children [10, 20, 21].

28.4 Radiological Features

The tight dural attachment to the skull results in the widely known characteristic appearance of EDH on computed tomography (CT): non-crossing cranial sutures, biconvex and lentiform shape, hyperdense (bright white) appearance (Figs. 28.1 and 28.2). An exception is along sagittal suture where periosteum forms the outer wall of superior sagittal sinus. Huisman et al. found that only 11% of EDH can cross sutures and complicates the differentiation from subdural hematoma [2]. A suture-crossing EDH is usually located in the frontoparietal region and is associated with larger hematoma volume and bone involvement (fracture, suture diastasis). In about 10% of cases, EDH occurs in the absence of a fracture. Rocchi et al. proposed that dural detachment from the inner table, due to the different elasticity coefficients between dura and bone, explains the presence of acute epidural hematoma without fracture [30]. EDH may be of arterial or venous origin, with common sources the branches of the middle meningeal artery and diploe. In infants, fracture margins and dural surface are the main source of bleeding [5]. The "swirl" sign in CT scan is the presence of heterogenous low density foci in an acute lesion and indicates fresh extravasating arterial blood [23].

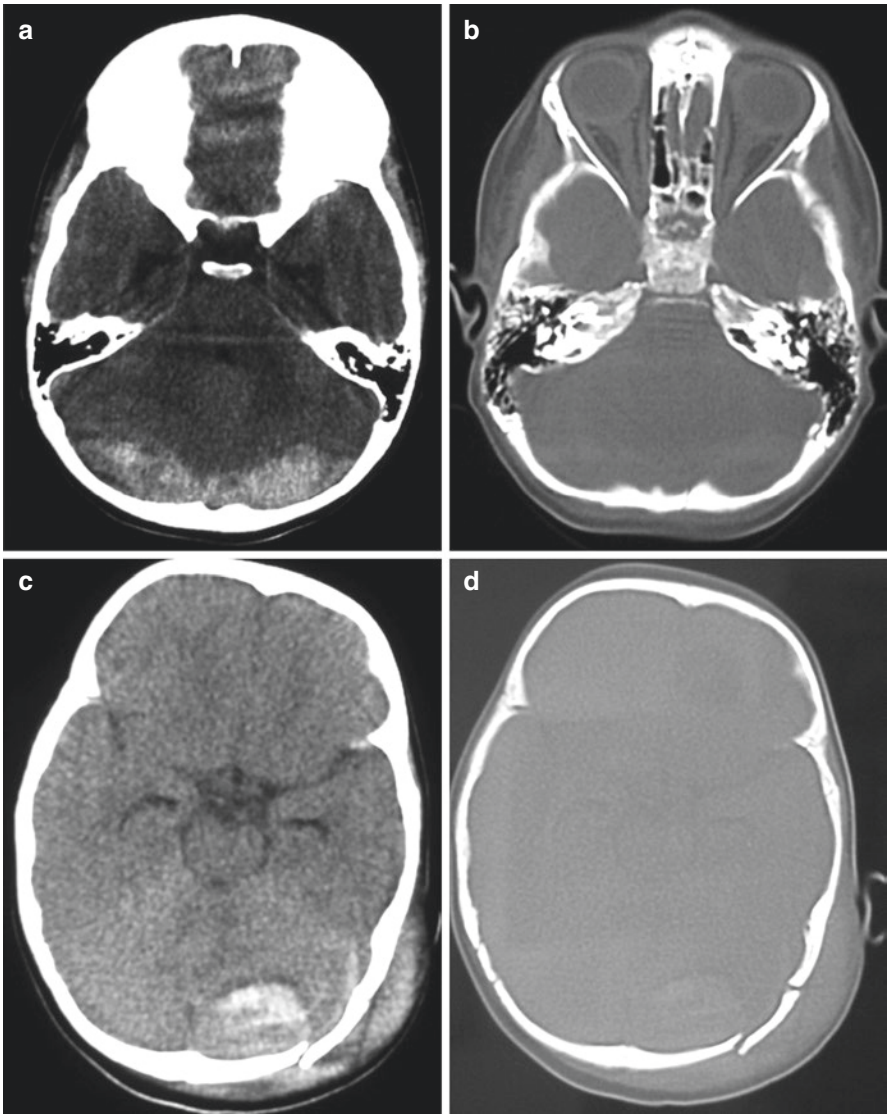

Fig. 28.2 (**a**) An 8-year old boy was admitted after a fall from 2 m height with headache and vomiting. The GCS score was 14. CT revealed a posterior fossa EDH with (**b**) a concomitant occipital fracture. The hematoma was evacuated via a midline suboccipital craniotomy. (**c** and **d**) A 10-year old boy presented in the emergency department after a bicycle accident. The GCS score was 12. On physical examination there was a large left occipital subgaleal hematoma in the left side. CT scan revealed an occipital bone fracture with a concomitant EDH

Delayed EDH refers to a hematoma that is insignificant or not present on the initial CT scan after TBI. On subsequent CT sizeable epidural bleeding can be found. Delayed EDH comprised (7–10) % of all EDHs and is associated with presence of a skull fracture [4, 31]. In posterior fossa EDHs ventricular dilatation and hydrocephalus is observed in less than 20% of cases [10]. CT scan is advised for almost all patients, whose mild trauma is perceived as nontrivial by the attending neurosurgeon, using criteria that include GCS, trauma mechanism, and age. The timing of the repeat CT scan depends on the neurosurgeon's personal judgement [31].

Magnetic resonance imaging (MRI) is an excellent tool for imaging intracranial hemorrhage and is increasingly used for the emergency investigation of children with head injury [32]. Fast MRI protocols with total acquisition time of 3–4 min are currently available. A retrospective study included 574 children with TBI (mean GCS 9 ± 5.7) that were scanned with both CT and MRI within a 5-day period. CT and MRI showed similar sensitivity. CT missed 12 patients, mainly with diffuse axonal injury, subarachnoid hemorrhage small subdural hematomas, whereas MRI missed 13 patients, mainly with fractures [33]. With MRI children are not exposed to the harmful effects of ionizing radiation.

28.5 Treatment

The acute management of TBI is based on ATLS (Advanced Trauma Life Support) algorithm. Based on GCS TBI is classified into mild, moderate, and severe. Adequate perfusion and oxygenation of the brain is important for the prevention of secondary injury [1]. Intracranial hypertension will occur in 75% of all severely head-injured children and any delay in treatment may result in irreversible neurological deficit [29]. Most EDH patients have mild or moderate TBI.

Asymptomatic and clinically tolerated EDH could be treated conservatively with serial neurological examinations. This type of management demands close monitoring with frequent assessment of neurological status. Paiva et al. proposed conservative management when hematoma thickness was less than 10 mm and midline shift was less than 5 mm [11]. Conservative management of posterior fossa EDH is trivial. Sencer et al. proposed during the followup early repeat CT scans that may be lifesaving [10]. Past studies before 1990 reported that surgical treatment was performed more often, possibly because it was more difficult to repeat CT scans at that time. Paiva et al. observed that there was no significant difference in the mortality rate (3.4% versus 2.5%) over the decades [11].

The typed of craniotomy performed depends on the location and maximum thickness of the hematoma. The mean time interval from injury to surgery has been

reported to be 4.5 h (range: 2–15 h). According to Gerlach et al. 50% of operations were performed within 6 h of injury [6]. After hematoma evacuation and appropriate hemostasis, dural tenting sutures should be placed near the bone edge followed by a central (Poppen's) tenting suture, named after J. L. Poppen. In case of infants a large bone flap permits complete evacuation of the hematoma and appropriate hemostasis from usual osseous or dural origins of bleeding. Puncture and needle aspiration of cephalohematoma may be effective when care is taken to prevent infection and rebleeding, and progress is monitored by ultrasonography [16]. This method has resulted in the disappearance of EDH with no recurrence. The common features of this combination were a communication between the cephalohematoma and the EDH through the cranial fracture and in hyperacute or chronic stages when the hematoma is liquified [28].

The most common indications for operative treatment is a decline in neurological examination even if the amount of blood does not meet the absolute surgical indication criteria, the size of hematoma and any progression on repeat CT scan especially in the first 24 h. Thickness of EDH of more than 15 mm and a midline shift greater than 4 mm were predictive for surgical therapy in many studies. Several studies suggested that hematoma volume larger than 30 ml, thickness of more than 15 mm and midline shift of more than 5 mm constitutes strong indicators for craniotomy. Bejjani et al. found that the most important radiographic parameters dictating surgical evacuation were maximum hematoma diameter of more than 18 mm and midline shift of more than 4 mm [23]. Subjectivity of the attending surgeon still plays a major role and there is a gray zone of uncertainty in the process of decision making, particularly in a group of children presenting with unspecific clinical signs and symptoms. EDH thickness between 8 and 12 mm, no midline shift and GCS between 12 and 14 have been defined as intermediate size EDH, and for these cases a careful and individualized clinical management is suggested [23]. Champagne et al. concluded that close follow-up in the short and long-term period is required in cases of conservative management [7]. Spazzapan et al. proposed that conservative management can only be performed in an intensive care unit (ICU) and in hospitals with neurosurgery department [4]. Heyman et al. stated that in newborn absolute indications for surgery are hematomas more than 1 cm thick and more than 4 cm long in the anteroposterior orientation or associated with a depressed cranial fracture or hydrocephalus [27]. In cases of recurrent epidural hematoma, it generally results from continued bleeding from the inner table of the skulI, not from rebleeding of meningeal artery.

For posterior fossa EDHs indications for surgery are hematoma volume of 10 cm^3, hematoma thickness of 15 mm, midline shift of 5 mm, and obliteration of perimesencephalic cisterns [10, 19, 20, 22]. Signs of acute neurological deterioration or fourth ventricle compression, cases of ventricular dilation or development of mass effect are absolute indications of emergency evacuation [19]. In the case of small EDH with minimal ventricular dilatation, close observation until resolution of lesion is needed before treating the hydrocephalus.

28.6 Outcome

In EDH the prognosis worsens as age increases. Rocchi et al. reported that in children under 9 years of age, midline shift is a prognostic criterion more important than hematoma volume [30]. Additionally, presence of skull fractures in children is not a prognostic factor compared to adults. Poor prognostic factors reported for EDHs include GCS < 8 at admission, bradycardia, seizures, focal neurological deficits and mydriasis [4, 6, 30]. In the study from Gerlach et al. the motor response in GCS is considered as the most reproducible and carries the best prognostic information [6]. Seeling et al. found a 41% mortality rate in comatose patients (GCS < 8) with EDH [34]. There were no deaths among patients with a GCS score of 8 or higher in the series of Bricolo et al. [35, 36]. Delays in transfer to the hospital is the main factor associated with high mortality [9, 36]. Gerlach et al. reported the highest mortality in patients who had both posterior fossa and frontotemporal hematoma along and fixed and dilated pupils at presentation [6]. Faheem et al. observed that mortality was higher in patients who were operated 24 h after the injury and lowest in patients operated within 6 h after injury [36].

Co-existing brain swelling, acute subdural hematoma, depressed skull fracture [20], and penetrating injuries, especially with lower GCS score, carry a higher risk for posttraumatic seizures, and often require prolonged anticonvulsant therapy for 6–12 months. Heyman et al. and Leggate et al. reported that seizures were the most frequent infantile morbidity [5, 27]. In general terms, mortality rate varies in literature from 0% to 12% and even higher in pre-CT era [6, 20, 30, 37]. Recent reports estimate a percentage less than 5% [11, 14, 38]. Early diagnosis and rapid surgical evacuation is of paramount importance. The overall outcome from several studies reported to be complete recovery in 82.9%–94.8% of patients at 6 months after discharge [6, 39].

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Chapter 29
Subdural Hematoma

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29.1 Introduction

Subdural hematomas (SDH) are common in children with traumatic brain injury (TBI) and occur most often in infants. Virtually all SDH are caused by injury of a dural vein close to the venous sinuses. It can be caused due to trauma with or without skull fracture or because of rotational, acceleration-deceleration forces as seen in abusive head trauma and whiplash injury. Non-traumatic SDH such as during labor can also be found [1]. These neonatal subdural hemorrhages are typically subclinical and resolve in one month. This chapter review SDH causes, clinical and pathologic findings.

SDH is a collection of blood between the dura and arachnoid membranes, yet outside of the brain. While most SDHs are traumatic, rare cases of SDH after aneurysm rupture, tumor hemorrhage or bleeding disorders have been reported [2]. In infants symptoms might be poor feeding and in older children headache, nausea, vomiting, confusion and drowsiness. Acute SDHs is diagnosed within 2 days of trauma. Subacute SDHs present 3 to 14 days after trauma, though chronic SDH present 15 days or more after trauma [3]. Large SDHs require emergent surgical evacuation. Detailed patients' history such as cause of injury, the height of a fall, type of flooring, speed of the vehicle, etc. are important.

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29.2 Epidemiology

SDHs may be found at all ages, but they are prevalent in children. In a study of 111 asymptomatic infants 8% had a SDH, all resolved within a month without any treatment [1]. Incidence of SDH in newborn children ages 0 to 1 year was reported to be 24 out of 100,000 [4]. Mortality rates in treated patients are roughly 8% for patients younger than 65 years and 33% for patients older than 65 [5]. Estimated death rate in patients with acute SDH requiring medical procedure is 40% to 60% [6] SDH occurs in 10.9 per 100,000 children of 0 to 2 years, and 20.8 per 100,000 infants [7]. Most SDH occurs in infants aged 0 to 4 months [8].

29.2.1 Risk Factors

Increased mortality in acute SDH is associated with [2]

- Acquired clotting abnormalities [9, 10].
- Trauma [6]
- Higher APACHE (Acute Physiology, Age, and Chronic Health Evaluation) III score on presentation [6].

Comorbidity risk factors for children with chronic SDH include:

- Epilepsy.
- Thrombocytopenia.
- Anticoagulant treatment, including ibuprofen.

29.3 Pathogenesis

SDH is a result of bleeding between dura matter and arachnoid (subdural space), across which cortical (crossing over) veins drain the brain surface into the dural sinuses. If these veins rupture, blood fills the subdural space in all directions, gradually producing mass effect. Rarely there is a rupture of the arachnoid and CSF accumulation in the subdural space. The injury severity necessary to cause SDH varies. Severe trauma with skull fracture may not have an underlying SDH, whereas SDH may happen after trivial injury to the head. A SDH is more common in older patients since cerebral atrophy is associated with the development of chronic SDH. SDH is additionally more frequent in males. Furthermore, anticoagulant agents are associated with increased risk of SDH following even a minor head injury [11]. Increased risk for SDH also have patients on hemodialysis, epilepsy (increase risk of falls) and with intracranial hypotension. Rarely, SDH develops after aneurysm rupture, arteriovenous malformations, brain tumors. Coagulopathies, bone marrow transplantation, and thrombolysis in acute myocardial infarction [12–17].

29.4 Diagnosis

29.4.1 Imaging

Acute SDHs can be readily identified on a non-contrast CT and is typically crescentic and cross sutures. Subacute SDHs may appear isodense to surrounding brain parenchyma and difficult to differentiate. MRI is superior in identifying SDH, its size and mass effect. Nevertheless, CT is readily available, rapid and widely used in trauma patients. Moreover, MRI requires non magnetic ventilators and oxygen tanks. Furthermore, in traumatic brain injuries assessment of the cervical spine for possible fractures is essential. Fractures can be readily identified on CT. Chronic subdural hematomas are hypodense on CT.

29.4.2 Clinical Findings

Headache, confusion or drowsiness, symptoms of increased intracranial pressure, poor eating, or new seizures can be present in children. Findings of skull base fracture that may correlate with intracranial hemorrhage are:

- Bilateral periorbital (raccoon eyes) ecchymosis.
- Retroauricular ecchymosis (Battle's sign).
- Otorrhea or cerebrospinal rhinorrhea.

Mistakes are common in diagnosing SDH especially in adults. Intracranial neoplasms and strokes are some disorders that are frequently mistaken for an SDH. Therefore, a proper diagnosis is of fundamental importance. Given their variable clinical manifestation and often missed head injury history, 72% of chronic SDHs are misdiagnosed [3].

29.5 Mechanisms

29.5.1 Traumatic Etiology of SDH in Children

Few investigations have indicated that most SDH in newborn children are the effect of trauma [18]. Within this group, a more significant number of cases result from abusive than accidental injury. Feldman et al. [19] found that 59% of SDH cases were due to abuse and 23% resulted after accidental injury. A report from the Royal College of Pediatrics and Child Health assessed that 51% of pediatric SDH resulted from abuse [7]. The relationship between SDH and maltreatment in newborn children has been known for quite a while. The differentiation of accidental from non-accidental traumatic causes is vital. As noted in the beginning of this chapter, most

pediatric SDH are the consequence of injury. High-speed impact, for example, motor vehicle accidents and accidental crashes, without a doubt can cause SDH. Rotational forces or deceleration of the head may cause SDH.

29.5.2 Non-accidental (Abusive Head Trauma)

Over 30 years ago, an hypothesis was proposed to clarify SDH in abusive head trauma [20]. This theory suggested that shaking could cause brain damage and vein rupture producing subdural hemorrhage [21]. In any newborn presented with abusive head trauma, injury to the tendons, ligaments, muscles and nerves of the neck and the cervical spine is expected [22]. The pathologic investigations of Geddes et al. [19] indicated that most babies with inflicted traumatic brain injury sustained hypoxic damage and brain swelling. The authors suggested that apnoea is the cause of this hypoxic damage.

29.5.3 Accidental (Falls from a Low Height)

Falls from a low height are an infrequent cause of SDH in infants and older children. It is important to clarify the mechanism of injury. Notwithstanding, numerous studies showed that low-level falls can cause intracranial injury. Biomechanical studies showed that falls even from low-level of 3 to 4 feet can create far more significant forces in the brain than shaking [20]. Plunkett and Kim et al. reported that an infant or child may sustain a fatal head injury from a fall of less than 10 feet [23, 24]. Schloff et al. [25] reported four infants in two of which an intracranial injury was reported after a fall of under 8 feet.

29.6 Management

SDHs can be managed conservatively if the patient has no neurological deficit, hematoma thickness is <10 mm, midline shift <5 mm, no pupillary abnormalities, and no intracranial hypertension [6].

Time to surgery is of prognostic significance and patients treated within 2 to 4 h after the beginning of neurological symptoms had a mortality in the range of 30%–47%, instead of 80%-90% mortality when treatment was more than 4 h [6].

Initial management invovles:

- Non-contrast CT suspected with SDH.
- Complete blood studies

  - Coagulation profile
  - Surgical evacuation when needed.
  - Avoid steroids.

- In case of an infant rule out abusive head trauma.

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Chapter 30
Traumatic Axonal Injury - Intracerebral Hematoma

Dionysoula Skiada and Spyridon Voulgaris

30.1 Introduction

Traumatic brain injury (TBI) is a leading cause of death and severe disability in infants and children [1]. The cause of TBI depends on age, with falls and inflicted trauma being more common in children under the age of 4. Motor vehicle crashes is the leading cause of death past the age of 14. The youngest age group, especially children under 4 years of age, encounter worse prognosis following moderate to severe TBI compared to older children or adults, suggesting an age dependent outcome. The age-related mechanism underlying brain injury is not completely clear. A possible explanation may be that trauma to a developing brain might disrupt the normal brain development, which has a direct impact on the patients' neurocognitive outcome. Furthermore, neuroinflammation after TBI seems to activate resident microglia and release proinflammatory and anti-inflammatory cytokines and chemokines, such as IL-6 and IL-10, into the cerebrospinal fluid. Higher levels are found in children under 4 years of age. Microglia is thought to play an important role in neuroinflammative response of the brain after TBI, either in acute or in chronic neurodegeneration [2].

The term diffuse axonal injury was introduced in 1980s to describe a diffuse topographic distribution of traumatic findings. The term currently used is traumatic axonal injury (TAI) since these lesions are found in white matter tracts and grey-white matter junction. TAI can be found in up to half of severe TBI cases and can be also occur in mild and moderate injury. TAI is a result of high-force deceleration or rotational injuries. Cerebral contusions in children are also frequent after TBI. The purpose of this chapter is to provide a practical overview of traumatic axonal injury and cerebral contusions in children.

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30.2 Traumatic Axonal Injury

TAI refers to a widespread axonal damage as a result of acute or repetitive TBI. This type of TBI is caused by various mechanical forces applied to the brain, leading to deficits in cerebral connectivity that may or may not recover. The mechanical forces applied to the brain are usually associated with sudden acceleration, deceleration, and rotation of high magnitude. As a result, there is brain tissue injury which is microscopically characterized by widespread axonal stretching and disruption of nerve fibers [3, 4]. There is usually axonal damage in multiple regions of the brain parenchyma, often causing impairments in cognitive, sensory, and motor function because of disrupted neuronal connectivity, with consequent white matter atrophy, brain volume reduction and injury to unmyelinated fibers. TAI is clinically characterized by coma without the presence of a focal lesion. A period of lucidity at the onset may exist. Usually, brain regions that are commonly affected are parasagittal white matter, corpus callosum, brainstem and cerebellar peduncles [5]. The corpus callosum is the most vulnerable structure in TAI. There has been reported a relation between acute injury severity and the persistence of corpus callosum injury, along with a reduction in its volume which is thought to result from Wallerian degeneration following TBI. Children with severe TBI demonstrated reductions in corpus callosum area which persisted from 3 months up to 3 years, while children with mild and moderate TBI had increases in corpus callosum size consistent with normal development [6]. The posterior half region of the splenium is the most vulnerable to the TBI (80% of all the corpus callosum injuries), in both direct (TAI) and secondary injuries (elevated intracranial pressure). The anterior region is also vulnerable to injuries, especially to secondary ones. Children presented with increased ICP soon after TBI, demonstrated a reduction of anterior corpus callosum size and a white matter loss within a 5-year follow-up. This explains future cognitive impairment. There are various neurocognitive and psychomotor processing tests that evaluate the corpus callosum atrophy following TBI.

TAI was first described by Adams and colleagues in 1982 in histological findings in trauma patients after their death, who were subject to rotational acceleration—deceleration forces [7]. Motor vehicle crashes are a leading cause of TAI. The Adams classification is used to grade TAI (mild, moderate, severe) in relation to the findings on neuroimaging, however no proven association with patient's outcome has been reported [8]. At first the loss of consciousness was attributed to brainstem injury, but then it became clear that patients with other types of axonal damages were also presented unconscious. These patients have also deficits in memory and information processing in general. In addition, due to high energy kinetic forces passing through the pituitary stalk, hypopituitarism due to hypothalamic injury with the consequent hormone and electrolyte derangements is also a common finding [9].

Brain trauma leads apart from primary damage, to secondary axotomy which is a slower process. Multiple changes take place microscopically, including these of cellular death, synaptic dysfunction, activation of glial cells and anomalous protein deposition (Tau and Aβ proteins). In addition, it has been recognized that anomalous

protein deposition secondary to axonal injury might be related to the future manifestation of traumatic encephalopathy in some patients and neurodegenerative diseases, such as the Alzheimer's disease. In infants and young children there is a special interest due to the injury pattern, as the effect of a proportionally larger head to body size ratio with less neck control than in an adult would seem to predispose them to greater acceleration-deceleration forces. In addition, children's thinner cranial bones are providing them with less protection to their brain.

30.3 Neuroimaging in DAI

As far as neuroimaging is concerned it is usually very difficult to identify TAI based on CT findings. In patients presented with TAI there is usually a great mismatch between the CT findings and clinical presentation. Only 10% of patients have hemorrhagic punctuate lesions of the corpus callosum, or in the gray-white matter junction or in the pontine-mesencephalic junction near the cerebellar peduncles [10, 11]. Within two weeks after injury, neuronal loss in some patients can be demonstrated on CT as a discrete ventricular enlargement without evidence of hydrocephalus. Nevertheless, CT scan is necessary during emergency care, to evaluate these patients, as it is fast and accurate for identifying life-threatening conditions that may require intervention, such as extra-axial hematomas.

MRI is the gold standard for TAI diagnosis (Fig. 30.1). Nowadays, MRI is increasingly used for the emergency investigation of children with head injury and has the major advantage of no exposure to the harmful effects of ionizing radiation [12]. Fast MRI protocols with total acquisition time of 3-4 min are currently available. Compared to CT, MRI has higher sensitivity for TAI, subarachnoid hemorrhage and small subdural hematomas. Hemorrhages are represented by a loss of signal in gradient echo (GRE), whereas areas of edema present as high signal in T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences. These signal loss areas representing TAI hemorrhages may be visible for years after brain trauma. The initial density of the lesions in T2-weighted sequences is associated to the gravity of the brain injury. Nevertheless, the number of lesions demonstrated by conventional MRI is only the tip of the iceberg. More advanced techniques, such as susceptibility-weighted imaging (SWI), diffusion-weighted imaging (DWI), diffuse tensor imaging (DTI), have higher sensitivity to detect neuronal damage in areas that appear normal on conventional MRI examination. SWI demonstrates six times more hemorrhagic lesions and two-fold higher hematoma volume than conventional two-dimensional GRE imaging [13]. Nevertheless, SWI might overestimate hematoma volume due to its high sensitivity to heme products. DWI is superior for the evaluation of non-hemorrhagic lesions and is of prognostic significance. DTI has an important advantage to identify microstructural white matter abnormalities because of its ability to image water diffusion characteristics by using various parameters, such as fractional anisotropy, mean diffusivity, and tract volume. Diffusion tensor tractogragy, enables a 3-D visualization of specific neural tracts, using DTI axial

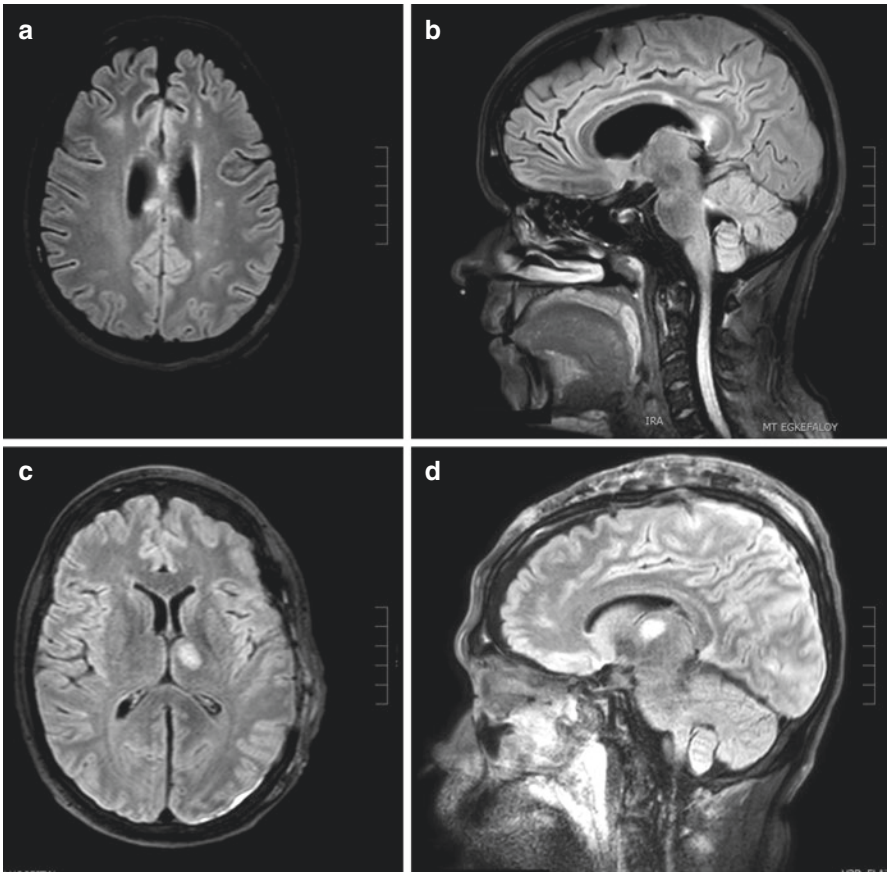

Fig. 30.1 A case of a motor-vehicle accident. The patient was presented in the emergency department in comatose state (GCS 3/15). Brain CT demonstrated bifrontal small posttraumatic subarachnoid hemorrhage. Brain MRI (**a**, **b**) that ensued showed multiple hemorrhagic contusions subcortical, in the corpus callosum and in the brainstem (DAI type III). The patient was treated conservatively. (**c**, **d**). A case of a motor-vehicle accident. The patient presented at the emergency department in comatose state (GCS 5/15). Brain CT demonstrated a large left frontotemporoparietal acute subdural hematoma with midline shift. The patient was operated. Postoperative MRI revealed a contusion in the left thalamus. Three months later, the patient was discharged with no focal neurological deficit, apart from short-memory loss

and radial diffusitivity. A recent study showed that microstructural alterations in the white matter are dynamic and can be evaluated by DTI during first year after trauma. Furthermore, DTI metrics showed several correlations with the cognitive domains [14]. Magnetization transfer imaging (MTI), with the use of protons of large organic macromolecules, which are selectively saturated and placed to water surrounding the tissue, can reveal chemical changes in brain parenchyma. These areas are

characterized as decreased magnetization transfer ratio, and have been recognized in trauma patients even in the absence of pathological findings on conventional MRI. Unfortunately, long-study time and sensitivity to motion artifact are the major pitfalls of these examinations. MR spectroscopy may also detect reduced N-acetylaspartate which is associated with neuronal injury. MR spectroscopy is more sensitive than SWI. Finally, functional MRI is used in TAI patients in both acute and recovery phase. It is based on identification of the brain activity through the detection of its metabolic demands in oxygen. TAI patients demonstrate a reduction in frontoparietal activity, especially in the right middle and superior frontal cortex.

30.4 Biomarkers

To date several biomarkers, mainly evaluated in blood, have been used in TBI to predict severity, outcome, need for CT or for adjusting treatment. TBI leads to increased blood-brain barrier permeability, astrogliosis and several astrocyte related proteins are elevated in the serum and cerebrospinal fluid [15, 16]. S-100b, glial fibrillary acidic protein, neurofilaments chains and C-tau have been studied [8]. In a study of 40 patients that were studied within 6 h post-injury, the serum tau level in the TAI group was significantly higher than that in the non-TAI group. Nevertheless, no significant difference was found in serum tau level between patients with favorable or unfavorable outcome [17].

30.5 Management

The goal of the treatment of TAI patients is supportive care and prevention of secondary injury, since no specific treatment is currently available. An area of research is for neuronal regenerative therapies and for prevention of secondary axotomy. Several agents are currently under investigation such as calcineurin modulators, i.e. cyclosporin A and Tacrolimus, because of their capacity to suppress the formation of mitochondrial transition pore and apoptotic cell death [18, 19]. Minocycline is a tetracycline which crosses the bood-brain barrier and proved to hold anti-inflammatory and neuroprotective effect in TBI and in neurodegenerative diseases by reducing microglial activation and proinflammatory cytokine response [20]. Finally, stem cell therapy is under evaluation to replace damaged neurons, astrocytes and oligodendrocytes, as the regenerative neuronal tissue capacity is very limited, however potential tumorigenic potential is a drawback [21].

30.6 Intracerebral Hematoma

Cerebral contusions are relatively frequent in children and may be the result of focal brain injury or penetrating trauma [1]. They are usually found below the site of injury of external force (coup injury) and only rarely at the opposite site (contrecoup). They are usually located in the gray matter in the both frontal and temporal lobes and contusions and shearing injuries may overlap. The majority of intracerebral hematomas can be treated conservatively. However, cerebral swelling caused by primary contusions may produce significant mass effect or midline shift that would require surgical evacuation. In high-risk lesions close observation and repeated CT scan is recommended [1]. The 2012 Guidelines for Pediatric Head Injury recommended decompressive craniectomy with duroplasty in pediatric patients with signs of cerebral herniation or intracranial hypertension refractory to conservative treatment, unilateral craniectomy should be performed in lateralized swelling and bifrontal in diffuse brain oedema [21].

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Chapter 31
Penetrating Head Trauma

Marios Lampros, Georgios Alexiou, George Sfakianos, and Neofytos Prodromou

31.1 Introduction

Penetrating head trauma (PHT) is the most uncommon, yet most lethal type of traumatic brain injury (TBI) in both children and adults. The management of patients with PHT has been well studied in adults during periods of military conflicts. In children, no specific guidelines exist, and our knowledge for them is limited to a few reports and case series [1, 2]. The mean age of children with PHT is approximately 5–7 years, with half of them being under 5 years, while a male predilection is observed. Generally, the pediatric PHT is usually a result of criminal or violent action, but the frequency of accidental injury is higher in children of pre-school age [3]. In adolescents, a major increase in the frequency of PHT from firearms injuries is observed in recent years, especially in adolescents coming from families of low socioeconomic status [4]. Immediate neurosurgical intervention after PHT is of crucial significance for the patient's survival, and thus an appropriate early management is necessary [1]. In this chapter we discuss the mechanism of trauma, clinical evaluation, imaging findings, management, and prognosis of children with PHT.

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31.2 Mechanism of Trauma

PHT is defined as a head trauma in which the perforation extends in depth to at least the level of the dura. In cases where the penetrating object exits the skull, it is instead referred to as perforating head trauma. Specific mechanical and kinetic properties are required for the penetrating object to destroy the "hard and solid" structure of the skull. The most important factor that defines the extent of the injury is the kinetic energy of the object at the moment of collision with the skull [5].

Ballistic properties of the penetrating object that define kinetic energy (KE) are mass (m) and velocity (v) as described by the equation $KE = 1/2mv^2$. From this equation, it is obvious that velocity is the most determinant factor of the kinetic energy. Thus, it is reasonable to classify PHT in two categories based on the velocity (high and low) of the penetrating object [4, 5]. Although a clear cut-off value between high and low-velocity objects does not exist, objects with a velocity (predominantly missiles) over 600 m/s are considered of high velocity [4] (Fig. 31.1). High-velocity objects are related to the generation of secondary missiles from skull fragments. Examples of low-velocity penetrating objects are knives, nails, scissors, etc. [1].

PHT caused by low-velocity objects results in direct destruction of the brain parenchyma as a result of the crush injury. This type of PHT creates a wound track that is surrounded by an area of interstitial bleeding, the so-called "extravasation zone". Low-energy PHTs are related to injuries in the thinnest part of the skull such

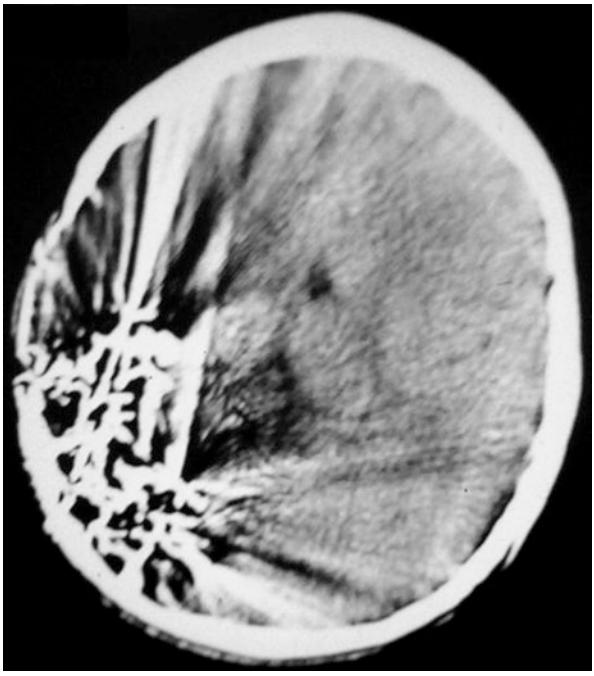

Fig. 31.1 Gunshot injury in a 4-year old boy

as the orbit. Concerning high-velocity PHTs, in addition to the direct trauma, they cause more extensive damage due to the generation of a pressure wave which causes radial stretching injury to the surrounding parenchyma and as a result a large temporary cavity is created. Finally, the temporary cavity will collapse due to absorption of the pressure wave from cerebral parenchyma and a residual permanent cavity remains. This phenomenon is called "cavitation" and is significant only in high-velocity injuries [6, 7].

31.3 Penetrating Objects

In cases of PHT from high-velocity objects, missiles are the predominant cause [1, 8]. Bullets from Full Metal Jacket (FMJ) handguns are probably related to a greater extent of cavitation injury [6]. Moreover, the trauma from missiles is related to the generation of secondary projectiles. These projectiles can be small skull or scalp fragments or bullet fragments. The frequency of gun-shot injuries is higher in the United States of America (USA), and less common in Asian countries [8].

In PHT caused by low velocity objects, a wider range of penetrating materials has been reported. Knives account for approximately 30% of the penetrating objects, followed by nails and wires. Moreover, PHT from scissors, metal spikes, pencils, glasses, some bizarre cases from chopsticks, and potato peelers have been reported. In adolescents and adults, cases of low-velocity PHT are less frequent and the majority of cases concern trauma from knives [3] (Table 31.1).

Table 31.1 Summary of PHT classification, management, imaging, complication, and prognosis

Types of PHT	Penetrating objects	Emergency management	Neuroimaging procedure of choice	Operation Targets	Complications	Prognosis
High velocity (over 600 m/s)	Bullets	According to ATLS protocol	CT DSA for vascular complications	Debridement, hematoma evacuation, edema reduction, fragments removal	Septic (abscess, meningitis, ventrculitis) Vascular (post-traumatic, aneurysms, AV fistulas) Seizures/ epilepsy neurological deficits	Highly lethal
	Skull and scalp fragments					
Low velocity	Knives (more common)					More favorable
	Wires					
	Nails					
	Bizzare accidents					

PHT Penetration Head Trauma, *ATLS* Advanced Trauma Life Support, *CT* Computed Tomography, *DSA* Digital Subtraction Angiography, *AV* Arteriovenous

31.4 Clinical Evaluation and Injury Sites

In all cases of PHT, the patient is evaluated and resuscitated according to the primary survey of ATLS (Advanced Trauma Life Support) protocol. When the patient is hemodynamically stable, an unenhanced brain computed tomography (CT) scan should be performed that will determine the further management of the patient. As with all trauma cases the rule of the first "golden hour" should be followed with no delay with unnecessary clinical evaluation. If possible, the collection of information related to the mechanism of trauma and the type of the penetrating object should be obtained, again without delay of the primary survey [9–12].

Approximately 60–90% of patients with PHT from gunshots will expire before hospital admission, and half of the children will expire during the hospitalization. Thus, due to the level of emergency, the only neurological evaluation that can take place in these patients during admission is usually through the Pediatric Glasgow Coma Scale (GCS) and evaluation of pupil reflex. It has been observed that 30% of these patients will have a GCS score of 8 or lower and need emergency intubation. In PHT from projectiles, the injury usually concerns the frontal lobe in 30% of cases, followed by temporal (15%) and parietal (15%) lobes. Multiple sites of injury or bihemispheric injury are present in about 10–20% of all cases and are poor prognostic factors for patient's survival. Posterior fossa and brainstem regions are unlikely to be injured by a bullet, however a penetrating trauma in these regions is almost always fatal [9, 10].

The evaluation of children with PHT can be challenging and the extent of injury may be underestimated by the physician. In fact, 70% of the children with low-velocity PHT are fully conscious during the admission, while less than 10% will have a GSC under 9 as reported by Domingo et al. [3]. Possible risk factors associated with underestimation of the injury severity are the normal level of patient's consciousness, the absence of neurological findings at the time of admission, and the small size of entrance wounds in the scalp [2]. All the burden of neurological manifestations may occur in patients after PHT, including seizures, hemiplegia, sensory deficits, and visual disturbances [3]. Nevertheless, the absence of clinical symptoms is not sufficient to exclude brain injuries after PHT, and an aggressive evaluation is suggested in all patients admitted with PHT [11]. As with PHT from high-velocity objects, the frontal and parietal regions are most commonly injured [3].

31.5 Neuroimaging

The neuroimaging procedure of choice for evaluation of both children and adults with or suspected PHT is the CT scan. Once the primary survey is completed and the patient is stabilized, an emergent unenhanced brain CT scan should follow to reveal the extent of the damage. Ideally, a portable CT scanner is preferred to reduce transfer delays. The latter is invaluable in cases of PHT from shotguns. Any skull

base fractures should be identified early, due to the risk of delayed complications. Track hematomas are a typical and expected finding in the majority of cases. In low-velocity PHT, the lesions are usually local to the track, while in gunshot injuries, lesions can be found in remote areas due to the developed pressure waves and due to the presence of secondary bullet or skull fragments. The entry site in the skull is identified as a stellate or depressed fracture in gunshot injuries, while in PHT from knives a slot fracture is more common. Brain parenchyma is evaluated for the presence of hematomas, edema, ischemia, herniation, foreign bodies, pneumocephalus, vascular injuries and features suggesting diffuse axonal injury (DAI). The hematomas may be intraparenchymal (more common), subarachnoid (SAH), extradural or subdural. Epidural hematomas are related to depressed skull fractures. Interestingly, in low-velocity PHT, CT may be without pathological features in a significant percentage of patients (about 20%). In cases where the penetrating object contains metal materials, significant artifacts are expected that may limit the evaluation of the image. An enhanced CT scan is performed in cases where the initial unenhanced CT suggests lesions in major vessels [1–3, 13, 14].

In the era of CT scan, plain X-rays are of limited significance in the evaluation of patients with PHT. They are utilized in cases where a CT scan is not available and may reveal a skull fracture and ballistic features of the penetrating object. Thus, they may be utilized as a forensic, rather than as a diagnostic tool [13].

Magnetic Resonance Imaging (MRI)v is rarely used in the early management of patients with PHT. Apart from the time delay, the main reason for that is the risk of causing more damage due to the displacement of the penetrating object in cases when it contains ferromagnetic materials. Nevertheless, if there is a certainty for the material's content or the penetrating object has been successfully removed and the procedure delays will not influence the patient's survival, MRI is the most sensitive and specific imaging technique for evaluation of neurotrauma [14].

Digital Subtraction Angiography (DSA) in the early management of the patient is preferred in cases where a brain vessel injury is suspected from the CT/ CT angiography findings. It is the method of choice for the evaluation of post-traumatic aneurysms, arteriovenous fistulas, and arteriovenous malformation (AVM). These complications are more frequent in children than in the adult population after PHT. Thus, delayed DSA is recommended in all children after PHT, especially after low-velocity PHT to prevent a catastrophic aneurysm rupture [2, 15].

31.6 Management

Up to date, no specific guidelines exist for the management of children with PHT. During the resuscitation period, the primary survey of ATLS is applied in all cases regardless of the age of the patient and the mechanism of trauma. The airway should be secured, and the cervical spine should be stabilized. In children, the scalp is highly vascularized. Thus, they are at risk of severe bleeding after PHT that may lead to hemodynamic shock if not appropriately managed. Neurological parameters

that are evaluated during the resuscitation period is the GCS and the pupil reflex. These two parameters and the CT findings will define the further management of the patients. After patient stabilization, a fast and targeted examination of the scalp for the assessment of the entrance wound is suggested. Moreover, any signs suggesting cerebrospinal fluid (CSF) leakage or skull base fracture should be noted (e.g. hemotympanum, Raccoon's eyes). In children, excessive CSF leakage may be noted after penetration of the fontanelles [1, 10, 12].

The further surgical management of the patient varies between different institutions and is depended on the patient's consciousness level and CT findings. If the patient has bilateral mydriasis and the GCS is 3, then prognosis might be poor. In the absence of any intracranial pathology or necrotizing tissue, simple closure of the wound can be performed, and the prognosis is promising. However, if signs of necrosis in the scalp, skull or dura are present then wound debridement is necessary with graft replacement. Currently, it is not clear if craniotomy or craniectomy is the optimal choice for patients, but in recent years, craniotomy is recommended in cases where no significant brain edema is expected. Evacuation of large space-occupying hematomas causing significant edema should be immediately performed. Missiles or in-coming skull fragments are generally removed if they are implanted proximal to the brain surface and their removal is not accompanied by a high risk of fatal outcomes or severe disability. The benefit from intracranial pressure (ICP) monitoring after PHT is not clear, and thus its application is contentious. However, it is a common practice for many surgeons to apply ICP monitoring after PHT, suggesting that an increase in ICP is a bad prognostic factor. Dural sealing is suggested in the case of wound proximity to open sinuses to reduce the infection risk. Administration of broad-spectrum antibiotics is necessary after PHT as it significantly reduces the risk of infectious complications. Finally, administration of a prophylactic anti-convulsive regimen after PHT is a common practice in most institutions [2, 9, 10, 16, 17].

31.7 Complications

The risk of infectious complications after PHT is increased in children. This is probably due to the increased frequency of PHT from toys or organic materials (e.g. woods). Generally, stab wounds and gunshot injuries, if not accompanied by the presence of in-coming scalp fragments (skin and hair), carry a relatively low risk of infection (5–15%). It is estimated that the rate of infection in children after PHT from low-velocity objects is about 40%, and thus prophylactic antibiotic regimen is suggested in such cases. The most common infectious complications are brain abscess (50–70%), followed by meningitis (20–30%), and less frequent ventriculitis, scalp or skull infections. Factors related to the track of the wound that increases the risk of infectious complications are trans-orbital, trans-ventricular traumas, and traumas involving air sinuses. CSF leakage is a major risk factor for the development of ventriculitis, a highly lethal complication. The prophylactic antibiotic

regimen is guided against the skin flora (Staphylococcus species and Gram-negative bacilli). Different regimens have been suggested according to guidelines [2, 3, 18, 19].

Vascular complications following PHT include the formation of traumatic aneurysms and arteriovenous fistulas. These complications occur in approximately 10% of children and are more common in low-velocity PHT. For this reason, early and delayed angiography is suggested to identify these complications and prevent catastrophic bleeding. Rupture of traumatic aneurysms is among the most common causes of delayed mortality and morbidity in patients with PHT. DSA is the preferred imaging technique, and apart from its diagnostic purpose, it can be used for endovascular treatment (balloon or coil embolization). Vasospasm after PHT can occur due to the post-traumatic SAH or more commonly after secondary rupture of a post-traumatic aneurysm. In such cases, prophylactic nimodipine is administrated to prevent ischemic complications [3, 20–22].

Early and late post-traumatic seizures are another well-known complication after PHT. Early prophylactic anti-convulsive regimen to prevent early-onset seizures is a common practice, although its efficacy is probably limited in the prevention of late-onset seizures. Early-onset seizures are probably indicative of the extent of cerebral damage. Retention of a foreign fragment is a risk factor for late-onset epilepsy, but the risk is probably lower than initially believed. Intraparenchymal hemorrhages and focal deficits are other risk factors of epilepsy development [18, 23, 24].

31.8 Prognosis

Not surprisingly, the PHT is the type of TBI with the greatest morbidity and mortality rates. In high-velocity PHT the majority of patients will die before hospital admission. In children arriving at the hospital, mortality is approximately 30–60%. However, in children surviving the accident the outcome is favorable and it is estimated that 80% of them will only have mild or moderate disabilities with a Glasgow scale outcome score of 4 or 5 [16, 25]. In low-velocity pediatric PHT, the prognosis is much more promising with a mortality rate of about 10% as reported by Domingo et al. The main causes of death in this group are large hematomas and latent traumatic aneurysm ruptures. In this group, a full recovery is expected in 60% of the children [3].

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Chapter 32
Spine Trauma

Vino Siva and Marios C. Papadopoulos

32.1 Introduction

Paediatric spinal trauma is relatively rare, accounting for 2–5% of all spinal trauma [1, 2]. Nonetheless, these injuries are a significant cause of morbidity and mortality in this population and pose special challenges for clinicians involved in their care. Gathering an accurate account of the neurological symptoms may be difficult and clinical examination is frequently challenging. This is compounded by the variation in the extent and type of injury dependent on the child's age and thus the level of activity interacting with the anatomical and functional developmental changes of the maturing spine.

In this chapter, we review the epidemiology, mechanisms and characteristics of traumatic spinal injury (TSI) in children and discuss general management principles including the role of surgery in this population. It is not possible, in one chapter, to provide a comprehensive review of the entire subject, but we hope to provide a broad overview with particular focus on the most common spinal injuries the reader may face in clinical practice.

32.2 Epidemiology

Paediatric spine fractures represent 1–2% of all paediatric fractures, with the vast majority (80%) occurring in the cervical spine [3, 4]. Thoracic and lumbar fractures represent only 0.6–0.9% of all spinal trauma cases, with their proportion increasing with age [1]. The incidence of TSI has two peaks, in children under 5 years and in

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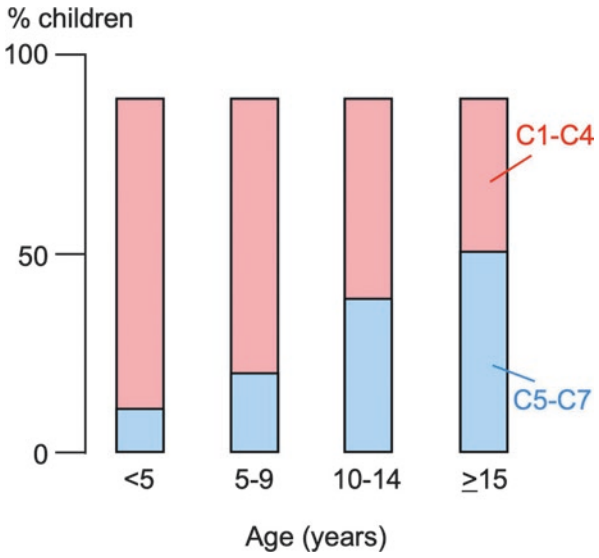

Fig. 32.1 Injury level (C1–4, C5–7) versus age. Data from the US National Pediatric Trauma Registry (n = 75,172) over a 10-year period, 1988–1998 [6]

those over 10 years old [5]. It is common to have seasonal peaks relating to school holidays [5].

One of the largest epidemiological studies from the US National Pediatric Trauma Registry over a consecutive 10-year period found that 1.5% of the 75,172 children registered in the database had cervical injury, with a male:female ratio 1.6:1 [6]. Upper cervical injury (C1–4) was prevalent across all age groups and almost double that of lower cervical (C5–7) injuries (52%, C1–4; 28%, C5–7). Lower cervical injuries became increasingly more prevalent in older children (85% occurring in children >8 years) (Fig. 32.1) [6, 7]. An overwhelming majority of cervical injuries were due to blunt trauma (95% of cases), of which road traffic accidents represented the largest proportion (61%). Of these, 42% were passengers, 14% pedestrians and 5% cyclists [6]. Passengers of motor vehicles were found to be unrestrained in 61% of cases. Falls, as a mechanism of injury, was more prevalent in the younger age group (18% in children ≤8 years vs. 11% in those >8 years), and sports-related injuries more common in older children (3 vs. 20%). Non-accidental injury should be recognised by the clinician, especially in younger children. Shaken young babies develop cranio-cervical junction injuries, whereas beaten children sustain injuries related to where the direct force was applied.

32.3 Children Are Not Small Adults

Children sustain distinct types of spinal injuries, not commonly seen in adults, related to their evolving spinal anatomy, the age-specific biomechanical properties of the spine and its supporting ligamentous and muscular structures [6].

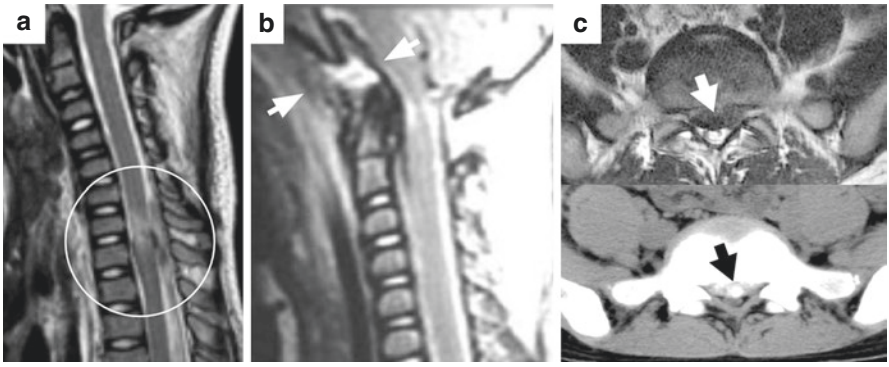

Fig. 32.2 Radiologic examples SCIs in children. (**a**) MRI of SCIWORA (circled). (**b**) MRI of atlanto occipital dislocation (arrows). (**c**) Top (MRI) and bottom (CT) of vertebral apophyseal fracture at L5/S1 (arrow)

In contrast to the adult spine, the paediatric spine exhibits intrinsic ligamentous laxity and elasticity, along with smaller and more horizontally orientated facet joints [1, 7]. These features, in addition to a markedly changing large head to torso ratio, along with the less developed paravertebral muscles, predispose infants and younger children to flexion-extension spinal injuries [5]. Such unique biomechanical characteristics explain why younger children (<8 years) suffer fewer fractures and higher rates of spinal cord injury without radiographic abnormality (SCIWORA) (Fig. 32.2a). Exposure of the hypermobile paediatric spine to hyperextension forces can lead to transient dislocation followed by self-reduction, resulting in spinal cord injury (SCI) even with normal bony alignment and no fracture on X-ray or CT [5, 7]. Patel et al.'s epidemiological study of the US National Pediatric Trauma Registry found that cervical spine dislocations were twice as likely in younger children than older ones (31% at age ≤ 8 years; 17% at age > 8 years) [6]. SCI occurred in 35% of children with almost half having SCIWORA. The changing head to torso ratio results in a fulcrum at C2–3 in infants, gradually descending with maturity to the adult position at C5–6 [8].

32.4 Initial Management of Paediatric Trauma

The early management of children involved in trauma follows the standardised approach of the Advanced Trauma Life Support (ATLS) protocols. The spine should be immobilised in a neutral position at the scene and throughout transfer to a Major Trauma Centre to avoid the risk of progression of neurological deficit through instability that has been overlooked.

Cervical injury should be suspected in high velocity injuries, in children with torticollis, neck pain or spasm, impaired consciousness and those with permanent or transient neurological deficit (including radiculopathies). It is common to face

difficulty fitting a rigid collar due to poor collar sizing or agitation. The UK National Institute of Clinical Excellence (NICE) guidelines and Advanced Paediatric Life Support (APLS) courses support a pragmatic approach whereby the spine is maintained in a neutral or comfortable position using blocks or rolled-up towels on either side of the head secured with tape [5, 9, 10]. In young children, the comparatively larger head may be forced into slight flexion when lying flat on a spinal board and, therefore, a degree of thoracic elevation may be required to accommodate this [7]. Rigid cervical collars can potentially exacerbate atlanto-axial distraction injuries; in suspected cases, sandbags placed on either side and secured with tape may be more appropriate than collars.

The primary SCI, sustained at the time of the insult, is generally irreversible. Secondary SCI, thought to be due in part to cord oedema, ischaemia and complex inflammatory processes, should be aggressively managed to reduce progression of neurological deficit. Cord hypoperfusion is a significant contributor to this, hence treatment of systemic hypotension is an important goal. Appropriate organ support including the use of vasopressors necessitate transfer to an Intensive Care Unit (ICU). Despite much research on neuroprotective therapies to reduce secondary SCI, currently, there are no drug treatments in clinical use. The controversy around corticosteroids in SCI persists. The National Acute Spinal Cord Injury Studies (NASCIS II and III) showed beneficial effect for methylprednisolone if given within 8 h of SCI for children aged >13 years, but others have found the benefits to be outweighed by the significant adverse effects of steroids including respiratory infection and sepsis [11–13]. In adults, the available evidence supporting the use of corticosteroids is unclear, and specific evidence in the paediatric population is even more sparse [13].

32.4.1 Recent Developments in Early Management of Acute SCI

Recently, techniques have been developed to monitor from the injury site by inserting a pressure probe under the dura to record intraspinal pressure (ISP) (Fig. 32.3) [14]. This allows the spinal cord perfusion pressure (SCPP) to be computed as mean arterial pressure minus ISP. The concepts of ISP and SCPP for SCI are analogous to the concepts of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) for brain injury. The optimum SCPP ($SCPP_{opt}$) can then be computed as the SCPP that optimises autoregulation (quantified using the spinal pressure reactivity index, sPRx) [14, 15]. $SCPP_{opt}$ varies between patients and temporally in each patient thus supporting individualised management. Multi-modality monitoring from the injury site has also been described using microdialysis to assess spinal cord metabolism [16]. Evidence from these monitoring studies [17] and from serial MR scans of SCI patients [18] suggests that the dura is a major cause of cord compression after SCI and a randomised controlled trial, termed DISCUS, is being set up to evaluate the

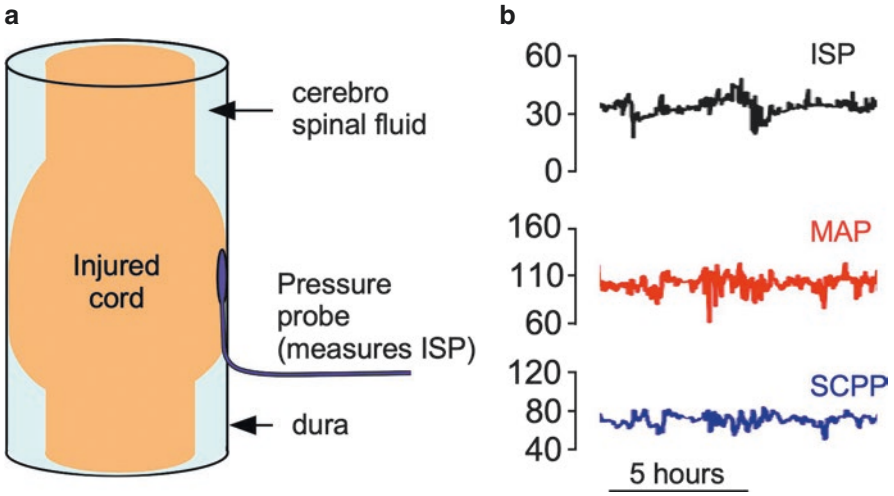

Fig. 32.3 Monitoring from injury site after severe SCI. (**a**) Schematic showing position of pressure probe between dura and swollen cord. (**b**) Monitoring of ISP, MAP (mean arterial pressure from radial artery) and SCPP (computed as MAP minus ISP)

role of expansion duroplasty in acute, severe SCI. The concepts presented here of ISP, SCPP, sPRx, $SCPP_{opt}$ and duroplasty have been developed in adult patients with SCI. Whether these concepts also apply to children remains to be shown.

32.5 Cervical Radiology

Consultation with a specialist Paediatric Radiologist is vital when interpreting paediatric spinal imaging, because it is easy to confuse normal anatomical variants for pathology. It is beyond the scope of this chapter to provide a thorough review of this subject, but some key points to consider are listed:

1. Prevertebral soft tissue swelling may be a normal finding in a crying child or during flexion. Such x-rays are best repeated when the child settles [19].
2. Radiological measurements differ in children compared to adults, for example the atlanto-dental interval is >5 mm in children compared to >3 mm in adults.
3. Pseudo-subluxation (commonly C2 on C3) may be evident due to cervical spine elasticity. Such subluxation is usually <2 mm and the spino-laminar line is not disrupted [9].
4. Epiphyseal growth plates (synchondroses) may be misinterpreted for fractures – theses tend to be symmetrical, and it may be useful to compare images of a patient of a similar age.

32.6 Specific Cervical Spine Injuries

32.6.1 Atlanto Occipital Dislocations (AOD)

AODs (Fig. 32.2b) are rare and sustained through high velocity injuries such as road traffic accidents. They occur three times more commonly in children than adults due to the higher head-to-torso ratio amongst other anatomical differences [20]. Most (~80%) patients have neurological symptoms at presentation, often associated with severe brain damage. A missed diagnosis in such patients often results in high mortality and morbidity. Early stabilisation is required to prevent this. CT is the initial modality of choice in high velocity injuries to identify the bony injury, followed by MRI to identify ligamentous injury. Horn et al. used CT and MRI to stratify patients into two groups (Table 32.1) [21]. Grade 1 injuries may be trialled with a halo brace for 12 weeks followed by flexion-extension X-rays to confirm stability. If the halo brace is unsuccessful, then occipital cervical fusion is required. Grade 2 injuries have gross disruption of ligamentous structures thus necessitating occipital cervical fixation upfront [21].

32.6.2 Atlas and Axis Fractures

Jefferson fractures, caused by axial loading of the head on the lateral masses of the atlas, is rare in children. Unlike the anterior and posterior arch fracture seen in adults, children may just have a single break with a hinge on the synchondrosis [3]. CT may suggest injury to the transverse ligament if there is fracture at the insertion sites on the medial lateral masses. MRI is useful to determine the integrity of the transverse ligament. If the transverse ligament is torn, C1–2 fusion is necessary. More commonly, if the lateral mass is fractured and the transverse ligament disrupted, a halo brace achieves healing in 74% of injuries, negating the need for surgical fixation [22].

Odontoid fractures are relatively common, and usually not associated with neurological deficits. The developing C2 vertebra has five ossification centres and six synchondroses, which close by 13.5 years [3]. In young children odontoid fractures usually propagate through the dento-central synchondrosis and are classed as Salter Harris type I (Fig. 32.4). The dens is usually angulated posteriorly, evident on a lateral X-ray. It is important not to confuse the mild angulation of the dens for a dens

Table 32.1 Atlanto axial dislocation according to Horn et al. [21]

Grade	CT	MRI
Horn grade I	Normal	Moderately abnormal
Horn grade II	Abnormal	Grossly abnormal

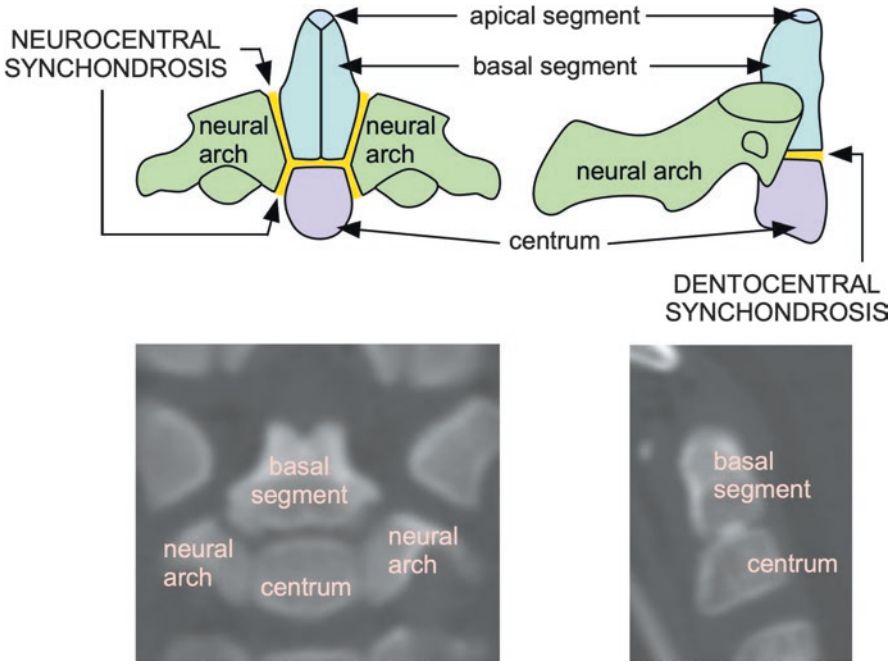

Fig. 32.4 Development of the C2 vertebra. Schemtacics and CT of the synchondroses and ossification centres of the C2 vertebra

fracture; dynamic imaging may be required to evaluate stability [3]. Displaced odontoid fractures may be reduced without traction using mild extension and posterior translation and placed in a Minerva collar for 6–10 weeks. Dynamic X-rays will help confirm stability and union.

Once dens synchondroses have closed, odontoid fractures may be classified as per the Anderson and D'Alonzo classification. Type I and III fractures are generally stable and managed with external orthoses, as are minimally displaced (<5 mm) type II fractures. Type II fractures with more significant displacement may require surgical intervention either odontoid screw or atlanto-axial fusion.

32.6.3 Subaxial Fractures and Ligamentous Injuries

These injuries are more common in older children and have adult fracture morphologies. Beyond the age of 8 years, the subaxial spine is well developed and bears close resemblance to that of an adult spine [23]. Typical fractures include compression vertebral body fractures, facet fractures with subluxation/dislocation, and spinous process fractures. The management is generally similar to that of an adult. Younger patients with subaxial fractures, can be managed in a hard, cervical collar

depending on the injury type, stability and presence of neurological deficit [23]. Although numerous calssification systems have been proposed to guide management of adult cervical fractures, none have been widely accepted or validated in the paediatric population. Nevertheless, the Subaxial Cervical Spine Injury Classification (SLIC) is a useful framework to manage these fractures [23].

32.7 Lumbar Spine Injuries

Knowledge of patient age and the various stages of development are crucial for accurate radiological diagnosis. Three ossification centres develop in each vertebra: the centrum plus right and left neural arches; these centres fuse between 2 and 6 years. There are five secondary ossification centres that fuse with the primary ossification centres in teenagers except the endplate ossification centres that fuse by the age of 25 years (Fig. 32.5) [5]. The spinal canal reaches near-adult volume by 6 years and the spine reaches near adult state by 10 years [1]. Due to a combination of ligamentous elasticity, shallow facet joint orientation, incomplete ossification and underdeveloped paravertebral musculature, the paediatric spine maintains its flexible state into early adolescence.

These normal developmental findings may be misinterpreted as pathological on imaging: the neurocentral synchondrosis can appear as a groove on either side of the vertebral body, and incomplete fusions of the endplates may be misconstrued as fractures [5]. Patients without injury may have anterior-to-posterior vertebral body height ratio as low as 0.89; this ‘physiological wedging’ of the vertebral bodies may be confused for compression fractures.

32.7.1 Compression Fractures

These commonly occur at the thoracolumbar junction and are the most common fracture. Children are more susceptible to these types of fractures owing to the physiological wedging and kyphosis of their spine during maturation. Axial loading due to falls or sports injuries are commonly associated with this fracture. Higher energy injuries may cause multiple compression fractures and one should have a low threshold for investigating for intra-abdominal injuries [24]. Though most such fractures have <30% loss of vertebral height, loss of >50% vertebral height makes it likely that the posterior ligamental complex is disrupted. Most of these fractures may be managed in a thoraco-lumbo-sacral orthosis (TLSO) for 8 weeks with good outcome. Evidence of end plate damage and an associated kyphosis of >30%, even in the context of stable injuries, make progressive deformity likely [1, 5].

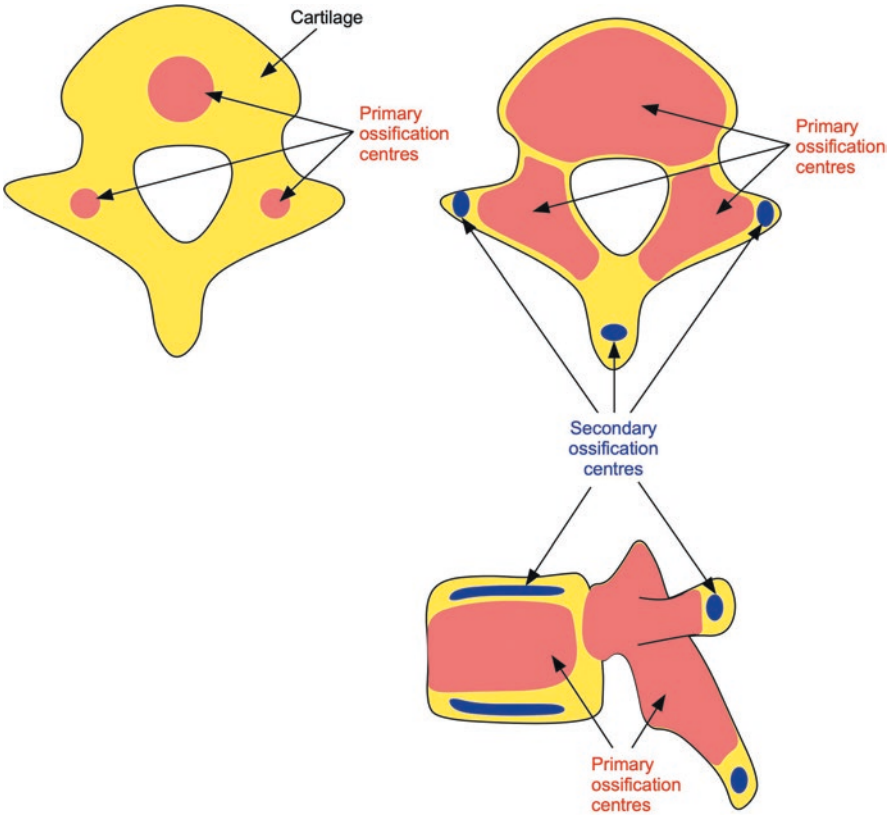

Fig. 32.5 Ossification centres of a vertebra. Primary (red) and secondary (blue) centres. Three primary (centrum, right, left) and five secondary (tip of spinous process, tip of left and right transverse processes, upper and lower ring epiphyses) centres

32.7.2 Burst Fractures

These fractures account for up to 20% of all vertebral body fractures and occur with axial loading without flexion. They are associated with higher energy injuries, are characterised by disruption of the posterior wall, and may be complete or incomplete. Retropulsed fragments into the spinal canal are commonly seen. Premature epiphyseal fusion may occur in younger children when the germinal layer is damaged [24]. CT is the usual initial imaging of choice then MRI to visualise neural structures and the posterior ligamental complex. Surgical management ranges from decompression with fixation to isolated fixation depending on the presence of neurological deficit and the degree of canal compromise. Whereas it is common to instrument two vertebral levels above and two below in adults, such fusions may lead to stunted truncal growth in children and crankshaft deformity, whereby the

posterior spinal fusion causes progressive rotational and angular spinal deformity due to continued growth of the anterior elements.

32.7.3 Vertebral Apophysis Fracture

The apophyseal ring ossifies by the age of 6 years and fuses by 18 years. It is attached to the annulus fibrosus. An osteo-cartilaginous portion lies between the vertebral body and apophyseal ring and is susceptible to repeated stresses. Patients classically describe a 'pop' at the time of injury with radicular leg pain, akin to disc herniation in adults [1, 5]. These distinct fractures are typically seen in adolescents and young adults from activities such as lifting heavy objects, falls or twisting injuries. CT may reveal a detached end plate fragment and MRI an associated disc herniation (Fig. 32.2c). If conservative measures are ineffective, surgical intervention such as microdiscectomy or posterior decompression often have good outcome [1, 5].

32.8 Spinal Orthoses and Surgical Considerations

In general, stable fractures are managed conservatively in a brace and unstable fractures require surgical stabilisation. In the absence of validated paediatric spinal trauma classification systems, the authors find it useful to use the frameworks used for adult spine to guide management.

Of the numerous braces available for thoracic and lumbar immobilisation, the authors have found that the TLSO brace is easily accessible (in the UK) and provides satisfactory outcome. For upper thoracic fractures, a Sterno-Occipito-Mandibular Immobiliser (SOMI) may be used in conjunction with a TLSO. Whatever the brace, interval review and imaging with X-rays provide a good safety net for patients whose fracture may progress. Typically, bracing therapy is applied for 10–12 weeks, but the duration depends on the type of injury and surgeon preference.

The decision to surgically intervene is determined by considering local fracture-related factors (need to decompress neural structures, stability of fracture, long-term healing potential) and systemic factors (haemodynamic status of patient, safety of general anaesthetic, need for haemodynamic management first). The authors find the Thoracolumbar Injury Classification and Severity (TLICS) score, which has been validated in children, a useful framework to guide management, but this needs to be placed in the context of the overall fitness of the patient and systemic injuries (Table 32.2) [23, 25]. Surgical stabilisation can generally be performed via posterior approach using adult-type instrumentation in children above 9 years of age. Younger children have smaller pedicles and smaller spinal canals which may make pedicle screw placement challenging; and sublaminar hooks unsafe. Computer navigation

Table 32.2 Summary of the Thoracolumbar Injury Classification and Severity scoring system (TLICS) [1, 23]

Feature	Score
Morphology	
Compression	1
Burst	2
Translation/rotation	3
Distraction	4
Neurology	
Intact	0
Nerve root	2
Cord (incomplete injury + 1)	2
Cauda equina	3
Posterior longitudinal ligament	
Intact	0
Indeterminate	2
Injured	3
Recommended treatment	
Non-surgical	**0–3**
Surgeon's choice	**4**
Surgical	**>4**

and robot assisted surgery may prove useful in such cases, though the latter is in the early stages of clinical practice [5].

32.9 Conclusions

The morphology of spinal fractures, their diagnosis and their management substantially differ in children compard with adults. In this chapter we highlighted several key differences to enable the treating clinician to make a common-sense approach to such injuries.

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Part VI
Cerebrovascular Disorders

Chapter 33
Arteriovenous Malformations

Torstein R. Meling

33.1 Introduction

Arteriovenous malformations (AVMs) are rare, complex lesions that consist of pathological vessels in the cerebral circulation characterized by a direct shunting between *feeding arteries* and *draining veins* without any intervening capillaries and a cluster of tortuous, dilated vessels forming the AVM *nidus* [1]. They are typically classified according to their location, nidus size and compactness, and draining vein patterns (deep vs. superficial) (Table 33.1). Furthermore, AVM-associated aneurysms can be found in 17– 29% of pediatric cases and they can be flow-related, intranidal, or venous [3, 4].

The exact pathophysiology of de novo AVMs is not completely understood, but probably involve a combination of genetic and molecular factors [1]. The embryological basis of AVMs is due to either the persistence of a primitive arterio-venous connection or the development of a new connection after a normal closure process [5]. AVMs are generally thought to be congenital, but they frequently grow during childhood, adolescence, and young adulthood. However, an increase in the number of reported de novo cerebral AVMs challenges the assertion that all AVMs develop in utero and therefore, the possibility of these lesions presenting postnatally cannot be excluded [1].

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Table 33.1 The Spetzler-Martin grading system [2]

Graded features	Points assigned
Size of AVM	
• Small (<3 cm)	1
• Medium (3–6 cm)	2
• Large (>6 cm)	3
Eloquence of adjacent brain	
• Non-eloquent	0
• Eloquent	1
Pattern of venous drainage	
• Superficial only	0
• Deep	1

The Spetzler-Martin AVM grade (1–5) equals the total number of points

33.2 Epidemiology of Pediatric Arteriovenous Malformations

Brain AVMs are infrequent in the general population and even rarer in the pediatric population [6]. In a 2012 national survey on the Danish incidence of the disease, Skjoth-Rasmussen et al. [7] found the incidence to be 0.4 per 100,000 person-years. Other population-based studies demonstrate an incidence of approximately 1.34 per 100,000 patient-years, with an estimated prevalence of AVM hemorrhage among detected cases to be 0.68 per 100,000 person-years [8]. With respect to gender, retrospective clinical series show similar incidences or a slight male preponderance [7, 9–14]. The median or mean age at presentation is typically around 12–14 years, with a range of 7–18 years [9, 10, 13, 15], but AVMs can also be found in neonates [7].

33.3 Clinical Presentation of Pediatric Arteriovenous Malformations

In the pediatric population, AVMs have a tendency to cause intracerebral hemorrhage, and they are responsible for 39% of cerebral hemorrhages in this age group [16]. The most common presenting signs and symptoms of pediatric AVMs are focal neurological deficit, headaches, and seizures [12] that result from AVM ruptures or micro-hemorrhages. Therefore, the necessity of an early diagnosis and treatment is crucial for a patient population with a long-life expectancy. However, due to the frequent absence of symptoms, the diagnosis of AVM tends to be made only after it has bled.

Basal ganglia, cerebellar, and posterior para-callosal AVMs were more common in pediatric than in adult patients. In contrast, frontal and temporal AVMs, were less common in pediatric than in adult patients [15].

33.3.1 Hemorrhagic Presentation

In clinical series, 41–69% of the pediatric AVM patients presented with intracerebral hemorrhage [9, 11, 12, 17–21]. Pediatric AVMs tend to rupture more frequently than in adults [15, 22], with an estimated risk of hemorrhage of 2–4% per year [5]. This leads to an estimated morbidity and mortality rate for each hemorrhagic event of 50% and 5–10%, respectively, in children [23].

In the absence of treatment, the cumulative risk of future hemorrhage is approximately 16 and 29% at 10 and 20 years after diagnosis of AVM without hemorrhage and 35 and 45% at 10 and 20 years when presenting with hemorrhage [24]. A useful formula for calculating a patient's risk of lifetime hemorrhage in percentage is the following: 105—patient's age in years [25]. Thus, for pediatric patients with a very long residual life expectancy, the cumulative risk of hemorrhage is high.

Among pediatric AVMs, the small and deep-seated ones are at higher risk of hemorrhagic presentation [9, 18, 26–30]. In a multicenter, retrospective cohort study with total of 357 pediatric patients, the risk factors associated with hemorrhagic presentation were deep venous drainage (OR 3.2; $p < 0.001$), which was the strongest independent predictor, followed by female sex and smaller AVM volume [18]. Periventricular nidus location [21], infratentorial location [12, 30], and single draining vein [21, 29, 30] are additional risk factors. Lastly, AVM-associated aneurysms increase the risk of hemorrhage [3, 4].

33.3.2 Seizure Presentation

Patients with cerebral hemorrhage are prone to having an acute seizure occurrence and in clinical series, 27–58% of pediatric AVM patients present with seizures [11, 31–33]. Although seizures are the most common symptom in *unruptured* brain AVMs [33], children present less often with epilepsy than adults [15].

Previous studies have shown a significant association between AVM size and seizure occurrence [33–36]. It is hypothesized that cause seizures by creating a hypoxic environment in surrounding brain tissue and that larger AVMs tended to have more arteriovenous shunting of blood, a factor associated with focal cerebral ischemia [35].

33.4 Management of Ruptured Pediatric Arteriovenous Malformations

When discussing management of pediatric AVMs, it is important to differentiate between ruptured and unruptured AVMs.

Patients who present with an intracerebral hemorrhage (ICH) from a ruptured AVM should be initially stabilized according to acute management guidelines for ICH [37]. Management begins in the pre-hospital phase with adequate ventilatory and cardiovascular support. Patients with a GCS ≤ 8 should be intubated [37].

A pediatric patient without risk factors for primary ICH such as hypertension, presenting with an abruptly decreased level of consciousness, should lead to a high degree of suspicion for a ruptured AVM and prompt expedited imaging. In the hospital, the ICH diagnosis is typically based on a non-contrast head computer tomography (CT), where calcifications raise a suspicion of an underlying vascular malformation. Critical CT features including the presence of intraventricular hemorrhage (IVH), hydrocephalus (HC), or impending herniation should be noted and dealt with expeditiously [38].

Conventional cerebral digital subtraction angiography (DSA) is the gold standard for AVM diagnosis, but non-invasive vascular imaging with CT angiography (CTA) or magnetic resonance angiography (MRA) are appropriate as initial screening tools [39]. The DSA will visualize AVM characteristics including its size, compactness, location in eloquent tissue, draining veins, and high-risk features that will influence risk of rupture, prognosis, as well as help guide management decisions. AVM-associated feeding artery or nidal aneurysms place a patient at high risk for re-bleeding, and they are often treated during the catheter-based DSA or during a microsurgical resection of the AVM (Fig. 33.1).

The mortality of an AVM rupture ranges from 10 to 30% [39] and definitive microsurgical AVM resection is often recommended after hemorrhage for all but the highest risk lesions (SM grades 4 and 5) given the increased risk of re-rupture [40]. Microsurgical resection of ruptured AVMs has a very high obliteration rate and the effect on the risk of re-rupture is instantaneous. Overall postoperative angiographically confirmed obliteration rates range from 95 to 100% in pediatric populations [9, 14, 41]. However, besides the size, location and the vascular AVM morphology, concerns in children include timing, small blood volume and limited cardiac and metabolic reserve.

Microsurgery often commence after a cooling-down period of 2–6 weeks after an AVM rupture, as early ICH removal may be associated with an increased risk of permanent neurological deficits due to friable brain parenchyma immediately following rupture [40], and the hematoma and edema may obscure or compress the AVM acutely, leading to early imaging that may not reflect the true extent of the lesion. LoPresti et al. [42] compared initial decompressive craniectomy at time of rupture followed by interval surgical AVM resection to initial AVM resection. They found that children presenting with AVM rupture who require emergent decompression may safely undergo emergent craniectomy with interval AVM resection and

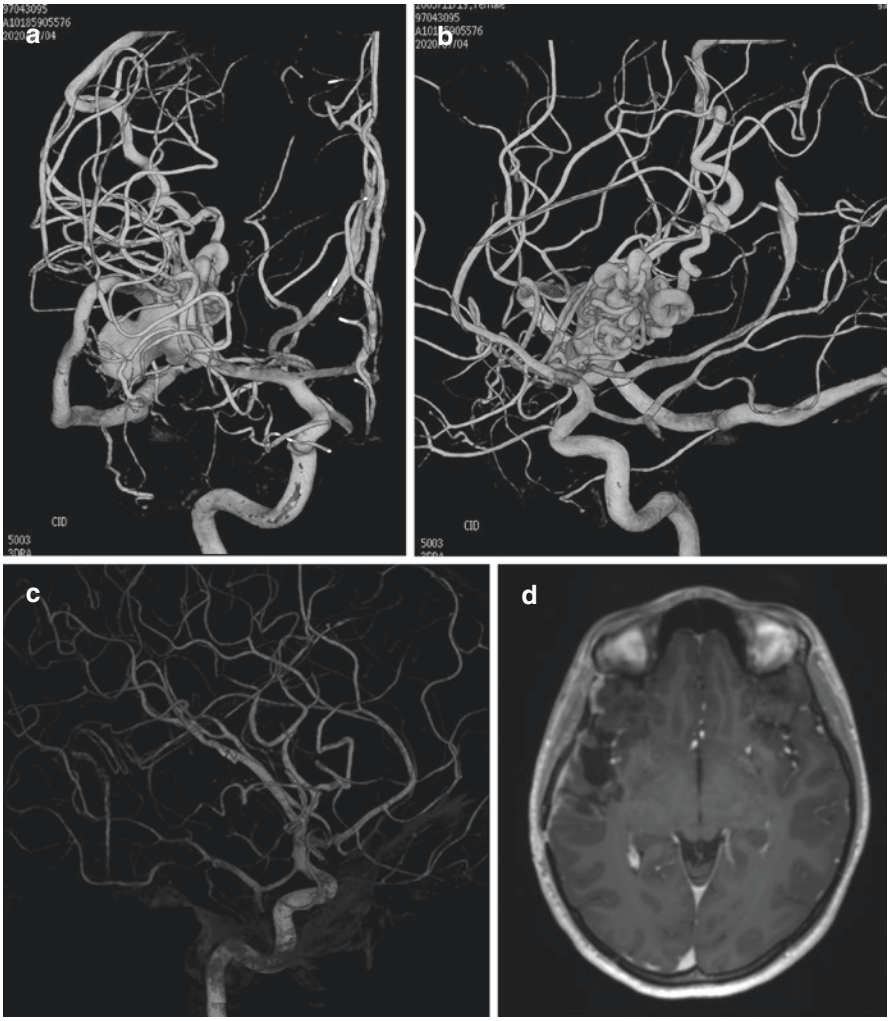

Fig. 33.1 14-year-old girl with an episode of sudden headache without loss of consciousness. CT revealed a subarachnoid hemorrhage and a DSA showed a giant aneurysm (25 mm) in the Sylvian fissure (**a**) with a small right-sided insulo-temporal AVM (Spetzler-Martin grade 1) medial to the giant aneurysm (**b**). She underwent emergency surgery with clipping and resection of the aneurysm, followed by a complete resection of the AVM, as verified by a postoperative DSA (**c**). 6 months after surgery, she was mRS 0 without any sequelae and an MRI showed no residual lesion (**d**)

cranioplasty without additional risk of morbidity or mortality [42]. In contrast, if the ICH causes a significant mass effect and neurological deficits, urgent intervention is recommended [43] (Fig. 33.2).

In the rather rare instances where a life-threatening ICH results in expanding edema, intracranial hypertension, and herniation, a decompressive craniectomy with or without clot/AVM evacuation may be warranted [39].

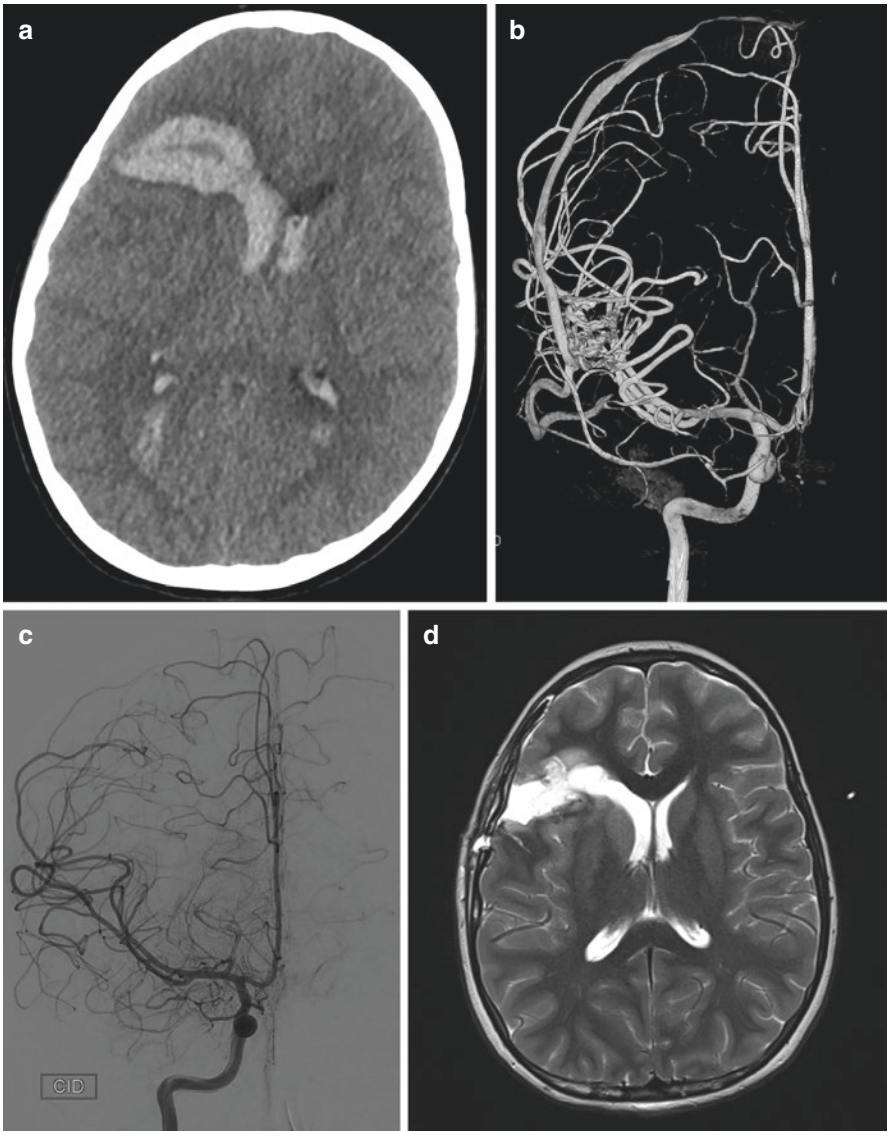

Fig. 33.2 6-year-old left-handed boy with an episode of sudden loss of consciousness whilst playing computer games. Quickly deteriorated with hemiplegia and dilated pupil. He was intubated, sedated and hospitalized. CT revealed a massive right-sided intracerebral and intraventricular hemorrhage (**a**) with effacement of the basal cisterns and midline shift. DSA showed a medium-sized AVM in eloquent cortex (Spetzler-Martin grade 3) with a superficial venous drainage that was filled by feeding arteries coming off the middle cerebral artery (**b**). He underwent emergency surgery and because if an ongoing hemorrhage and extremely raised intracranial pressure, we decided to resect the AVM as we evacuated the hematoma. A complete resection of the AVM was verified by a postoperative DSA (**c**). 6 months after surgery, he had already made an excellent recovery (mRS 1) and an MRI showed no residual lesion (**d**)

33.5 Management of Unruptured Pediatric Arteriovenous Malformations

Different therapies exist and their aim is to prevent catastrophic intracranial hemorrhages and alleviate neurological symptoms. Since pediatric patients have longer life expectancies and higher rates of AVM recurrence than adults, treatment durability and efficacy is of paramount importance [44]. Especially in deep-seated pediatric AVMs, where their location and the young patient age make treatment riskier; choosing the right approach is of crucial importance [45]. However, in contrast to adult AVMs where a European consensus on treatment has been proposed [46], the best approach is yet to be defined in pediatric AVMs. Although there is one randomized trial comparing interventions to medical management of AVMs in adults [47], the ARUBA trial included exceedingly few microsurgical cases and pooled treatments that are extremely heterogeneous with respect to obliteration rates, timing of effect, and hemorrhage rate per 100 patient-years after therapy, thereby making it impossible to draw sound conclusions [48, 49]. Nonetheless, it is clear that if treatment is indicated, the primary strategy should be defined by a multidisciplinary team prior to initiating the treatment and should aim at complete eradication of the AVM [46].

33.5.1 Microsurgery for Unruptured Pediatric AVMs

Microsurgical resection of AVMs remains the most time-tested and immediate treatment for cure of these lesions. As for microsurgical resection of ruptured AVMs, most modern series on microsurgery for unruptured pediatric AVMs report complete obliteration rates of close to or at 100% [9, 14, 41], especially after inclusion of high-quality intra-operative DSA to confirm resection of the AVM. Furthermore, the effect on the risk of re-rupture is instantaneous (as opposed to radiotherapy, see below) and rarely involve more than one séance (as opposed to endovascular therapy, see below). However, there are associated treatment risks and in order to better classify AVMs and to better stratify associated risks of microsurgical resections, Spetzler and Martin [2] established a five-tier grading system based on AVM size, pattern of venous drainage, and eloquence of the lesion (Table 33.1). Analysis of multiple series have shown this grading system to reliably predict permanent major morbidity or mortality at the following levels: Grade I (4%), Grade II (10%), Grade III (18%), Grade IV (31%), and Grade V (37%) [50].

In our current thinking, small lesions in non-eloquent tissue (Spetzler-Martin Grade I and II) should primarily be treated by microsurgical resection with or without adjunct endovascular embolization [51–53]. Preoperative embolization can greatly facilitate surgical excision, but it should be used only when the combined risk of embolization plus surgical excision is lower than the estimated risk of surgical excision alone. In general, embolization should not be presented to the patient as

an acceptable alternative to surgical excision in patients with Grade I or II AVMs which can be surgically excised with less morbidity than the morbidity of embolization as demonstrated by most modern surgical and embolization series. In contrast, Spetzler-Martin Grade III AVMs are the most heterogeneous grade and require surgeons and neurointerventionalists to tailor the therapy more selectively. These lesions have been subclassified within the Grade III spectrum by Lawton et al. [54] and some Grade III lesions may be treated with endovascular embolization followed by surgery. Grade IV and V lesions are often considered high risk and preferentially managed medically [40].

With respect to outcomes of microsurgical resection, there are no large series of pediatric patients with only unruptured AVMs. In a series of 117 children with cerebral AVMs of whom 56% were ruptured, Gross et al. [14] found, that 94% had good functional outcomes (mRS Scores 0–2), and these outcomes were significantly influenced by the mRS score on presentation before surgery. In a study by Ravindra et al. [13] of 97 pediatric patients where 66% presented with hemorrhage, focal neurological deficit on presentation, AVM size >3 cm, and lesions in eloquent cortex were independent predictors of persistent neurological deficits at long-term follow-up. 92% had an mRS score 0–2 on long-term follow-up.

33.5.2 Stereotactic Radiosurgery for Unruptured Pediatric AVMs

Stereotactic radiosurgery (SRS) is a radiation technique that uses technology to converge a high dose of radiation on a precisely defined target volume while minimizing irradiation to surrounding tissue. SRS plays an important role in the treatment of unruptured AVMs, with modalities including gamma knife radiosurgery (GKRS), linear accelerator (LINAC), and proton beam. Radiosurgery destroys the AVM and causes the blood vessels to close off over time. However, major drawbacks of SRS include a 1–3-year latency period until obliteration and significantly lower complete obliteration rates compared to microsurgery [55].

With respect to AVM obliteration after SRS, a recent multicenter, retrospective cohort study by Chen et al. [56] with 539 pediatric patients with unruptured AVMs estimated the probabilities of complete obliteration to only 64%, 77%, and 88% at 5, 10, and 15 years, respectively. A recent meta-analysis by Borcek et al. [57] pooled data from 20 studies with 1212 patients and found that SRS resulted in complete obliteration in only 66% of patients. Furthermore, the efficacy of GKRS correlated with the size of the AVM: 91% for small, 86% for medium, and 64% for large AVMs [58]. In studies on Spetzler-Martin grade IV AVMs treated with GKRS, actuarial obliteration rates at 5 and 10 years were 19% and 35%, respectively [58].

With respect to complications after SRS, hemorrhagic stroke, death, and permanent radiation-induced changes were found in 6%, 3%, and 8%, respectively, in the study by Chen et al. [56]. In addition, SRS treatment of pediatric AVM patients have

an approximately 2% annual risk of morbidity and mortality, which appears to plateau after 10 years [56]. Similarly, the meta-analysis by Borcek et al. [57] found an overall complication rate (including new hemorrhage, new neurological deficits, and mortality) of 8.0%. and several studies show similar findings with respect to obliteration rates and complication rates [10, 22, 58–64].

With respect to post-SRS hemorrhage, Chen et al. [65] found cumulative probabilities of 5%, 10%, and 15% over 5, 10, and 15 years, respectively. Similarly, Hasegawa et al. [59] found cumulative hemorrhage rates after GKRS at 9% and 12% at 5 and 10 years, respectively. Several SRS studies show an annual risk of post-radiosurgery hemorrhage between 1% and 3% [59, 61–63, 65–68], which is not that dissimilar to the natural history of the disease.

Repeat SRS may be considered if DSA after 3 years shows that the AVM nidus is not obliterated, as some studies in adults have shown that total obliteration is achieved in 60–70% after repeat SRS [69, 70]. However, the post-SRS hemorrhage rate was 3% per year and symptomatic radiation-induced changes were seen in 10% of patients [70].

Although it seems that GKRS does not expose young patients to a higher risk of sequelae than that for older patients [71], the rates are not negligible. In a cohort of 75 pediatric patients, Borcek et al. [67] found that 5% of their patients experienced ICH, 16% developed new deficits, and the annual rate of developing new deficits was 6% during the follow-up period. In a retrospective study of 105 pediatric AVM patients, Pan et al. [58] reported that GKRS treatments were associated with an 8% morbidity rate. In their meta-analysis, Borcek et al. [57] reported a post-SRS new neurological deficit rate of 3%. Chen et al. [60] found symptomatic radiation-induced changes in 7%, similar to the results of a multicenter, retrospective cohort study of 357 patients by Starke et al. [66] where symptomatic radiation-induced changes occurred in 8%. Other authors report similar or lower rates [61–64, 68].

There is limited experience using proton beam SRS for unruptured pediatric AVMs and so far, the results seem inferior to those of GKRS. Walcott et al. 2014 [72] reported 44 consecutively treated pediatric patients and found a 41% obliteration rate after a median follow-up of 52 months. 17 patients underwent repeat proton beam SRS and 9% experienced hemorrhage after treatment.

33.5.3 Endovascular Therapy for Unruptured Pediatric AVMs

Endovascular therapy (ET) may play a role in the treatment of unruptured pediatric AVMs, be it as an adjunct to SRS and/or microsurgery [73] or as curative, standalone therapy in 10–20% of these lesions [74]. The procedure involves the injection of glue or other non-reactive liquid adhesive material into the AVM in order to block it off. For this purpose, a small catheter is passed through a groin vessel all the way up into the blood vessels supplying the AVM. The development of more performant endovascular embolization agents and catheters has led to an increased use of ET in pediatric AVMs [45].

The clinical experience in pediatric AVM patients is limited, especially in the very young. ET typically requires multiple sessions [73, 75, 76], but can achieve fairly high rates of complete obliteration in carefully selected patients (typically smaller AVMs with single feeding arteries). In a single-center, retrospective analysis of 23 children who underwent embolization using Onyx, de Castro-Afonso et al. [75] obtained complete angiographic AVM obliteration in 91% at 6-month follow-up after an average of 2 sessions. However, in several other studies, the obliteration rates have been alarmingly low, such as Soltanolkotabi et al. [76] who achieved complete obliteration in merely 12% of their 25 pediatric patients who underwent Onyx embolization. In a series of 48 pediatric AVMs, Berenstein et al. [77] reported an angiographic cure rate of 22% and a complications rate of 7% after ET and Blauwblomme et al. [78] found that patients who underwent partial embolization of a AVM had an annual bleeding risk of 4.7% compared to 1.6% per year for AVMs not submitted to partial embolization (surgery or complete embolization). El-Ghanem et al. [5] identified three studies comprising a total of 139 pediatric AVMs patients treated with ET where the complete obliteration rates ranged from only 12 to 22%. However, with the advent of novel endovascular techniques such as transvenous access to the AVM, the outcomes of this treatment modality will hopefully improve [79].

Besides a widely varying obliteration rate, embolization-related complications are observed in 7–26% [5, 75, 76]. Furthermore, ET carries a risk associated with radiation in the pediatric population, as multiple sessions are often required [5, 75, 76]. Due to their increased sensitivity and life expectancy, the window of opportunity for expressing radiation damage is greater [80]. It is suggested to stage embolization of complex lesions in pediatric patients to limit both the contrast agent dose and the radiation exposure [81]. Additionally, it is believed that less dramatic alterations in cerebral hemodynamic, achieved through staged embolization, results in lower potential for morbidity [44].

33.5.4 Multimodality Treatment of Pediatric AVMs

In complex or deep-seated AVMs, achieving a nidus obliteration often requires the combination of microsurgical resection, endovascular embolization and SRS [45, 82, 83]. The obliteration rates in case of multimodal therapy range between 18 and 93% [45], but the main advantage of this treatment strategy is a potential reduction of the risk of temporary and permanent complications [82, 84, 85]. It should be noted that a large meta-analysis of 1716 adult patients indicate a reduced efficacy of GKRS in AVMs previously embolized [86], meaning that the if embolization is clinically indicated, it is recommended to be deferred until after SRS is delivered.

Considering the multiple treatment modalities available and subtleties in the temporal administration of these, patients with AVMs should be evaluated by an interdisciplinary neurovascular team consisting of neurosurgeons, neurointerventionalists, radiosurgeons, and neurologists experienced in the diagnosis and

treatment of brain AVM [46]. It is also clear that if treatment is indicated, the primary strategy should be defined by the multidisciplinary team prior to initiating the treatment and should aim at complete eradication of the AVM [46].

33.6 Follow-Up of Pediatric Arteriovenous Malformations

Long-term follow-up with imaging after AVM treatment is very important. Pediatric AVMs tend to have higher recurrence rates after treatment compared to adults, perhaps in part due to their longer life expectancy and the growth spurts [87]. In a recent systematic literature review by Jimenez et al. [88], 57% of patients who did not have follow-up imaging re-presented with rupture of a recurrent AVM. In several series, up to 7% of pediatric patients with brain AVMs develop radiographic recurrence after long-term follow-up despite initial complete surgical resections that were documented by intra- or postoperative angiography [19, 89]. We therefore recommend that angiographic scans be obtained intraoperatively or early postoperatively to document complete resection and again at 1, 3 and 5 years after surgical resection [89].

33.7 Outcomes in Children with Cerebral Arteriovenous Malformations

When discussing outcomes of pediatric AVMs, we should differentiate between ruptured and unruptured AVMs. Ideally, outcomes should also be stratified with respect to AVM features and treatment modalities, but this is not possible due to the scarce data available in this patient population.

33.7.1 Functional Outcomes in Children with Cerebral Arteriovenous Malformations

With respect to functional outcomes in children with brain AVMs, good outcome (mRS 0–2) is seen in 54–92% of patients [9, 13, 17, 19, 20, 41, 90]. In a recent meta-analysis, Lu et al. [91] identified 14 studies describing outcomes of 699 pediatric AVM patients and found an mRS 0–2 in 87% of the patients. Favorable functional outcome was seen in 78% of those with hemorrhagic presentations and in 91% of those with non-hemorrhagic presentations [91].

Risk factors for poor outcomes include low pre-treatment mRS and Glasgow Outcome Score, flow-related aneurysms, focal neurological deficit on presentation, AVM size >3 cm, lesions in eloquent cortex [9, 13, 90]. In contrast, studies indicate

that small AVM size and surgical treatment correlated with a favorable long-term outcome [15].

The plasticity of the developing brain provides better tolerance to neural injury and a better potential for recovery, compared to adults . It seems that pediatric patients suffering AVM hemorrhage have better outcomes than adults, despite a poor neurological state initially. In a study of 15 pediatric patients with GCS scores <9 following AVM hemorrhage (11 patients had fixed pupils on clinical examination), Singhal et al. [92] found an overall mortality rate of 20% and 1 year after the AVM hemorrhage, 92% of the surviving patients were functioning independently.

33.7.2 Seizures in Children with Cerebral Arteriovenous Malformations

With respect to seizures in children with brain AVMs, it is the second most common initial manifestation in children and can affect their intellectual capacity and neuropsychological status, among other deleterious effects [93]. Regretfully, the seizure control rate is low in patients with unruptured AVMs [94] and even when the AVMs nidus is obliterated or removed through microsurgery, SRS, or ET, many patients still suffer from seizures that can affect their quality of life [34, 95–97].

Seizures can present as a complication following AVM treatment [95]. In a meta-analysis of 24 studies with a total of 1157 patients, Baranoski et al. [98] found that new-onset seizures occurred more frequently in patients undergoing ET (39%) compared to microsurgery (9%) SRS (5%) ($p < 0.3$ and $p < 0.01$, respectively). Risk factors for seizures post-treatment include seizure presentation, male gender, larger AVM size, and temporal location [11, 31].

For patients with pre-treatment seizures, good seizure outcome is achieved in 74% [32]. In a retrospective analysis of a cohort of 89 pediatric patients, Liu et al. [33] found that 55% of the children were classified as Engel class I after treatment. Studies indicate that microsurgical treatment is correlated with a higher proportion of seizure control [98].

33.8 Conclusion

Despite their low incidence, cerebral AVMs carry significant risk of morbidity and mortality in the pediatric population. Furthermore, AVMs are increasingly diagnosed in children due to an increasing use of CT and MRI imaging, posing difficult questions regarding the optimal management of incidental or pauci-symptomatic lesions. Intracranial hemorrhage as the initial presentation is more common than in adults, prompting urgent care. Contemporary approach includes surgery, embolization, or radiosurgery; alone or various combinations thereof. Considering the

multiple treatment modalities available and subtleties in the temporal administration of these, AVM patients should be evaluated by an interdisciplinary neurovascular team experienced in the diagnosis and treatment of brain AVM [46]. If active treatment is indicated, the primary strategy should be defined by the multidisciplinary team prior to initiating the treatment and should aim at complete eradication of the AVM [46].

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Chapter 34
Cavernous Malformations

Michael Karsy, Richard H. Schmidt, and Robert J. Bollo

34.1 Introduction

Cerebral cavernous malformations (CMs), also known as cavernomas or cavernous angiomas, represent a distinct class of intracerebral vascular abnormality defined by an abnormal collection of thin-walled sinusoidal blood vessels without intervening brain parenchyma [1–3]. Although they are occasionally referred to as cavernous hemangiomas, CMs are distinct vascular lesions unlike cavernous hemangiomas, which are vascular neoplasms [4]. CMs demonstrate a discrete, lobulated appearance from normal neural tissue along with hemorrhage of various age, along with hemosiderin and gliosis. Despite low rates of annual hemorrhage ranging from 0.3 to 2.3% per patient-year, symptomatic hemorrhage resulting in neurological deficit or seizure can be seen at substantial rates, depending on the number of lesions, lesion location, lesion size, and presence of developmental venous anomalies (DVA) [5–11]. This chapter will review some of the epidemiology, diagnosis, and surgical and nonsurgical management of these lesions.

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34.2 Epidemiology

CMs represent the second most common type of cerebrovascular lesion, accounting for 10–15% of all vascular malformations and showing a prevalence of 0.5–0.8% of the population [3, 11]. Estimates of CMs in pediatric patients remain limited due to fewer studies on the topic and lower prevalence. One study demonstrated a prevalence of 0.23–0.88% in pediatric patients age <1–17 years, with rates approximating those of adults only in older children [12]. The annual U.S. incidence of CMs ranges from 0.15 to 0.56 per 100,000 person years [13]. In one study of patients aged 50–80 years undergoing MRI, the prevalence of CMs was 1:200 patients but only 1:2700 showed symptoms [14]. Thus, likely there are significant numbers of pediatric patients that will have incidentally identified CMs requiring management.

34.3 Diagnosis

34.3.1 Clinical Presentation

Most patients present between the ages of 30 and 50 years, although CMs can also occur in children, and with an equal prevalence between men and women [2, 7, 15–18]. Reasons for presentation, namely hemorrhage or seizure, are similar in pediatric CMs [15–18]. Most cavernous malformations are supratentorial, but 10–23% are found in the posterior fossa and 5% in the spine. Patients often present with focal neurological deficit, seizure, or headache [2, 19]. These symptoms may or may not fit with lesion hemorrhage, but prior hemorrhage increases the risk of subsequent bleeding, with 20–80% of subsequent bleeding occurring in a known lesion rather than a new lesion. In familial diseases, up to 50% of patients may present asymptomatically [2, 19]. Symptoms often correlate with lesion size and location, with higher risks of deficits for lesions in the thalamus, basal ganglia, brain stem or spinal cord. Lesions have also been known to increase in size, especially in familial cases. One study of 202 patients showed that an initial presentation of acute hemorrhage was seen in 37.1% of patients and incidental lesion was seen in 40.6% of patients, while focal deficit without hemorrhage (6.5%) or seizures without hemorrhage (14.8%) were less common [2, 19]. Another study of 167 pediatric patients (mean age 10.1 years old) with CMs demonstrated presentation with hemorrhage in 62% of cases, seizures in 35% of patients, and incidental finding in 26% of cases [17]. An annual hemorrhage rate of 3.3% was seen and associated with prior hemorrhage, brainstem location and DVA. In addition, permanent neurological morbidity was 29% per hemorrhage event, increasing to 45% for brainstem, thalamus or basal ganglia lesions versus 15% for supratentorial lobar or cerebellar lesions. The reported rate of hemorrhage may be overrepresented in the literature; clinically significant hemorrhage risk has been estimated to be 0.3–2.3% per patient year [5–11].

An increased risk of hemorrhage in pediatric patients, up to 36–60%, has been reported but likely represents smaller sample size studies [20–22].

34.3.2 Pathophysiology

Approximately 20% of cases are familial, with resultant loss of function in one of several genes: *cerebral cavernous malformation 1* (*CCM1/KRIT1*), *CCM2/malcavernin*, or *CCM3/ PDCD10* [23, 24]. These genes stabilize endothelial tight junctions and influence cell proliferation as well as angiogenesis. CCM genes are inherited in an autosomal dominant pattern with variable penetrance, but a somatic mutation is thought to also be required for lesion development. Familial CMs are more common among Hispanic Americans, and these are most often related to the loss of *CCM1*. Patients with multiple lesions or a single lesion and family history should be recommended for genetic testing. Patients with an earlier presentation with symptomatic lesions and those with *CCM3* mutation are predicted to have a worse disease course, with increased likelihood for CM hemorrhage as well as another neurological issues such as scoliosis or other primary brain tumors (meningioma, astrocytoma, vestibular schwannoma) [24].

Radiation is another risk factor for CM, with one series showing a median latency of 12.0 years from prior radiation to CM formation [25].

34.3.3 Imaging Findings

Computed tomography (CT) demonstrates a 70–100% sensitivity but <50% specificity for identifying CMs [3, 26, 27]. CT demonstrates well-circumscribed, nodular lesions of mixed density along with hyperdensity representing possible calcifications, or hemorrhage. Cystic components can be a feature of CMs that may be apparent on CT scans. Contrasted CT may show only a small amount of enhancement.

Magnetic resonance imaging (MRI) represents the gold standard for identifying CMs with greater sensitivity and specificity [3, 26–28]. Lesions present as well-defined, lobulated lesions with central cores of mixed signal intensity correlating with the various timing of hemorrhage. Perilesional cysts can be seen from prior hemorrhages and blood breakdown. Perilesional hypointensity can be seen attributed to ferritin deposition from red blood cell breakdown. Calcification can present as T2 hypointensity. T2-weighted imaging also shows a characteristic "popcorn"-like appearance, although this is not specific to CMs. T2 gradient echo or susceptibility-weighted imaging demonstrates the best sensitivity for identifying even microscopic CMs. DVA can be seen in up to 30% of sporadic CM cases in some series and may increase the risk of hemorrhage [5]. Other lesions that should be considered as mimickers of CMs include arteriovenous malformations, mixed

vascular lesions, oligodendrogliomas, hemorrhagic primary or metastatic tumors, infections, and inflammatory lesions.

CMs are typically occult angiographically although areas of a vascularity, early or late vascular draining, capillary blushing, or neovascularity can occasionally be seen [3, 29]. X-rays and cerebral angiograms do not play a part in the current management of CMs.

34.4 Pathology

CMs demonstrate thin-walled, sinusoidal spaces lined by a single layer of endothelium with stroma absent of elastin, smooth muscle, or other organized tissue [3]. The lack of brain parenchyma is characteristic of CMs, unlike in arteriovenous malformations, venous anomalies, or telangiectasias. Lesions may not always be confined and compact, and this may allow elongation into the brain parenchyma. Perilesional gliosis, microhemorrhages, hemosiderin, and hemosiderin-laden macrophages are common findings at the time of resection.

34.5 Treatment

34.5.1 Nonsurgical Treatment

Nonsurgical management with observation and repeat imaging is preferred for patients with incidental lesions or those with vague, nonspecific complaints, especially in the absence of other high-risk features (e.g., seizures, DVA, noneloquent cortex). Early referral to a cerebrovascular neurosurgeon is recommended for follow-up and discussion of treatment options. Specifically, for pediatric patients, a pediatric neurosurgeon or neurologist is the next level of referral. Use of anticoagulation in patients with known CMs is relatively contraindicated, and the risks/benefits of these treatments should be discussed with experts before use. Management of seizures with antiepileptic medications is recommended. Various medical treatment options have been discussed in the literature as potentially reducing CM size and hemorrhage risk, including propranolol [30–35] or statins [36]. However, there have been no randomized trials assessing medical therapies and there is no definitive medical treatment in CMs. Similarly, radiosurgery has been suggested as a potential treatment option [37, 38], but more recent studies suggest that reduction in hemorrhage risk after radiosurgery may approximate the natural history of CMs. Thus, radiosurgery is not regularly recommended for treatment.

34.5.2 Surgical Indications

Surgical treatment is considered in symptomatic patients (e.g., focal deficits, recurrent hemorrhage, seizures, intractable headaches), patients with lesions that present to the surface where surgical risk may be reduced, and those with lesions with potential for worsened neurological impairment during subsequent hemorrhage [2, 3]. The surgical decision-making process remains challenging because of the natural history of CMs and the variable risks of surgery that come from lesion location [15–18]. No consensus exists as to whether lesions should be surgically resected after a first hemorrhage or only with recurrent hemorrhage. In patients with multiple lesions, the symptomatic or epileptogenic lesion should be targeted. Mortality and morbidity for recurrent hemorrhage in supratentorial CMs remains relatively low. However, mortality ranges from 0 to 20% in patients with lesions in the brainstem that have repeat hemorrhage. In addition, neurological worsening can be seen in 20–40% of patients and permanent worsening can occur in up to 20% of patients. On the other hand, surgical morbidity for the resection of deep seated tumors or those in critical locations can range from 38 to 59% with permanent deficits seen in 25–36% of patients [39, 40]. Thus, the decision to monitor patients versus pursue treatment depends on lesion location, patient age, and risk of eloquent cortex. Surgical approaches generally involve an open craniotomy for CM resection. Some recent reports describe the use of laser interstitial thermal therapy (LITT) for the treatment of supratentorial [41] or brainstem [42] CMs, potentially offering a more minimally invasive method of lesion treatment without the same comorbidity of open surgery.

34.6 Conclusions

CMs remain a relatively common type of vascular lesion that can present with seizures, hemorrhage, focal neurological deficits, or headaches. Understanding of CM presentation and treatment remains more limited than the adult population, but generally follows similar rates of symptomatic hemorrhage and surgical risk. Most lesions are sporadic, but well-known familial gene mutations can account for 20% of cases. MRI remains the imaging modality of choice for diagnosis and follow-up. The choice of medical management with repeat imaging or surgical intervention involves understanding of the natural history of CMs in the context of the patient's neurological issues. Referral to a pediatric or cerebrovascular neurosurgeon is warranted to aid in clinical decision-making. With modern treatment options, as well as emerging options such as pharmacological treatments and LITT, outcomes can be quite reassuring for the management of CMs.

34.7 Cases

34.7.1 Case 1

A 46-year-old woman with a history of familial CM presented with recurrent hemorrhage of a pontine CM (Fig. 34.1a). The patient had three prior resections of a frontal, temporal, and dorsal pontine lesion. Her symptoms included worsening cranial nerve palsies, dysarthria, and left-sided weakness. She underwent treatment with LITT (Fig. 34.1b), which achieved involution of the lesion, and had no further neurological issues from the pontine lesion at 1 year after treatment (Fig. 34.1c). She has had progressive hemorrhage of a left periventricular cerebellar peduncle lesion, which now being considered for LITT treatment. No pediatric patient in the literature has to date been treated by LITT for CMs in the brainstem.

34.7.2 Case 2

A 16-year-old girl with a history of familial CM presented with large left subfrontal and right temporal CMs (Fig. 34.2a, b). She had demonstrated intractable headaches for 3 years as well as suspected partial complex seizures that were not traceable on electroencephalography. Her symptoms left her unable to attend school or social activities despite multiple medications. She underwent resection of the right temporal lesion at age 19 (Fig. 34.2c, d) and was subsequently able to complete high school, get married, and have a child.

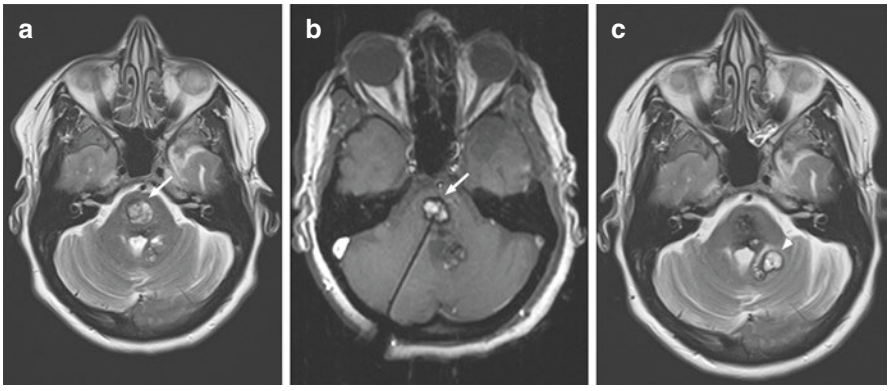

Fig. 34.1 Case 1—LITT treatment of a pontine CM. (**a**) Preoperative axial T2-weighted MR imaging demonstrates a pontine cavernous malformation (arrow) with heterogenous hyper- and hypointense features. (**b**) Perioperative axial T1-weighted, contrast-enhanced MR image shows the right cerebellar approach for LITT treatment of the pontine lesion (arrow). (**c**) At 1 year after surgery, the axial T2-weighted MR image shows involution of the pontine lesion but formation of a new left cerebellar peduncle CM (arrowhead)

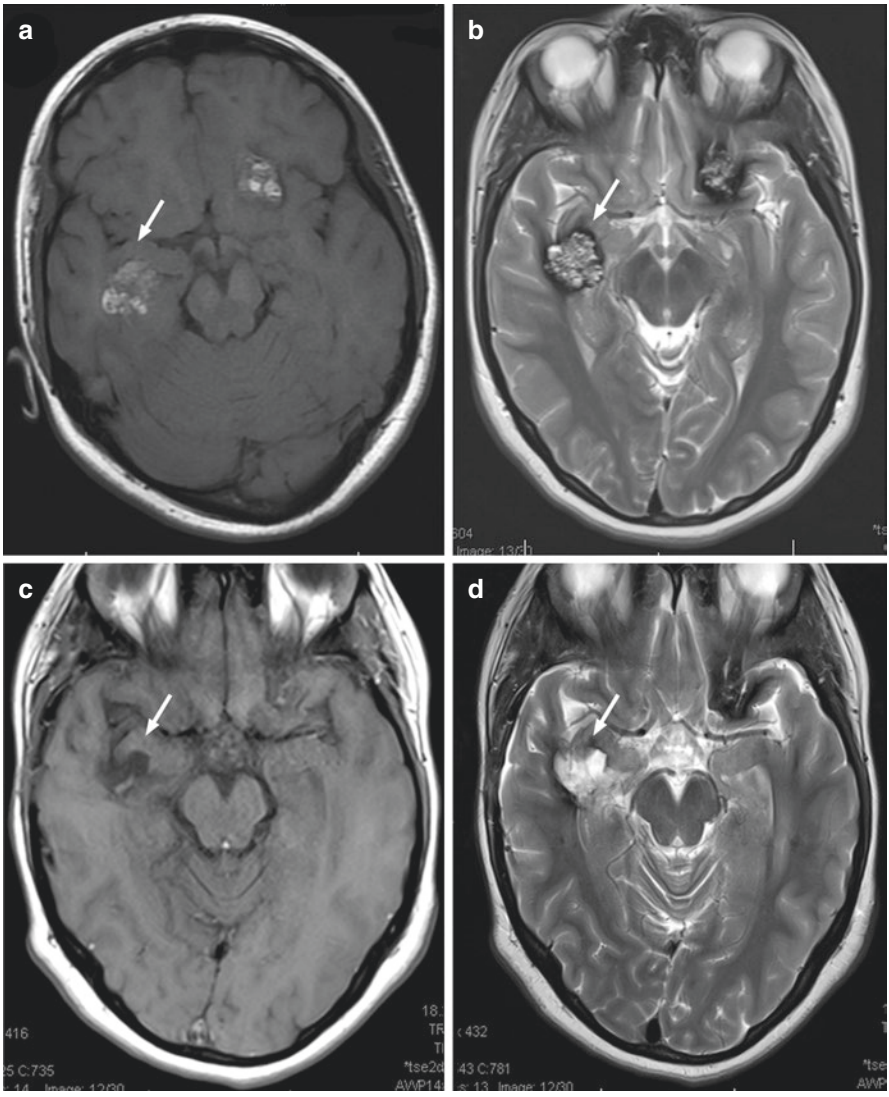

Fig. 34.2 Case 2—Resection of a symptomatic right temporal CM. Preoperative axial (**a**) T1-weighted and (**b**) T2-weighted MR images demonstrate right subfrontal and left temporal (arrow) CMs. Postoperative axial (**c**) T1-weighted and (**d**) T2-weighted MR images are shown after resection of the right temporal CM (arrow)

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Chapter 35
Intracerebral Aneurysms

Jillian H. Plonsker, Robert C. Rennert, Usman A. Khan, and Michael L. Levy

35.1 Introduction

Pediatric aneurysms are a rare but potentially devastating entity when not appropriately recognized and managed. The medical comorbidities that are thought to contribute to aneurysm formation and rupture in adults, such as hypertension and smoking, are mostly absent in children, which indicates that children likely experience a different set of risk factors. Numerous studies have demonstrated reproducible gender differences as well as differences in aneurysm shape, size, and location when comparing pediatric and adult aneurysms. While the overall management is similar to adult patients, there are several key differences to consider. Pediatric patients have a longer life expectancy than adults, therefore treatment modality must take durability into account. Additionally, radiation exposure and iodinated contrast carry greater risks in a very young child than they do in an older patient. However, open microsurgical treatment can also be fraught with risk for the unprepared surgeon. Blood loss is a critical factor to consider in small patients and the surgical approach should be tailored to mitigate this risk. Further, there is an elevated risk of connective tissue disease which may increase the risk of intraoperative rupture. Despite these risks, pediatric patients are very resilient and tend to have excellent recoveries and outcomes.

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35.2 Etiology and Epidemiology

The true prevalence of pediatric intracerebral aneurysms is difficult to report due to the low rupture rate, but it is generally estimated to be between 0.5 and 4.6% of all intracerebral aneurysms based on multiple large series [1–7]. Numerous studies have demonstrated that intracranial aneurysms are more common in males at a rate of 1.3–2.7:1. This trend appears to reverse after puberty, becoming more similar to adults with 3:1 aneurysms occurring in females [8, 9]. While this phenomenon is not well understood, it may be associated with the higher rate of post-traumatic aneurysms in young boys compared to young girls, or that genetic factors contribute more to aneurysm formation in males.

The commonly attributed acquired risk factors associated with adult aneurysm formation such as chronic hypertension, atherosclerosis, drug and alcohol use, and cigarette smoking are largely absent in the pediatric population. Therefore, the pathogenesis and morphology are thought to be different than adult aneurysms. Familial syndromes such as polycystic kidney disease, aortic coarctation, tuberous sclerosis, Ehlers-Danlos syndrome, Marfan syndrome and fibromuscular dysplasia have all been associated with aneurysm formation in children [10]. However, in one series of 59 pediatric patients, only five patients had a known familial disease, so there is still much to learn about the cause of aneurysm formation in pediatric patients [11].

35.3 Aneurysm Characteristics

Pediatric aneurysms differ from adult aneurysms in size, shape, and morphology. While the most common site for aneurysm formation is children is the internal cerebral artery bifurcation, children have a higher rate of aneurysm formation in the vertebrobasilar circulation, up to 30–40% in multiple series, representing a threefold increase as compared to adults [2, 4, 7, 8, 12–16]. Conversely, the anterior cerebral artery is a less common site for aneurysms in children than in adults.

Generally speaking, aneurysms may be saccular, fusiform, dissecting, or complex, with aneurysms in the posterior circulation more likely to be dissecting and aneurysms in the anterior circulation more likely to be saccular [11]. It is thus not surprising that pediatric aneurysms are also more likely to be complex than adult aneurysms, with children having higher rates of dissecting, post traumatic, mycotic, and multiple aneurysms [6, 11, 12]. Giant aneurysms, generally defined as greater than 25 mm in diameter, are also more common in pediatric patients, particularly in very young patients (Figs. 35.1 and 35.2). Pediatric patients can occasionally present with “aneurysmal malformations”, which are vessel dilations with early venous outflow, similar to an arteriovenous malformation but without a nidus (Fig. 35.3). Accordingly, recent clinical series from the Barrow Neurological Institute, UCSF, and Xuanwu Hospital in Beijing, have reported an incidence of giant aneurysms as

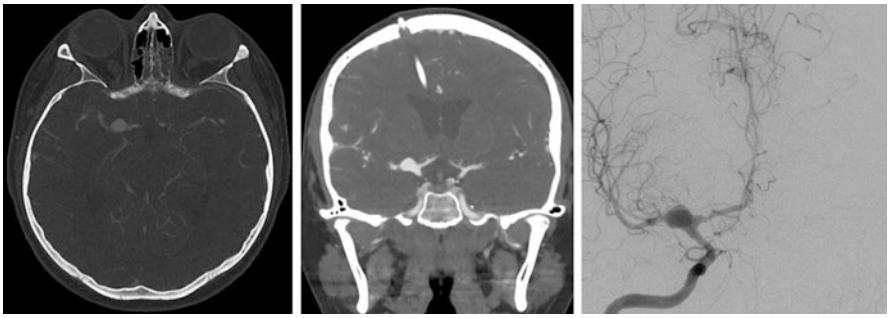

Fig. 35.1 17-year-old female presenting with subarachnoid hemorrhage and hydrocephalus with a fusiform M1 aneurysm

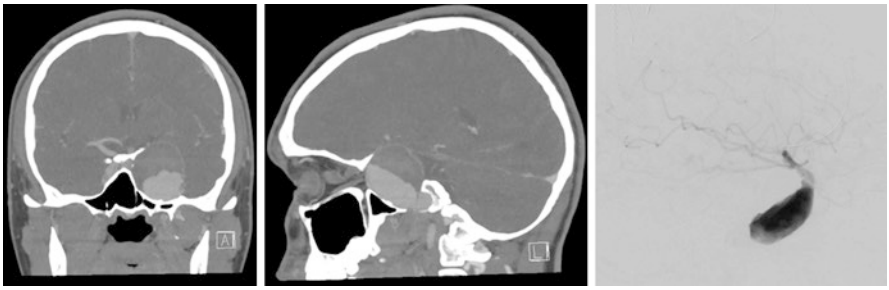

Fig. 35.2 13-year-old male presenting with subacute headaches with a giant fusiform cavernous ICA partially thrombosed aneurysm causing remodeling of the skull base

high as 32–45% amongst all pediatric aneurysms, though these numbers may reflect the large referral base of these centers [7, 14, 17].

35.4 Clinical Presentation

Intracranial aneurysms often go undetected or are discovered incidentally, but there are several mechanisms by which they may become symptomatic. The most common presentation of symptomatic intracranial aneurysms is subarachnoid hemorrhage (aSAH; >50%), which includes a sentinel hemorrhage or "warning leak", or more serious rupture of the aneurysm. Patients classically describe a sudden-onset "thunderclap headache." aSAH may also cause focal neurologic deficits, seizures, vomiting, meningismus, or depressed level of consciousness in more severe cases. These additional signs and symptoms are important to consider in patients too young to describe headache symptoms. Patients with aSAH are graded according the Hunt Hess Classification (Table 35.1). Lower scores after initial resuscitation

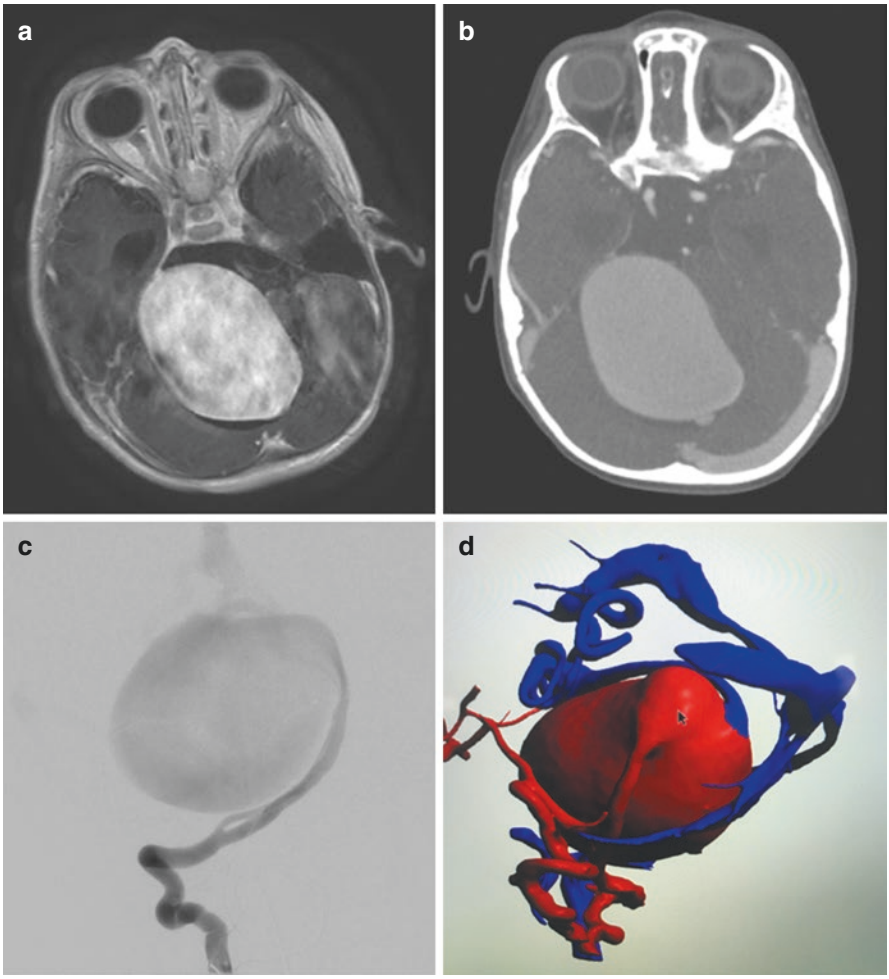

Fig. 35.3 21-month-old male found to have a giant posterior fossa aneurysmal AV malformation diagnosed during work up for motor and speech delay. (**a**) MRI with contrast, (**b**) CT angiogram, (**c**) DCA, (**d**) 3D reconstruction demonstrating arterial inflow and venous outflow from aneurysm

have been correlated with better outcomes. Children often present with lower HH grade than adults with aSAH [9, 10].

Seizures are a relatively uncommon consequence of aSAH with an incidence of 7–25% in children at presentation. Seizures may nonetheless be more common in infants and in children with giant aneurysms [10, 18].

Approximately one third of pediatric aneurysms present from mass effect of the unruptured aneurysm dome. Given the higher incidence of giant aneurysms in children, the risk of mass effect in these patients can be significant and can result in focal neurologic deficits and/or seizures.

Table 35.1 Hunt Hess grading system

1. Mild headache or no symptoms
2. Moderate-severe headache, CN palsy
3. Lethargy or confusion, mild focal neurologic deficits
4. Stuporous, more severe focal deficit
5. Comatose, severe neurologic

Table 35.2 Common presentations

• Subarachnoid hemorrhage (headache, vomiting, AMS)
• Seizure
• Neurologic deficit
• Headache
• Incidental

Approximately 5–15% of pediatric aneurysms are discovered after or result from a trauma. Suspicion for an aneurysm should arise in trauma patients with atypical intracranial hemorrhage patterns, hemorrhages out of proportion or not matching the traumatic mechanism/site. As traumatic aneurysms tend to be dissecting or pseudoaneurysms [12, 19], and can develop in a delayed fashion, it is common practice at our institution to obtain additional immediate and delayed vascular imaging in trauma patients with suspicious intracranial hematomas. Common presentations of subarachnoid hemorrhage are summarized in Table 35.2.

35.5 Evaluation

All patients suspected of aSAH require a detailed history, physical exam, neurologic evaluation, and diagnostic imaging. Non-contrast computed tomography (CT) scan of the head should be the first line for screening and has a sensitivity of at least 85%, and greater than 90% when performed within 6 h of symptom onset [20]. Magnetic resonance imaging (MRI) takes longer to perform but is an alternate non-invasive imaging modality. It is slightly less sensitive than CT in the acute period after hemorrhage but has improved sensitivity in the subacute period and additionally spares the patient radiation [21]. Lumbar puncture is the traditional next step to rule out subarachnoid patients in patients with a negative non contrast CT scan or MRI. The presence of blood that does not clear over time or xanthochromia in cerebrospinal fluid (CSF) may indicate aSAH. However, lumbar punctures are painful and may require anesthesia in pediatric patients, therefore some argue that the negative predictive value of a CT scan is sufficient without lumbar puncture.

If aSAH is detected, non-invasive vascular imaging such as a CT angiogram (CTA) is warranted. This provides rapid identification of any vascular malformation and provides basic information about location, size, and morphology of any detected

aneurysms. MR angiogram (MRA) is an alternative vascular imaging option that spares radiation in children, though it is generally not as useful as CTA and lacks sensitivity for small aneurysms <5 mm [22]. The gold standard for diagnostic imaging of aneurysms is catheter angiography, known as diagnostic cerebral angiography (DCA). This is the most sensitive for identifying aneurysms especially when visualization of small aneurysms may be obscured by blood clot on CTA. DCA can also provide more detailed 3-dimensional information about aneurysm morphology, which is of use to the treating surgeon. DCA in children nonetheless requires special attention to appropriate anesthesia, contrast load, fluid balance, and radiation exposure.

Standard laboratory studies are also recommended in the workup of aSAH (CBC, BMP, PT/INR, PTT, type and screen), especially if surgical intervention is expected.

35.6 Treatment

35.6.1 Medical Management

Patients presenting with aSAH almost always require urgent definitive treatment to prevent re-rupture of an unsecured aneurysm. The medical management of aSAH is similar to adults. Patients should be admitted to an intensive care unit with the ability to perform frequent neurologic exams. If hydrocephalus is present, an external ventricular drain should be placed. While the aneurysm remains unsecured, CSF should not be aggressively drained due to a theoretical risk of transmural pressure swings causing re-rupture of the aneurysm. Regardless of HH grade on presentation, patients should be observed with frequent neurologic checks for a period of approximately 2 weeks after rupture due to risk of vasospasm. Fluid balance and sodium should be monitored due to the risk of cerebral salt wasting. Vasospasm seems to be less common in children than in adults, however, it can occur in up to 21% of cases [6]. Studies have also demonstrated no increased mortality nor increased rates of cerebral infarction in children with angiographic vasospasm, which may indicate a decreased clinical importance of vasospasm compared to adults, though this remains poorly characterized [3].

Some unruptured aneurysms may be observed with serial vascular imaging after evaluation by a pediatric neurosurgeon. For example, mycotic aneurysms may regress after appropriate antibiotic therapy. Similarly flow-related or nidal aneurysms may regress after treatment of the arteriovenous malformation (AVM), although when possible these are secured as part of AVM treatments. Small aneurysms (<2 mm), or aneurysms outside the subarachnoid space also may be appropriate for observation. However, the long life-span of children inherently increases lifetime rupture risk, which argues for more aggressive definitive treatment.

35.6.2 Endovascular Treatment

The past three decades has seen the rise of endovascular treatment of aneurysms, including coiling, stent/coiling, flow diversion, and parent vessel occlusion. This has been shown to be safe in both children and adults and carries less morbidity than a surgical operation (Fig. 35.4). The potential downsides of endovascular treatment include radiation exposure and contrast load, both of which are significant risks in small children, and the need for antiplatelet agents in the case of stent or flow diverter placement. Further, endovascular treatment is potentially less durable over time, with one pediatric series reporting a 14% aneurysm recurrence rate after coiling compared to a 0% recurrence rate after clipping [17]. In older adults, durability may be reasonably traded for lower morbidity, however, in children with a long-projected lifespan this trade-off requires special consideration. Accordingly, serial post-treatment imaging is necessary due to the theoretical risk of recurrence. This can be performed with CTA, DCA, or MRA, with MRA often used to avoid radiation in children while providing adequate reduction of implant-related artifact.

35.6.3 Open Microsurgery

Despite the rapid growth of endovascular surgery, direct microsurgical treatment of aneurysms remains a key modality in pediatrics due to the morphologic complexity of many pediatric aneurysms and need for a durable outcome. Further, craniotomy allows for hematoma evacuation or debulking of the aneurysm if it is causing symptomatic mass effect. The increased frequency of large, friable, complex, and posterior circulation aneurysms in children nonetheless requires the pediatric

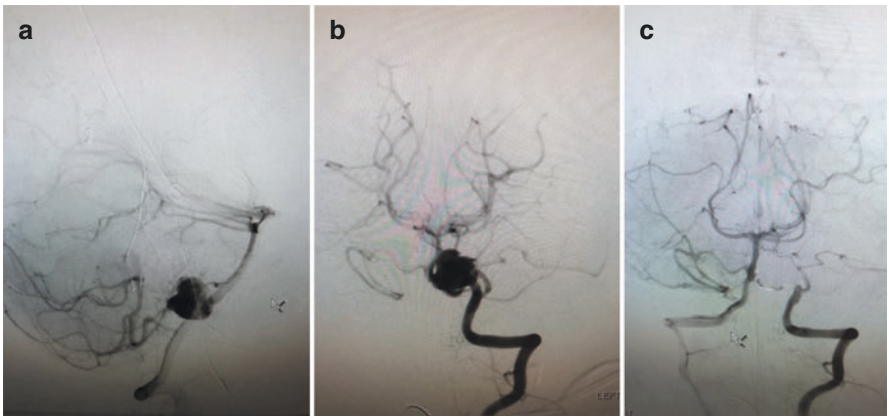

Fig. 35.4 13-year-old male with a fusiform left vertebral artery aneurysm, angiography. (**a**) lateral L vertebral artery injection, (**b**) AP L vertebral artery injection, (**c**) AP posterior circulation status post coiling

neurosurgeon to feel comfortable with a variety of surgical and skull base exposures and techniques.

Strict avoidance of hypertension and large blood pressure shifts is critical to avoiding intraoperative rupture, therefore placement of an arterial line is standard. The anesthesiologist should additionally be prepared for blood transfusion in the case of arterial bleeding. Neuronavigation may be helpful for more distally located aneurysms, however, is not typically necessary. While neuromonitoring may be useful for modulation of burst suppression and ischemia during temporary clip occlusion and is commonly used for elective cases, it has not been shown to significantly improve outcomes [23] and is often not used in ruptured cases due to time constraints. A foley catheter is commonly placed as mannitol (with diuretic effects) is often given to promote brain relaxation and reduce the need for cortical retraction. Lumbar drains are not routinely used when an EVD is not already in place, though an existing EVD may be used to augment brain relaxation.

While skull base approaches are not required for the majority of aneurysm surgeries, knowledge of orbitozygomatic and transcondylar approaches can improve visibility in appropriate situations. Simple saccular aneurysms can be treated by clip ligation. Complex or wide necked aneurysms may require multiple clips for reconstruction. The most complex aneurysms may require more advanced techniques. One series presents 20 aneurysms from a single institution, 7 of which were solitary saccular aneurysms treated by clipping. Nine patients were described as having complex or multiple aneurysms which required surgical techniques including hypothermic arrest, trapping, bypass, and parent vessel sacrifice [13]. Another series described 28 revascularization procedures in children, with the majority being extracranial-intracranial bypass either with or without an interposition graft, and the remainder being in-situ or end-to-end bypasses [7]. Bypass, while technically challenging, is an important tool to master for pediatric aneurysm treatment when aneurysms are not amenable to clip occlusion or there is concern that the parent vessel is intrinsically diseased and requires exclusion.

There are multiple options to confirm successful aneurysm obliteration and maintenance of vessel patency. Intraoperative angiogram can be performed with c-arm fluoroscopy and is the gold standard for visualization of dynamic blood flow. Downsides include additional radiation and contrast exposure to the patient, logistical challenges with patient positioning, and inferior views without the benefit of a biplane. Additionally, intraoperative angiography cannot easily confirm the preservation of small perforator arteries. Many centers now use indocyanine green video angiography, ICG for short, as an adjunct or replacement for intraoperative angiogram. ICG can be safely given intravenously and reaches the cerebral vasculature in approximately 30 s [24, 25]. A microscope fitted with a near infrared filter (IR800) will allow visualization of patent vessels via green fluorescence filling first in arterial and then venous phases. While one large single center retrospective study comparing ICG to intraoperative angiography found equal rates of clip repositioning between the groups [25], multiple other studies have shown that ICG is slightly less reliable than angiography [24, 26, 27]. Therefore, while ICG is a useful adjunct, intraoperative angiography remains the gold standard for intraoperative imaging.

Both immediate and delayed post-operative imaging, typically with formal catheter angiography, should be performed to rule out aneurysm remnant and recurrence. Post-operative serial monitoring is commonly performed with MRA, which again is noninvasive, has no radiation, and is nearly equivalent to DCA for detecting recurrence. Additionally, MRA is not subject to metallic artifact like CTA which improves visibility when there is a clip in place [22, 28].

35.6.4 3D Modeling

Preoperative planning and a thorough understanding of vascular anatomy are critical to successful outcomes, and pre-surgical simulation and modeling can be a useful tool. 3-dimensional virtual reality systems that reconstruct patients' vascular imaging into a model that the surgeon can interact with to identify relevant anatomy, analyze surgical approach, and even simulate clipping with different size and shaped clips have recently been developed (Fig. 35.5). In our experience, this can lead to improved preparedness for complex aneurysms in the operating room [29].

35.7 Outcomes/Complications

Despite the above challenges and potentially due to the plasticity of the pediatric nervous system, children with successfully treated aneurysms tend to have good long-term outcomes. Treatment complications can nonetheless happen, especially intraoperative rupture. It is our view that pediatric aneurysms, whether or not associated with known connective tissue disorders, are more likely to be friable and originate from diseased vessels, therefore they tend to be sensitive to manipulation. In the event of an intra-operative/procedural rupture, the open surgeon has a potential advantage as rapid control of the hemorrhage site can be obtained without

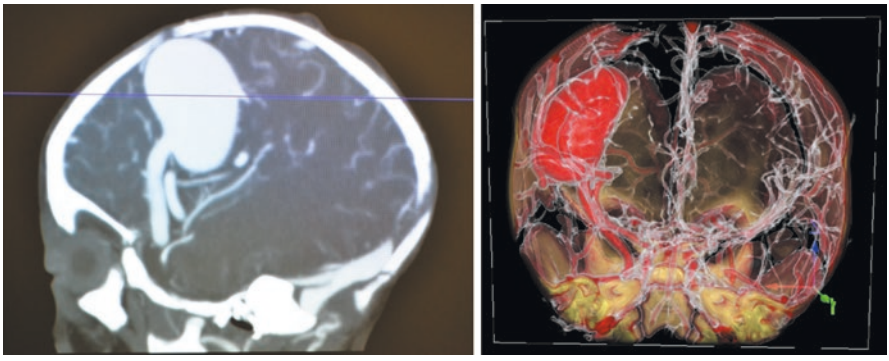

Fig. 35.5 An example of 3-dimensional modeling of a complex aneurysm in a young patient

globally elevated intracranial pressures. Blood loss is nonetheless a more critical consideration in children than in adults and is a significant risk modifier in open surgery. Stroke secondary to perforator occlusion is also a risk when there is poor visibility of the aneurysm neck and dome prior to clip placement. Intraoperative imaging with ICG or catheter angiography are tools that can mitigate this risk.

Hydrocephalus is an additional complication that can occur after aSAH due to blood settling in the subarachnoid spaces or ventricular system. This may cause acute hydrocephalus in the short term due to obstruction of CSF flow requiring EVD placement. It may also cause delayed communicating hydrocephalus in 10–20% of cases, likely due to arachnoid granulations preventing absorption. These patients may require permanent CSF diversion procedures such as a ventriculoperitoneal shunt [30].

Overall, there is no consensus on whether endovascular or open surgical treatment of pediatric aneurysms leads to better outcomes, and there is likely a long-term role for both approaches. In general, the literature reports higher rates of aneurysm obliteration and lower rates of recurrence with microsurgery, but sometimes better neurologic outcomes with endovascular treatment. Most series report high rates of favorable neurologic outcomes regardless of treatment modality in both ruptured and unruptured pediatric aneurysms, with low rates of rerupture. As with adults, lower HH grade on admission is associated with better neurologic outcomes [5, 15]. In one series, Amelot et al. report that despite a 19.6% mortality, 23/37 patients had good neurologic outcome at long term follow up, with 85% of patients treated endovascularly [16]. In another, Huang et al. report 95% good outcomes in both ruptured and unruptured patients, with 81% of treated patients treated with open surgery [2]. Conversely, Agid et al. report in their series on largely unruptured (>70%) aneurysms 77 vs. 44% of patients had good outcomes following endovascular and open treatment [31]. Finally, Sanai et al. report comparable neurologic outcomes with open or endovascular approaches, but a 94% complete aneurysm obliteration rate in the surgical group compared to 82% in the endovascular group. They also had a 14% recurrence in the endovascular group and zero cases of recurrence in the surgical group [17]. Regardless of the treatment modality chosen, long term patient follow-up with serial imaging is required in order to detect aneurysm recurrence or de novo aneurysm formation.

35.8 Pearls

- Pediatric aneurysms are exceedingly rare, but tend to have higher rates of dissecting, fusiform, or giant morphology leading to greater complexity.
- The complexity of pediatric aneurysms may require advanced surgical approaches and techniques.
- Additional treatment risks in children include sensitivity to radiation, contrast, and intolerance of intraoperative blood loss.

- The efficacy and safety of surgery and endovascular therapy seems to be comparable, but so far microsurgery appears to be more durable.
- The long life expectancy of children should be taken into account when deciding on treatment modality.

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Chapter 36
Moya-Moya Disease

Ahmad Sweid, Abdelaziz Amllay, and Pascal Jabbour

Moyamoya disease (MMD), also called spontaneous occlusion of the circle of Willis, is a chronic occlusive cerebrovascular disease of unknown etiology characterized by steno-occlusive manifestations at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network at the base of the brain (Fig. 36.1) [1]. MMD was first described in the Japanese literature in 1957 by Takeuchi and Shumizu as "hypoplasia of the bilateral internal carotid arteries" [2]. However, it was not until 1969 when Suzuki and Takaku coined the Japanese term "Moyamoya" which means "something hazy, like a puff of cigarette smoke" to describe the classical angiographic findings of neovascularization of the lenticulostriate collaterals as compensation for bilateral progressive arteriopathy [1]. MMD may lead to both types of strokes, ischemic stroke often presenting in childhood, and hemorrhagic stroke often presenting in adults.

MMD is defined as patients who have bilateral or unilateral presentation of terminal ICA stenosis with an abnormal vascular network at the base of the brain. Definitive diagnosis of MMD requires catheter angiography in unilateral cases, whereas bilateral cases can be promptly diagnosed by either catheter angiography or magnetic resonance imaging/angiography (MRI/MRA). MMD is used to refer to patients who do not have a co-morbid condition, while Moyamoya syndrome (MMS) or angiographic moyamoya refers to patients in whom Moyamoya develops secondary to an underlying disorder such as sickle cell disease, neurofibromatosis type 1, or Down syndrome, etc. [3] MMD is probably inherited in a polygenic or autosomal dominant manner with low penetrance [4]. Patients are usually of Japanese or Asian origin with 10% having a family history of Moyamoya. MMD,

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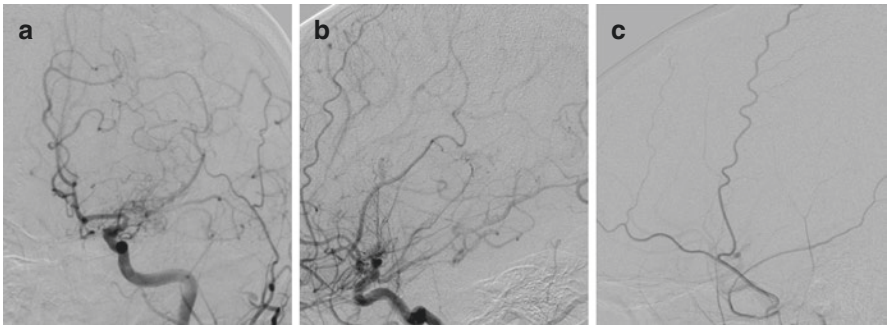

Fig. 36.1 Left cerebral MMD Suzuki Stage III. (**a**) and (**b**) antero-posterior and lateral digital Subtraction angiography of left Common Internal Carotid artery injection. (**c**) Left External Carotid artery showing opacification of the STA

especially in Asian regions, may cause non-atherosclerotic intracranial disease. Young patients may present with isolated middle cerebral artery stenosis that may progress into fulminant MMD [5].

In 1997, the Japanese research committee published guidelines for the diagnosis of MMD [6]. According to the guidelines, definite MMD is diagnosed by a conventional angiography exhibiting the following findings; stenosis or occlusion in the terminal ICA and/or proximal portion of the anterior cerebral artery (ACA) and/or middle cerebral artery (MCA); abnormal vascular networks (Moyamoya vessels) in the basal ganglia; and bilateral lesions. Patients with unilateral lesions are diagnosed as having probable MMD. When an underlying cause is found, such as Down syndrome, neurofibromatosis type 1, sickle cell disease, or radiation therapy, a diagnosis of MMS is made. Patients with unilateral disease are classified as probable moyamoya, and 30–40% of these individuals will progress to bilateral disease [7].

36.1 Epidemiology

MMD has been observed throughout the world, however, its incidence shows obvious regional and ethnic variations. MMD is more commonly observed in Eastern Asian countries, such as Japan, Korea, and China. The reported prevalence rate in Japan is estimated at 6/100,000, with a female to male ratio of roughly 2:1 [8]. This high rate is followed by the prevalence rate in China, which is estimated at 4/100,000 persons, with no female predominance [9]. Results from a 2005 American review suggest an incidence of 0.086/100,000, with reported incidence-rate ratios of 4.6 for Asian Americans (similar to rates in Asia), 2.2 for blacks, and 0.5 for Hispanics, as compared to whites [10]. Both the incidence and prevalence of MMD in the Japanese population has been increasing from 0.35 to 0.94/100,000 and 3.16 to 10.5/100,000, respectively, from 1994 to 2005 [8, 11]. Similarly, epidemiological data from Korea demonstrated an increase in the prevalence of MMD from 6.3/100,000 in 2004 to

9.1/100,000 in 2008 [12]. An epidemiological study from Taiwan reported an annual incidence of 0.15/100,000 [13]. A bimodal age distribution has been described for MMD, with the first peak occurring under 10 years of age and a second peak occurring in the fourth to fifth decade [8, 14]. Recent studies showed that familial history was found in 10–15% of MMD patients [15]. The risk of having MMD in family members is 30–40 times higher than the general population [11, 16]. However, it is imperative to highlight that the rate of familial MMD is influenced by the thoroughness of screening. A study showed that the rate of diagnosed familial cases increased from 7 to 15% with the application of transcranial doppler ultrasound as a screening modality for immediate family members of diagnosed MMD patients [17].

36.2 Pathophysiology of Moyamoya Disease

The stenosis affects the supraclinoid portion of the ICA during the initial stage, extends distally to the bifurcation, which then progresses to involve branches of the MCA and ACA. Rarely, the posterior circulation vasculature may be involved as well such as the PCA and basilar artery [18]. Involvement of the posterior circulation vasculature indicates a poor prognosis.

Progressive distal stenosis of the large vessels of the circle of Willis leads to a decrement in cerebral perfusion pressure and cerebral blood flow. As a compensatory mechanism, collateral neovascularization happens from the deep lenticulostriate and thalamo-perforating arteries [18, 19]. In the later stage of MMD, pial collateral arteries from the posterior circulation and trans-dural collateral arteries from the external carotid arteries originate [19]. The compensatory mechanism aims to maintain adequate cerebral perfusion pressure. An imbalance in this compensatory mechanism leading to a decrease in cerebral perfusion pressure leads to cortical or subcortical ischemic stroke [20].

Histological changes that take part in luminal stenosis are endothelial hyperplasia, fibrocellular thickening of the intima, and tortuosity and duplication of the internal elastic lamina [14, 21, 22]. There is neither evidence of an inflammatory infiltrate nor atheromatous plaque within the vascular walls. Rather, occlusion results from smooth muscle hyperplasia and the formation of an intraluminal thrombus [14, 22]. Histological study of postmortem collateral vessel specimens reveal overall thinned walls, atrophy of the media secondary to damaged smooth muscle cells and increased matrix deposition with cellular debris, and tortuosity, fragmentation, and thinning of the internal elastic lamina [23]. Microaneurysm formation within the weakened vessels are a potential source of intracranial hemorrhage, and have been found on both the anterior and posterior choroidal arteries [21].

The exact pathogenesis and etiology of MMD is still unknown, despite evidence showing the contribution of genetic and environmental factors. MMD was diagnosed in children following head and neck irradiation for neoplastic disease and following base of skull infection. Finally, a series from Boston Children's Hospital reported two sets of identical twin each with only one affected sibling, indicating an

environmental influence [24]. As for genetic role in MMD, evidence stems from familial MMD which is observed at a rate of 7–12% in Japanese population with a slightly lower occurrence in the USA [24–26]. Additionally, MMD is associated with certain genetic disorders such as Down's syndrome, neurofibromatosis one, and sickle cell disease [14, 21, 24, 27]. Moreover, the number of genetic mutations found in association with MMD has markedly increased within the past few years, particularly regarding individuals of Asian origin. A polymorphism in c.14576G > A in RNF213 was identified in 95% of east Asian Familial patients with MMD and 79% of sporadic cases. Patients having this polymorphism were found to have significantly earlier disease onset and more severe disease [28]. Besides, various genetic studies have demonstrated the implication of a group of genes including chromosome 3p, a principal site of proteins involved in multiple signaling pathways that control and regulate angiogenic and inflammatory pathways [29], and chromosome 6q25 associated with human leukocyte antigens [30–32]. Additionally, numerous growth factors expression were found to be aberrant in MMD patients (vascular endothelial growth factor, basic fibroblast growth factor, and transforming growth factor-b1) [33–36]. Furthermore, SH Hong et al. showed that in children with MMD, the allelic genes of HLA-DRB1*1302 and DQB1*0609 exhibit correlations with MMD occurrence. This study further suggested that a genetic polymorphism in the HLA-Class-II genome was one of the inducing factors of familial MMD [37].

36.3 Natural History

The natural history of untreated MMD is poor, with overall mortality reaching 4.3%. The progression is variable falling between two extremes, a slow progression with intermittent events or a rapid progression characterized by neurological and cognitive decline [24]. In a Japanese series, MMD patients were followed for a long period (>20 years) from childhood onset into adulthood and found that the childhood-onset disease does stabilize in around 75% of patients after adolescence and remain stable into adulthood [38]. Howeverm except for subgroups of patients, most MMD patients are associated with unfavorable outcome. In one study, 66% of untreated MMD patients develop symptomatic progression over a 5-year period following diagnosis [14, 39]. In addition, progression to the contralateral hemisphere my occur in a delayed fashion from disease diagnosis, reaching in one study to 150 months. As such, long term follow-up is very crucial [40]. Predictors of disease progression to the contralateral hemisphere are young age (<9 years) and presence of minor changes [15, 41, 42].

36.4 Clinical Presentation

Classic clinical presentation in children include transient ischemic attack (TIA), acute ischemic stroke (AIS), headache (33%), seizures (19%), and cognitive impairment. Symptoms frequency varies with the patient's age or the disease progression [43]. Symptomatology in children is due to cerebral hypoperfusion due to progressive steno-occlusive disease of large vessels. Diagnosis is usually made in the setting of either an AIS or a TIA. Currently, MMD accounts for approximately 6% of all causes of pediatric ischemic stroke [44, 45]. Contrast to adults, children rarely present with intracranial hemorrhage because of the latency of neovascularization. Cerebral hypoperfusion contributes to headache, seizure, cognitive impairment, mental retardation, seizures, or other signs of anterior circulation ischemia such as aphasia, dysarthria, and hemiparesis [14, 46, 47]. Less common presentations include syncope (4%), visual changes, and chorea [40, 48]. Symptoms may be provoked by hyperventilation during crying, eating hot noodles, or playing a harmonica or flute. Hyperventilation leads to hypocarbia which in turn leads to vasodilation and a subsequent a drop in hypoperfusion in vulnerable areas via a steal phenomenon. Any factor that leads to a decrease in systemic perfusion such as dehydration or infection may precipitate cerebral ischemia. MMD can have an aggressive course in children, and often there is a high likelihood for progressing into bilateral disease [40].

Ischemic infarcts are more likely to be bilateral or right-sided, contrasting to other causes of stroke which are more commonly left-sided [49]. The incidence of stroke recurrence was reported by a recent multicenter consortium to be 20%, with 9% having multiple stroke recurrence [49]. Seizures occur in 5% of patients starting in childhood due to cerebral hypoperfusion. Although considered uncommon, the posterior cerebral artery (PCA) involvement may occur and according to a recent study 29% had PCA involvement with 17% demonstrating PCA territory infarction [50]. Involvement of the PCA is an indicator of poor prognosis [40]. Recently, a correlation between the homozygous c.14576G > A variant of the ring finger protein 213 and early onset and aggressive PCA involvement has been shown [51], providing further evidence for the significance of PCA stenosis as a prognostic factor. It is crucial to note that the infarct topography in MMD patients does not fit the classic vascular territory mainly due to the presence of long standing hemodynamic insufficiency along with diversely developed collateral channels [52]. Headaches are a common presenting symptom of MMD, especially in pediatric patients. Although its etiology remains unclear. MMD's headaches improve after revascularization surgery, which implies a role for cerebral hypoperfusion in its pathogenesis [47, 53].

36.5 Diagnosis of Moyamoya Disease

MMD should be on the differential list for any child presenting with ischemic symptoms, especially in the setting of hyperventilation or acute stress. Confirmed diagnosis may be established with radiological studies (computed tomography—CT, Magnetic resonance imaging/angiography—MRI/A, Conventional angiography).

36.5.1 Head Computed Tomography

Head computed tomography (CT) is the initial imaging modality to rule out any hemorrhage, mass, or hydrocephalus that explains the symptoms. CT findings in patients with MMD may identify hypodensities suggestive of prior infarctions in watershed areas basal ganglia, deep white mater, and periventricular regions [14, 21, 54]. Also cerebral atrophy and encephalomalacia may also be detected in case of prior severe infarctions. CT angiography may be used to diagnose MMD and to evaluate neovascularization after surgical bypass [55].

36.5.2 Magnetic Resonance Imaging/Angiography

Brain MRI and MR angiography (MRA) are the imaging modality of choice for diagnosis and long-term follow-up, avoiding ionizing radiation and typically not requiring contrast administration. MRI can demonstrate the presence of acute or chronic ischemic events recognized as areas of diffusion restriction on diffusion-weighted imaging, gliosis, or encephalomalacia on T2-FLAIR imaging [56]. Cortical perfusion may be evaluated using a fluid attenuated inversion recovery MRI looking for linear high signal intensity due to a sulcal pattern (ivy sign) to infer cortical ischemia which may represent slow flow in the poorly perfused cortical circulation in children with MMD [14, 57]. The MR findings most suggestive of MMD are diminished flow voids in the ICA, ACA, and MCA bilaterally, with concurrent large flow voids in the basal ganglia and thalamus representing collateral neovascularization [58, 59]. The sensitivity and specificity for MRA or MRI to diagnose vascular stenosis was 100%, 93% and 100%, 77%, respectively [59]. Comparative studies between conventional angiography and MRA demonstrated that MRA accuracy to identify stenosis was 88%, 83%, and 88% of ICA, ACA, and MCA vessels, respectively [58].

Conventional angiography remains the gold standard for the diagnosis and surgical planning for patients with suspected MMD. Angiography allows a more dynamic

assessment compared to MRA or CTA by examination of the temporal arterial-venous cycle. Additionally, angiography allows the diagnosis and description of associated pathologies such as aneurysms or arteriovenous malformations [60–62]. A five or six vessel angiogram should be performed, and of utmost importance is the evaluation of the bilateral ECA in pre-operative planning to prevent disruption of these collaterals during the surgical revascularization. Angiographic appearance of MMD progresses through one of six stages as originally defined by Suzuki and Takaku: [63] (1) carotid stenosis without the presence of collaterals; (2) initial appearance of basal collateral vessels; (3) progressive stenosis of the distal ICA, with increasing prominence of the basal collaterals; (4) severe stenosis or occlusion of the anterior circulation with the formation of ECA collaterals; (5) prominence of the ECA collaterals, reduction, and stenosis of the basal collaterals; and (6) complete occlusion of the ICA, disappearance of the basal collaterals, with cortical blood supply solely provided though ECA collaterals.

Additionally, angiogram allows a more selective arterial evaluation which is especially paramount for bypass graft. A grading scheme has been developed to assess synangiosis induced collateral formations by Matsushima et al., with grade A representing synangiosis induced filling of greater than two thirds of the MCA circulation, grade B between one third and two thirds, and grade C signifying less than one third filling [64].

36.5.3 Electroencephalography and Cerebral Blood Flow Studies

Electroencephalography (EEG) is an additional diagnostic tool that aids in the evaluation of MMD patients. EEG can detect characteristic changes that are seen in MMD including posterior and or centrotemporal slowing, and a re-buildup phenomenon after the end of hyperventilation [65]. In normal children at the completion of hyperventilation a high voltage, monophasic slow waves (build up), returns to normal. While in MMD patients, there is a resurge of the high voltage waves (rebuild up) indicating a diminished cerebral perfusion reserve [14, 21, 54, 65]. Over time, re-buildup resolves and the EEG returns to baseline.

Additional imaging modalities that assist with evaluating cerebral perfusion include transcranial Doppler ultrasonography, CT and MR perfusion imaging, xenon enhanced CT, positron-emission tomography, and single-photon-emission CT [66–69]. Pre- and postsurgical single photon emission computed tomography (SPECT) and positron emission tomography studies have demonstrated abnormalities in cerebral hemodynamics preoperatively, even in the absence of infarction, with improvement post revascularization surgery [70].

36.6 Treatment of Moyamoya

Prompt diagnosis and early treatment remains the mainstay for optimal outcomes, as neurological status at time of intervention is the most significant predictor for long term outcome [14]. No curative treatment allowing regression of the occlusive arterial lesions has been proved in MMD, and current treatments are designed to prevent strokes by improving blood flow to the affected cerebral hemisphere.

36.6.1 Medical Treatment

Most patients with MMD benefit from medical therapy for symptom relief. However, nearly all patients have disease progression and ultimately require surgical intervention. Medical management has a limited role in the definitive treatment of MMD. The two drug families that are prescribed as an adjuvant treatment are antiplatelet therapy and calcium channel blockers. Aspirin (81 mg in children less than 6 years and adjusted during adolescents) is used as a lifelong treatment as a secondary or primary stroke prevention for embolic phenomena [14]. The second drug used is calcium channel block with existing evidence supports its use in recurrent postoperative TIA and intractable headaches [21, 54]. In MMS, treating the underlying etiology may decrease the risk of stroke for example giving blood transfusions or bone marrow transplant for sickle cell disease patients may decrease the risk of stroke [71].

36.6.2 Surgical Treatment

The goal of revascularization treatment is to decrease the risk of ischemic stroke in childhood and hemorrhagic events in adults [71]. In addition, revascularization also decrease the incidence and severity of associated symptoms such as headache [71]. Despite the lack of prospective randomized trials, several published studies have demonstrated the favorable outcomes of revascularization surgery, especially in the reduction of ischemic events [72, 73].

Indications for surgical revascularization include a TIA, AIS, cognitive decline, evidence of small vessel disease, progressive vasculopathy, or decreased cerebral blood flow [71]. Children are at a higher risk to progress and have poor outcomes, thus, asymptomatic children may undergo revascularization surgery to prevent ischemic events [71].

Surgical revascularization may take the either of two forms, a direct form or an indirect form. Direct pass involves directly anastomosing branches from the external circulation to the internal circulation via branches of the middle cerebral artery. This allows for immediate increase in cerebral perfusion pressure. Indirect bypass involves securing the external carotid artery on the dura matter and relying on

delayed neovascularization. There is no definite evidence to support the superiority of one approach over the other. Advantages of the indirect approach include lower morbidity risk, independence of a recipient vessel, and revascularization beyond the middle cerebral artery territory.

36.6.2.1 Direct Bypass: Superficial Temporal Artery-to-Middle Cerebral Artery Bypass (STA-MCA)

STA-MCA bypass remains the most common direct revascularization procedure for childhood MMD (Fig. 36.2). It falls under the direct bypass group, where the STA artery branches (frontal and/or parietal) is anastomosed to an M3 or M4 recipient branches. Alternatively the occipital artery may be used as a donor vessel if the STA is not a suitable donor [74]. The long term patency (5.6 years follow up) of the STA-MCA bypass was reported to reach 91% regardless of the clinical indication [75].

The main advantage of the direct bypass procedure is an immediate increase in blood flow to the affected brain. The disadvantages include the technical difficulty due to the small size of the donor and recipient vessels, especially in the pediatric population. Only the MCA territory benefit directly from the bypass, while the ACA and PCA may benefit via reversal of blood flow. The surgical technique itself puts the MCA territory at risk of ischemic events due to clamping of the MCA recipient branches [21].

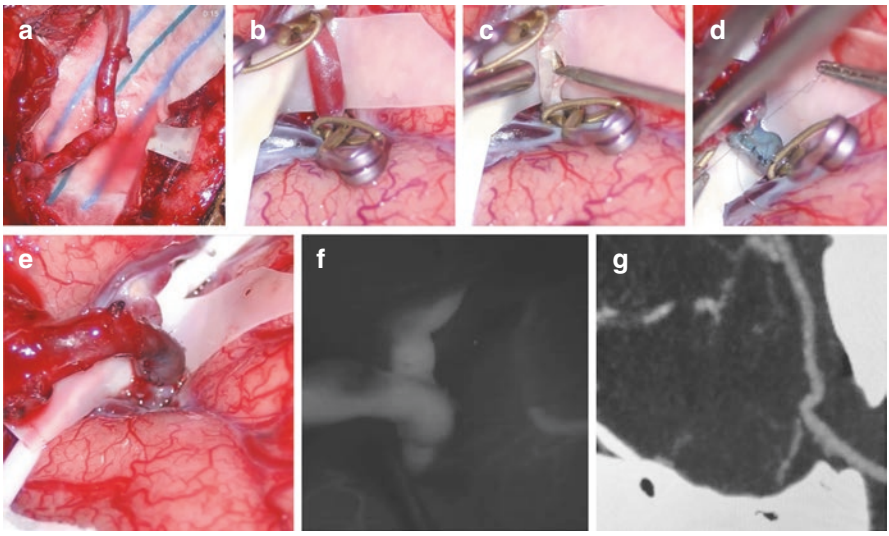

Fig. 36.2 STA-MCA bypass (**a**–**g**). (**a**) Dissected STA, (**b**) Dissected and clamped MCA branch, (**c**) arteriotomy of the recipient vessel, (**d**) Suturing the anastomosis between STA and the MCA branch using 10-0 Nylon, (**e**) Flowing bypass, (**f**) Indocyanine Green fluorescent showing patent bypass, (**g**) CTA reconstruction showing filling of the MCA via the bypass

36.6.2.2 Indirect Bypass

Indirect procedures are an alternative when direct procedures are not feasible, especially in the pediatric population. The advantages of the indirect approach include lower morbidity risk, technical simplicity, shorter operative time, independence of the recipient vessel, and reperfusion extends beyond the MCA distribution [14, 54, 76].

36.6.2.3 Encephalomyosynangiosis (EMS)

EMS is characterized by laying the temporalis muscle over the pia matter to incite angiogenesis which occurs over a delayed period (weeks–months) [77, 78]. EMS was first introduced in the 1970s for the treatment of MMD [77]. Despite a less invasive approach relative to the direct approach, EMS has significant disadvantages including postoperative complications such as risk of seizure, brain edema, and a mass effect associated with the large space-occupying muscle [76, 77].

36.6.2.4 Encephaloduroarteriosynangiosis (EDAS), Encephalomyoarteriosynangiosis (EMAS), Pial Synangiosis, Encephaloduroarteriomyosynangiosis (EDAMS)

EDAS is characterized by suturing the adventitia/galeal of an intact STA branch to a linear dural incision. EDAS was first introduced in the 1980s (Fig. 36.3) [79]. A modification of the EDAS technique is to include the temporalis muscle overlaying it over the cerebral cortex which is termed Encephalomyoarteriosynangiosis (EMAS). Another modification of the EDAS procedure is opening the arachnoid membrane. The procedure is termed Pial synangiosis, and it was introduced due to perception that the arachnoid membrane may act as insulating layer to vascular ingrowth in the standard EDAS procedure [24]. Combining the above mentioned indirect procedures (EDAS, EMS, Pial synangiosis) results in EDAMS which was introduced in 1984. The thought is that combining multiple indirect technique may allow for the greatest chance for neovascularization [80]. In addition to the typical limitations of the indirect approach, the critical disadvantage is that it render the STA ineffective for future STA-MCA bypass.

In one study, EDAMS was compared to EDAS both clinically and radiographically. EDAMS was more effective in achieving angiographic revascularization and reduction of pre-operative ischemic symptoms compared to EDAS alone [80].

Additional indirect procedures include Omental transplantation and Cranial bur holes [14, 81].

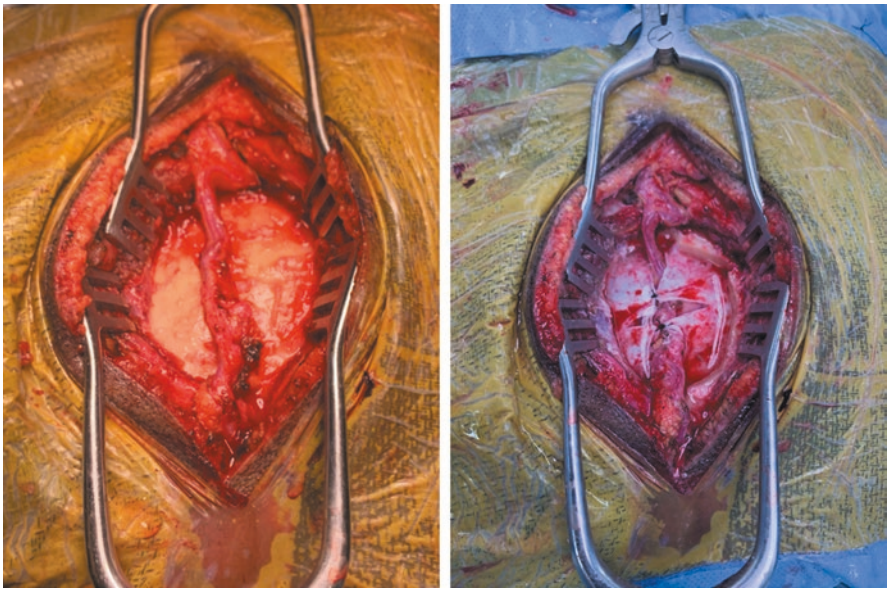

Fig. 36.3 Encephaloduroarteriosynangiosis (EDAS)

A direct synangiosis is commonly used in adults where a branch of the external carotid artery, usually the superficial temporal artery, is directly anastomosed to branches of the internal carotid artery include the middle cerebral artery or anterior cerebral artery.

The surgical treatment has a 3.5–4% morbidity rate and 0.7% mortality rate per treated cerebral hemisphere.

36.7 Familial Moyamoya Disease (FMMD)

The proportion of FFMD in one North American surgical series over 30 years period was 3.4% [82]. This percentage was lower than proportions reported from Asian countries ranging between 6 and 15.4% (6–15.4% in Japan, 9.4% in China, and 12% in Korea), and western Europe (7.4%) [8, 11, 27, 40, 82–85]. Male to female ratio is 1:1 in FMMD which is different than the differs markedly from the strong female preponderance reported for sporadic cases of MMD [10, 82, 84, 86, 87]. The age of onset was similar to the sporadic cases (8.1 years, 7.2 years in Japan, and 8 years in china). and FMMD in general have similar clinical presentation, except for a higher rate of asymptomatic patients due to the screening process [84, 88].

36.8 Outcomes

There is limited published data on the direct technique in the pediatric population, due to the inherent technical complexity of the procedure. Both techniques, direct and indirect, in a large retrospective study had the same efficacy in preventing a future stroke [89]. Another recent retrospective study of 102 patients looking at the efficacy of indirect technique (dural inversion) reported a 5-year risk of stroke or hemorrhage of 6.4% with an 88% good functional outcome [90]. Known prognostic factors following revascularization surgery are preoperative multiple cerebral infarctions, early onset at a young age, high Suzuki stages on cerebral angiography, the surgical procedure itself, and perioperative complications such as ischemic events [91–95]. Patients with irreversible ischemia have a higher likelihood of poor outcomes (infarction on presentation, OR 3.0; perfusion defect, OR, 14.0; postoperative stroke, OR 5.6) [40]. Symptoms remission following revascularization surgery is variable. Revascularization procedures are effective in reducing the risk of TIA and ischemic stroke. Favorable seizures outcomes are reported at 97%, while headache remains a challenge. Headache remits in 84%, and 16% develop new headache following revascularization surgery [96]. Intellectual delay remains a critical issue for certain patients. Prior studies reported that 10–30% of the patients had difficulty in social or school life because of intellectual impairment.

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Chapter 37
Vein of Galen Aneurysmal Malformations

Xiheng Chen and Xianli Lv

37.1 Introduction

Vein of Galen aneurysmal malformations (VGAM) is a rare congenital intracranial high-flow vascular malformations (incidence approximately 1 of 25,000), which is commonly seen in neonates or infants and rarely persist into adulthood [1–3]. It accounts for approximately 1% of all intracranial vascular lesions, representing 30% of pediatric vascular malformations [4–6]. The exact incidence of the disease is difficult to determine because of serious diagnostic confusion among various malformations that lead to dilatation of Galen veins or their embryonic precursors [7]. VGAM is located in the subarachnoid space of choroid fissure, which is related to the embryology of choroid plexus [8]. Berenstein et al. [9] and Garcia-Monaco et al. [10] further clarify the concept of VGAM, defining VGAM as a direct arteriovenous fistulas between choroidal arteries (both anterior and posterior) and persistent median prosencephalic vein of Markowski, (the precursor of the future vein of Galen and internal cerebral veins), not the vein of Galen, per se. This type of lesion is designated as true vein of aneurysmal malformation. In addition, some pial or dural arteriovenous malformations that lead to "real" (embryonic mature) Galen vein dilatation are called Galen venous aneurysmal dilatation, while Galen varices are dilated Galen veins without arteriovenous shunts [9]. This chapter will focus on the classification, etiology, pathophysiology, clinical manifestation, diagnosis and management of the VGAMs.

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37.2 Classification

Yasargil divided VGAMs into four types on the basis of angioarchitecture [11] (Table 37.1). Later Lasjaunias and his colleagues [12, 13] classified true VGAMs into choroidal and mural types, which is widely accepted. They didn't think Yasargil type IV was a true VGAM. The choroidal type is the most common type of VGAM, which is typically characterized by abundant supply of bilateral arteries from all choroidal arteries, pericallosal artery and/or subependymal branches of the thalamus before draining into the large venous pouch. These vascular connections are located in the extracerebral subarachnoid space, communicating with the anterior side of the median vein of the prosencephalon. The type is a very primitive condition. The mural-type VGAM accounts for about 1/3 of this lesion. It is characterized by direct arteriovenous fistula in the wall of the median vein of the prosencephalon, and the outlet stenosis is more common (Fig. 37.1). There are few connections arising from the collicular or posterior choroidal artery branches, which may be unilateral or bilateral [14].

37.3 Etiology and Pathophysiology

The arteriovenous shunting from choroidal arteries into a dilated midline deep venous collector, which Raybaud [8] first recognized as an dilated vein, a persistent median prosencephalic vein of Markowski (MPV), the precursor of the future vein of Galen and internal cerebral veins (ICV) [15]. This embryonic vein is only involved in draining the choroidal system and is not connected to the deep venous

Table 37.1 Classifcations of vein of Galen aneurysmal malformations

Classification	Description
Lasjaunias et al. [12]	
Type I	Choroidal
Type II	Mural
Yasargil [11]	
Type I	AVF btwn leptomeningeal arteries & feeders from P3, segments of PCAs, & vein of Galen
Type II	Feeders from thalamo-perforating vessels & from P1 and P2 segments of PCAs
Type III	Combination of types I & II
Type IV	
IVA	Aneurysmal dilation of vein of Galen due to shunting from an adjacent thalamic AVM
IVB	Aneurysmal dilation of vein of Galen due to shunting from an adjacent mesencephalic AVM
IVC	Thalamomesencephalic or mesodiencephalic plexiform malformation & a separate cisternal AVFadjacent to the vein of Galen

AV arteriovenous, *PCA* posterior cerebral artery

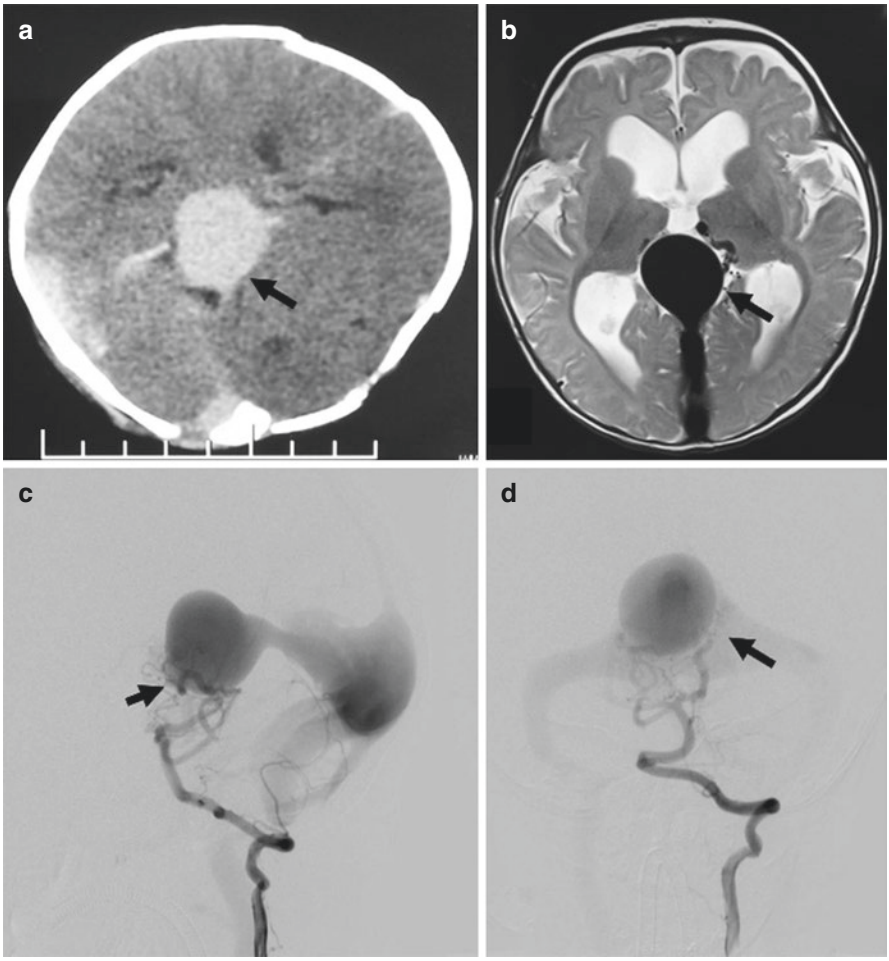

Fig. 37.1 An example of a mural VGA in a 4-month boy. (**a**), CT show a round mass in the quadrigeminal cistern behind the posterior edge of the third ventricle (Black arrow). (**b**), MRI, T2-weighted, axial view, revealed a large area of flow void along the course of the deep vein (Black arrow). (**c**), left vertebral artery angiogram, lateral view. (**d**) left vertebral artery angiogram, antero-posterior view. Showing the VGA supplied by the bilateral posterior choroidal arteries with outflow stenosis (Black arrow)

system. It does not develop the true vein of Galen until connections with the thalamostriate and internal cerebral veins develop. In patients with VGAMs, these communications with the thalamostriate and internal cerebral veins did not form, and the median prosencephalic vein of Markowski (MPV) did not degenerate normally. As a result, it becomes VGAM. This process is thought to develop within 6–11 weeks of gestation [8]. Although the Lasjaunias model of VGAM described the classic alternative drainage of ICVs, Hans Kortman et al. [16] found that the ICV

communicated with the venous malformation in approximately 1/3 of their cases. They thought that it was a major reason for procedural morbidity and mortality.

It is not clear what led to the formation of VGAM. But recently, a significant publication demonstrated that a loss of functional mutation in *EPHB4* took responsibility for true VGAM in 10% cases [17]. Further studies found similar mutations in about 30% of Galen venous malformations [18].

High-output heart failure, neurological symptoms secondary to cerebral venous hypertension and abnormal flow of cerebrospinal fluid (CSF)are the most common pathophysiological outcomes of VGAM [19]. Hydrodynamic disorders explain the pathophysiology of VGAM manifestations in neonates and infants. Any early intracranial high-flow shunt involving the entire cerebral venous system will interfere with brain drainage through its own drainage, causing potentially destructive brain damage and dramatic neurological consequences [20, 21]. The CSF absorption system of neonates relies on brain capillaries, and the medullary venous system plays an important role in brain water balance. Abnormal venous drainage can disrupt the water balance of the cerebrum. The increased pressure in the venous system caused by the arteriovenous fistula hinders the drainage of cerebrospinal fluid in the ventricles and white matter. This can lead to hydrocephalus, and subependymal atrophy and ventricular enlargement due to white matter congestion. The main cause of hydrocephalus is not that the midbrain aqueduct is mechanically compressed. Almost all patients have unobstructed aqueducts [22]. As long as the cranial sutures are open, adaptive macrocrania may occur. CSF shunt may worsen the condition due to increased shunt. Therefore, CSF shunt in VGAM patients is a contraindication.

37.4 Clinical Presentation

Clinical presentation is largely determined by the changing or evolving venous angioarchitecture. The vascular architecture of choroidal type is a very primitive condition, it is related to the poor clinical outcome of the neonate. The mural type is better tolerated than the choroidal condition, and therefore has mild cardiac symptom and better clinical prognosis [23]. Different age groups of patients with VGAMs have different clinical presentations. Isolated pulmonary hypertension and mild feeding difficulties can be seen in neonates. In infants and children, the hemodynamic effects of VGAM results in macrocrania, developmental delay, and seizures. Other manifestations such as epistaxis and proptosis could be explained by venous re-routing. Headache and vomiting were the most common symptoms in adults. Xu et al. [3] reported an adult patient with VGAM who presented with vertigo and dizziness.

37.5 Diagnosis

The diagnosis of VGAMs mainly depends on imaging examinations, such as Doppler ultrasound, Computed tomography (CT) scan, Magnetic resonance image (MRI) scan, cerebral angiography.

Ultrasound is a remarkable method to screen and evaluate VGAM, both in utero and the neonatal period [24]. In the third trimester of pregnancy, VGAM can be detected by fetal Doppler ultrasonography, showing a dilated turbulent venous sac behind the third ventricle, often accompanied by high-output cardiac hypertrophy [25]. Transcranial Doppler ultrasound can characterize the blood flow in the malformation. It is not only useful in delineating the blood supply and drainage vessels, but also more valuable in evaluating the therapeutic effect [26].

CT images of vein of Galen aneurysms generally show a round mass in the quadrugeminal cistern behind the posterior edge of the third ventricle (Fig. 37.1). The high density in the lesion may indicate the thrombosis of Galen venous aneurysm [27]. In addition, CT scan can show higher diagnostic value for intraventricular hemorrhage and hydrocephalus, and contrast media can better show the outline of the lesions.

The diagnostic effect of magnetic resonance image is better than that of color Doppler ultrasound. MRI and magnetic resonance angiography (MRA) can not only show normal and abnormal cerebral vessels, the relationship between abnormal blood vessels and brain functional areas, but also show the ischemic brain tissue after blood theft of arteriovenous malformations without injection of contrast agent. It not only helps to make treatment plans, but also helps to guide angiographers to select the most important blood vessels for research. Taffin and colleagues [28] observed that encephalomalacia on MRI was a major risk factor for poor prognosis and had nothing to do with cardiopulmonary status at birth. Nevertheless, the middle cerebral artery (MCA) pseudo-feeders seen on MRI was described as a risk factor for the occurrence of encephalomalacia [29]. This sign becomes the basis of clinical-management decision tree in some institutes.

Cerebral angiography can understand the feeding arteries, draining veins and stolen vascular malformations, and show the location and type of arteriovenous fistula. It has been reported that MRI is superior to digital subtraction angiography (DSA) in detecting deep venous communication with a VGAM, but because of the angioarchitectural complexity of these lesions, neither of them is reliable in confirming or excluding this point. Further research is needed to observe multiparameter imaging to evaluate this [16].

37.6 Management

The outcome of patients with VGAMs is poor, with a total mortality rate of 10.6% [23]. Due to small total blood volumes and the coexistentence of heart failure, surgical treatment had significant impact on neonatal mortality. For VGAM neonates with cardiac failure, the mortality rate of conservative treatment and surgical treatment is more than 90% [2]. Infants without heart failure had a mortality rate of 30–40% after surgery, and 46% of the survivors had significant morbidity [2, 24]. These outcomes are unacceptable. The ability of stereotactic radiosurgery to eliminate large-caliber fistulas is limited, and from a practical point of view, it is impossible to place headframes in young patients with open cranial sutures [30]. These led to the endovascular treatments for VGAMs, making it the preferred method for the treatment of VGAM [15, 31, 32].

Advances in endovascular embolization materials and techniques and a better understanding of clinical, anatomic, pathophysiological aspects, combined with advances in intensive care and cardiac failure management have significantly improved the treatment outcome and prognosis of VGAM [33]. The choice of embolic material depends on the hemodynamics and angioarchitectural characteristics of the lesion. Traditionally, NBCA (Cordis Microvascular, Inc.) has been used as the embolic agent in the transarterial approach, but recently Onyx (Medtronic-ev3, Inc.) is becoming more and more popular because of its advantages such as non-adhesion and long-injection time. Detachable microcoils are used as embolic materials for high-flow shunts [33]. Brinjikji et al. [31] suggest that endovascular treatment of VGAMs can bring good long-term results. Novertheless, they stressed that it is very important for the choice of patients and the timing of treatment. Studies using the Bicêtre Neonatal Assessment score (BNES) are reported to have experienced a higher rate of good neurological prognosis than those who did not use reassigned scores in neonatal patients [23, 34]. The BNES is a 21-point score that assesses a combination of cardiac, neurologic, respiratory, hepatic, and renal functions (Table 37.2). In patients with BNES < 8, If there is evidence that patients already have brain damage or severe multiple organ failure, it is usually recommended not to give endovascular treatment to these patients. Otherwise, there will inevitably be adverse outcomes. Aggressive medical treatment should be carried out under the supervision of a team of experienced pediatric cardiologists and neurointerventionists for neonates with congestive heart failure. If medication for congestive heart failure fails and MRI has no evidence of severe damage to the brain parenchyma (BNES 8–12), emergency endovascular therapy can reduce the expected mortality rate by nearly 100%, not necessarily a serious morbidity [34]. When there are signs of MCA pseudo-feeders on MRI, even if there is no drug-controllable heart failure at birth, Taffin et al. [28] suggest urgent embolization of the lesion, which can reduce cerebral venous pressure and relieve the “steal” of arteries associated with shunts, thereby preventing the risk of encephalomalacia damage. If the condition is stabilized (BNES 13–21), it is recommended that routine developmental and MRI follow-up assessments (every 3 months of the first year) be

Table 37.2 Bicêtre neonatal evaluation score (BNES)

Points	Cardiac function	Cerebral function	Respiratory function	Hepatic function	Renal function
5	Normal	Normal	Normal	–	–
4	Overload, no medical treatment	Subclinical, isolate EEG abnormalities	Tachypnea,finishes bottle	–	–
3	Failure; stable with medical treatment	Nonconvulsive intermittent neurologic signs	Tachypnea, does not finish bottle	No hepatomegaly, normal hepatic function	Normal
2	Failure; not stable with medical	Isolated convulsion	Assisted ventilation, normal saturation $FIO_2 < 25\%$	Hepatomegaly, normal hepatic function	Transient anuria
1	Ventilation necessary	Seizures	Assisted ventilation, normal saturation $FIO_2 > 25\%$	Moderate or transient hepatic function insufficiency	Unstable diuresis with treatment
0	Resistant to medical therapy	Permanent neurological signs	Assisted ventilation, desaturation	Abnormal coagulation, elevated enzymes	Anuria

EEG electroencephalogram, FIO_2 fractional inspired oxygen. Maximal score = 5 (cardiac) + 5 (cerebral) + 5 (respiratory) + 3 (hepatic) + 3 (renal) = 21

performed to detect any impaired cerebrospinal fluid physiology and to verify that all developmental milestones have been met. If a gradual increase in head circumference, aggravation of hydrocephalus, or any signs of early growth retardation are found during follow-up, endovascular treatment will be carried out at this stage. These patients usually need to undergo multi-stage endovascular embolization [34]. This mode of practice may bring more benefits to patients because the treatment of neonates is often accompanied by a high incidence of technical complications and poor neurological prognosis. Additionally, experiences of Bhatia et al. [35] suggest diligently assessing deep venous drainage patterns, avoiding excessive single-session embolization into the venous sac, embolizing distal fistulous feeders before more proximal feeders, using smaller diameter microcatheters (<2.0 F) may be preferable for neonatal procedures. If the conditions of neonate can be stable, delaying treatment for a few months may bring benefits to patients. Since complete occlusion rate of VGAM is only 60%, complete occlusion is not always the main goal of endovascular treatment [20], but to improve the physiological and neurological condition of patients. Therefore, staged endovascular embolization of VGAM is widely accepted at present [4, 23, 36]. Staged embolization can help avoid cerebral parenchymal bleeding and venous thrombosis [37].

For infants and children, the timing and course of the treatment of VGAM in infants and children are somewhat different from that in neonates. The immediate goal is to maintain the hydrovenous equilibrium, to preserve the normal brain development, and to eliminate the lesion [23]. Making clinical decisions on the treatment of asymptomatic patients is difficult. It is not necessary or recommend to

prematurely attempt to obliterate lesions or to take significant technical risks in the treatment of asymptomatic children whose VGAM does not pose an immediate threat to normal brain development. These lesions need to be closely monitored and treated accordingly. The BENS scoring system applied to neonates should not be used when evaluating infants and older children. In addition, if the patient has severe hydrocephalus with the indication of cerebrospinal fluid ventricular shunt, the shunt should be performed after endovascular embolization. Cases of spontaneous occlusion of VGAM have been reported, but it is extremely rare and often occurs late, by which time brain damage may already be irreversible [38].

37.7 Conclusion

A better understanding of embryology, anatomy and pathophysiology of VGAM, and the improvement of clinical evaluation (including symptoms, signs and imaging), coupled with the progress of intensive care and treatment of heart failure, advances in endovascular embolization materials and techniques, have greatly improved the treatment outcome and prognosis of VGAM.

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Part VII
Functional

Chapter 38
Temporal Lobe Epilepsy

Tristan Brunette-Clement, Aria Fallah, and Alexander G. Weil

Abbreviations

AChA	Anterior choroidal artery
AED	Antiepileptic drug
AF	Arcuate fasciculus
ATL	Anterior temporal lobectomy
CD	Cortical dysplasia
CSF	Corticospinal fluid
DALYs	Disability-adjusted life-years
DBS	Deep brain stimulation
DRE	Drug-resistant epilepsy
DTI	Diffusion tensor imaging
ECoG	Electrocorticography
EEG	Electroencephalography
ETE	Extra-temporal epilepsy
EZ	Epileptogenic zone
FCD	Focal cortical dysplasia
FDG	Fluorodeoxyglucose

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FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GTC	Generalized tonic clonic
GTR	Gross total resection
HS	Hippocampal sclerosis
ICA	Internal carotid artery
ILF	Inferior longitudinal fasciculus
IOFF	Inferior occipitofrontal fasciculus
IQ	Intellectual quotient
LGB	Lateral geniculate body
LITT	Laser interstitial thermal therapy
MCA	Middle cereberal artery
MEG	Magnetoencephalography
MHT	Multiple hippocampal transection
MRI	Magnetic resonance imaging
MST	Multiple subpial transection
mTLE	Medial temporal lobe epilepsy
MTS	Medial temporal sclerosis
PCA	Posterior cerebral artery
PET	Positron emission tomography
pTLE	Pseudotemporal lobe epilepsy
RFA	Radiofrequency ablation
RNS	Responsive neurostimulation
SAH	Selective amygdalohippocampectomy
SDE	Subdural electrodes
SEEG	Stereoelectroencephalography
SISCOM	Subtraction Ictal SPECT Coregistered to MRI
SPECT	Single-photon emission computed tomography
SSV	Superficial sylvian vein
SUDEP	Sudden unexpected death in epilepsy
TLE	Temporal lobe epilepsy
TPE	Temporal plus epilepsy
UF	Uncinate fasciculus
VNS	Vagus nerve stimulation

38.1 Introduction

Temporal lobe epilepsy (TLE) is a common cause of medically refractory epilepsy in children [1] and persistent seizures often leads to neurocognitive impairment and reduced quality of life [2–7]. There is now Level 1 evidence that temporal lobectomy significantly improves seizure control compared to continued medial therapy in carefully selected patients with drug-resistant TLE [8–13]. However, surgery

remains underutilized due to several well-identified factors, including barriers in physician referrals, physicians' subjective evaluation of low seizure frequency and view that surgery may not be beneficial, as well as patients' and parents' fear of brain surgery and its complications [1, 11, 14–17]. Therefore, raising physician awareness and proper patient counseling on the risks and benefits of epilepsy surgery is necessary for informed decision-making [17]. Patients with suspected refractory TLE should be referred to a specialized pediatric epilepsy center for early, comprehensive surgical evaluation. Such evaluation would involve a multidisciplinary team that would identify optimal surgical treatment based on non-invasive and invasive investigations, as appropriate. Modern surgical management involves an ever-expanding selection of procedures, each with their own indications, benefits and complication profiles, from various types of resective surgery (e.g. temporal lobectomy or lesionectomy), as well as minimally invasive ablative procedures, or neuromodulation. The choice of treatment option depends on treatment goals, patient preference, and provider expertise.

In this chapter, we review the aspects of pediatric TLE relevant to surgical decision-making, including epidemiology, clinical features, histopathology, natural history, preoperative workup, anatomy, and surgical options.

38.2 Epidemiology

Epilepsy is an important cause of disability worldwide. Recent estimates have suggested that epilepsy may represent 0.5% of disability-adjusted life-years (DALYs) due to all diseases and injuries globally, and up to 5% of DALYs due to neurological disorders [18]. The overall incidence of new-onset epilepsy in pediatric patients ranges from 33 to 82 per 100,000 children per year [6]. While TLE represents the most common surgically amenable drug-resistant epilepsy (DRE) in adults, surgically treatable epilepsy in children usually originates from the extra-temporal cortex [6]. Temporal lobe epilepsy accounts for approximately 15–20% pediatric DRE cases and is less common than extra-temporal epilepsy (ETE) [1, 6].

38.3 Clinical Features: Presentation, Semiology, and Etiology

TLE presents as a heterogeneous disorder in children and thus is more difficult to recognize clinically. Clinical seizure semiology and electrophysiological characteristics vary with chronological age as a function of changes in brain development, maturation, and underlying etiology. As such, pediatric TLE presents with an age-dependent presentation [19, 20], contrasting with the slightly more homogeneous presentation of TLE in adults.

While there is certainly some heterogeneity for TLE during adulthood, the most common form of surgically treatable TLE is medial *TLE (mTLE) syndrome*. In mTLE, patients develop epilepsy towards the end of the first decade of life following a remote history of complex febrile seizures in early childhood. Seizure semiology is well described and is most often related to hippocampal sclerosis (HS) on MRI [21, 22]. If a child is of school age (>6 years), one can expect seizure semiology and EEG to resemble more closely that of adults, including typical auras, psychomotor arrest, more complex automatisms, motor manifestations with versive movements and dystonic posturing, along with well-localized temporal ictal and interictal EEG patterns [23]. The underlying etiology in this age group more commonly involves HS in addition to FCD, low-grade neoplasms and vascular malformation.

By contrast, the clinical semiology is very different in preschool children. In the preschool age group, focal temporal lobe epilepsy patients present with non-focal ictal semiology three quarters of the time and generalized seizures in just under half of cases. This potentially misleading presentation should not deter clinicians from performing MRI or Video-EEG or referring to epilepsy centers for assessment [24]. Presentation is even more different in infants and toddlers (0–3 years of age), where auras are rare, and seizures usually begin with behavioral arrest, staring and lip cyanosis or apnea. Seizures tend to be longer and, in most cases, present with motor phenomena, including symmetrical or bilateral tonic or clonic movements or epileptic spasms in the presence of unilateral temporal origin [20]. Simple oroalimentary and gestural automatisms may be observed, but more complex automatisms are relatively inexistant [6, 20, 21]. In these very young patients, etiology is most often developmental (FCD, tubers) or low-grade neoplasms, and HS is seldom seen. In older preschool and early-school aged children (3–6 years of age), patients are more able to communicate subjective manifestations in accordance with neurodevelopment—auras may become more common and can involve fear (mesial TLE involvement) or auditory disturbances (lateral TLE involvement) seen with TLE in adults. While symmetrical simple motor seizures become less common, the ictal dystonic posturing and versive head turning often seen in adult mTLE occur more frequently. Automatisms become more complex and discrete with age [20]. Older children may display even more elaborate automatisms such as hand clapping, fumbling movements and deambulation [6, 21]. Such automatisms may involve a single extremity, in which case they reliably lateralize to the ipsilateral temporal lobe. Postictal confusion, disorientation, fatigue, headaches, and continued automatisms can last for minutes to hours [6, 21]. Older adolescents are the more likely to display typical adult TLE semiology. In this age group, auras are frequent, the most common being an epigastric-rising sensation. Other auras may help in localization; olfactory and gustatory auras may localize to the uncus; auditory and visual auras usually arise from the lateral temporal region, whereas psychic alterations (e.g., fear) can involve the amygdala [6].

In 1989, the International League Against Epilepsy divided temporal lobe epilepsies into two main types: medio-basal or amygdalohippocampal, and lateral or

neocortical TLE [22, 25]. It is, however, becoming increasingly apparent that extra-temporal networks can also contribute to the extent of the epileptogenic zone (EZ) in TLE, and this is particularly true in children. Even within the mesial temporal lobe, seizures may arise from the hippocampus alone or in combination with extra-hippocampal medial temporal structures such as the entorhinal cortex. Seizures may also originate in lateral or temporal polar neocortex (lateral TLE subtype) or both mesial temporal as well as neocortical structures may be involved together (medial-lateral subtype) [26]. Temporal plus epilepsy (TPE) occurs when seizure onset not only involves the temporal lobe but also close neighboring structures, namely the orbitofrontal cortex, operculum, insula, and temporo-parieto-occipital junction [25, 27, 28]. It is important to recognize that extratemporal-onset seizures may spread to the temporal lobe and mimic TLE semiology or electro-clinical features. These are known as pseudotemporal lobe epilepsy (pTLE) [25]. Because the latter two forms of TLE represent a significant portion of surgical failures, they require additional investigations to study extra-temporal regions [25]. It is thus important to recognize that patients with pediatric TLE may often harbor an extensive epileptogenic network.

38.4 Histopathology

In contrast to TLE in adults, where the most common histopathological etiology responsible for seizures is HS, cortical malformations and nonprogressive developmental tumors are the main pathological etiologies in pediatric TLE [21, 29]. By far the most common congenital anomaly identified in children is focal cortical dysplasia (FCD), although microgyria, or periventricular heterotopias may be seen (Fig. 38.1). Low-grade neuro-epithelial tumors (e.g. low-grade gliomas, gangliogliomas, dysembryoplastic neuroepithelial tumors) are also very common causes of TLE in children. Other, rarer, well-defined epileptogenic lesions include hamartomas, vascular malformations and porencephalic cysts [6, 21, 30]. While arachnoid cysts are common findings in children, their role in TLE is highly controversial and these patients should be classified as "nonlesional" TLE cases until proven otherwise. HS is rarer in young children and when present it usually presents in the form of dual pathology, involving concomitant extra-hippocampal neocortical pathology such as focal cortical dysplasia (FCD) [6, 21]. Specifically, medial temporal sclerosis (MTS) and CD have been shown to occur as a dual pathology in up to 80% of children with TLE [21].

It is important to have a high index of suspicion of 'lateral' temporal neocortical pathology even in the presence of a medial lesion [31]. Knowledge of likely pathology has management implications—Optimal surgical management of such dual pathology likely involves resection of not only the hippocampal but also extra-mesial neocortical foci [21]. A limited resection of MTS such as selective amygdalohippocampectomy is more likely to result in incomplete resection of the

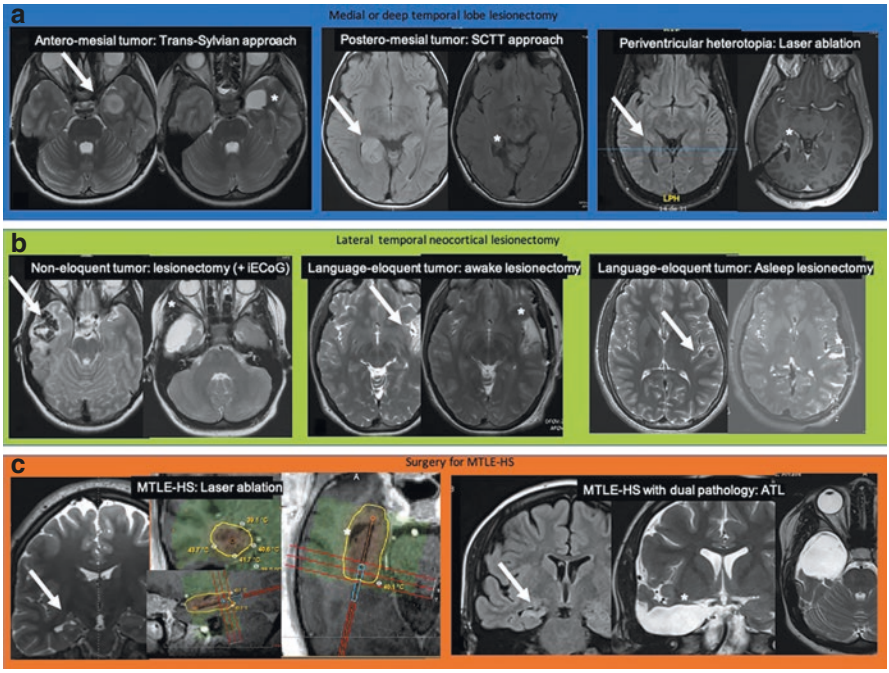

Fig. 38.1 Non-exhaustive portrait of 8 lesional TLE cases and various surgical approaches. MRI showing the lesion (arrow) and postoperative resection cavity (asterix). Left anterior peri-amygdala tumor resected through a trans-Sylvian approach (**a**); right postero-medial tumor resected through a SCTT approach (**b**); right periventricular heterotopia treated with LITT (**c**); right-hemisphere non-eloquent calcified DNET treated with lesionectomy using intra-operative ECoG which did not reveal additional interictal spiking (**d**); language-eloquent left temporal DNET that underwent lesionectomy under awake craniotomy (**e**); language-eloquent left temporal DNET resected under asleep craniotomy (**f**); MTLE-HS treated with LITT (**g**); MTLE-HS and lateral involvement on PET (dual pathology with subtle FCD) treated with ATL (**h**)

epileptogenic zone (leaving behind epileptogenic lateral temporal cortex pathologies) and be less effective in pediatric patients with TLE [9] (Fig. 38.2). Therefore, such patients require careful preoperative evaluation and surgical planning to achieve maximal safe resection, which is imperative to improve the likelihood of seizure control.

38.5 Natural History

Up to one third of children with a new diagnosis of epilepsy will progress to become medically refractory, meaning they will have failed to achieve sustained seizure freedom after at least two appropriately chosen, tolerated, and scheduled antiepileptic drugs (AEDs), either alone or in combination [6, 32]. It is well recognized that,

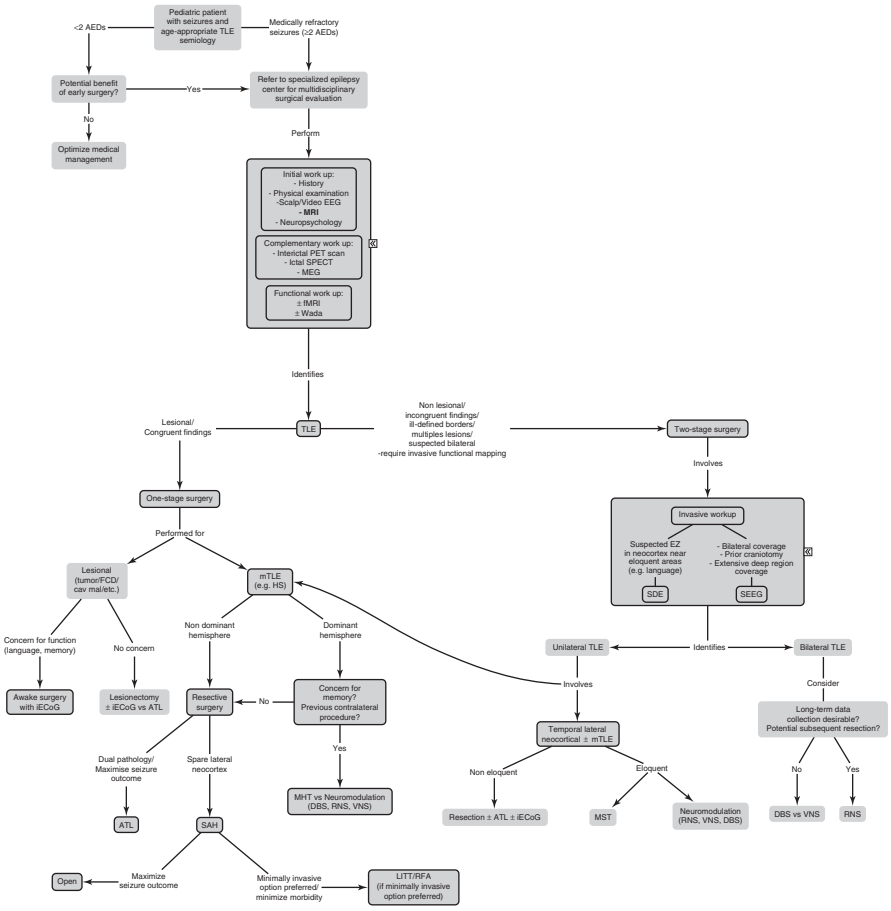

Fig. 38.2 Management algorithm for drug-resistant pediatric TLE

in these patients, achieving seizure freedom is unlikely with additional medication trials, despite the introduction of newer AEDs [11, 15, 33–35].

The temporal lobe, and the amygalo-hippocampal complex in particular, harbor high intrinsic epileptogenicity [26]. For this reason, when a patient presents with lesional TLE involving the lateral neocortical and especially the mesial temporal structures, the risk of intractable epilepsy is particularly high. This holds true for all lesional cases, whether FCD or developmental tumors [36–39].

Natural history of medically refractory TLE leads to well-documented poor outcomes in all areas of neurocognitive functioning, including cognition, behavior, language, and psychosocial development [3–5, 7, 11]. Specifically, dominant-hemisphere pediatric TLE has long-lasting impacts on verbal learning and memory, with affected children reaching poor performance levels [6] These patients typically suffer continued seizures, social isolation, unemployment, and

dependence [2, 5]. An intellectual quotient (IQ) below 90, seizure onset before 28 months of age, recurrent GTC seizures, left-sided focus, hyperactive or rage behaviors, and the need for special schooling predicted poor outcomes with continued medical treatment. Conversely, preserved intelligence, infrequent GTC seizures, and a positive family history of epilepsy predicted good outcome [5, 40].

The negative outcomes of pediatric TLE are thought to be multifactorial and involve the harmful effects of persistent damaging seizures, electrophysiological abnormalities, underlying brain dysfunction, as well as prolonged antiepileptic medication use during the sensitive periods of brain development and maturation [1, 11, 41]. For example, antiepileptic medication, even at therapeutic levels, may affect cognitive, behavioral and language function in children [7, 42, 43]. Although newer AEDs are generally considered to have fewer side effects than older AEDs, some entail higher risks of cognitive impairment, such as topiramate and zonisamide, or behavioral problems, namely levetiracetam [6, 44] Children with medically refractory epilepsy are also at higher risk of mortality, due to sudden unexpected death in epilepsy (SUDEP) and the underlying neurologic disorders [10, 11, 45]. It is well known that TLE surgery candidates with a longer duration of uncontrolled seizures, particularly if greater than 10 years, harbor a worse outcome, likely the result of the development of more diffuse epileptogenic networks. In some cases, initially unilateral TLE can kindle the contralateral hemisphere, leading to more difficult to treat bilateral TLE [46].

38.6 Noninvasive Workup

Patients whose epilepsy is deemed medically refractory should be promptly referred to a specialized center for a comprehensive evaluation. A multidisciplinary team of neurologists, neurosurgeons, neuropsychologists, neuroradiologists and other healthcare providers will be involved in surgical decision making and patient selection [47].

A noninvasive presurgical workup is the initial step in the evaluation strategy for drug-resistant epilepsy. It aims to localize a focal epileptogenic zone when present, as well as characterize epileptic activity to establish optimal surgical treatment. This workup begins with a thorough history and physical examination detailing seizure semiology, frequency, epilepsy duration, and epilepsy risk factors [48]. This should be followed by scalp electroencephalography (EEG) and magnetic resonance imaging (MRI), which make up the core of the presurgical testing [47].

EEG and long-term video-EEG are used to confirm epilepsy diagnosis and aid in localizing onset by correlating to semiology and are helpful in most patients with suspected TLE [6, 49, 50]. Enhanced spatial sampling may be obtained using high-density electrodes [6]. Interictal and ictal scalp EEG findings may be misleading in children, as generalized or multifocal epileptiform discharges may occur even in the presence of a focal temporal epileptic focus and lesion [51]. While older children and adolescents (over 6 years of age) usually have typical interictal EEG features

include temporal spikes or sharp wave discharges maximal over the anterior temporal region, and temporal intermittent rhythmic delta activity, infants and preschool children (under 6 years of age) are more likely to have extratemporal sharp waves or generalized or contralateral sharp waves [20]. While anterior and inferior temporal sharp waves suggest a medial temporal origin, lateral discharges may suggest temporal neoplasms [6, 52]. Ictal EEG will usually show moderate to high-amplitude rhythmic paroxysmal activity which may progress to generalized rhythmic slowing. While seizure patterns are often poorly localized or even falsely lateralized or generalized in the immature brain of younger children (age 0–3 years of age), ictal EEG patterns of preschool children and children over 6 years of age are more likely to be lateralized and localized to the temporal lobe, respectively [6, 20, 53].

MRI is a very important tool used to identify focal epileptogenic radiographic lesions, which are present in over half of refractory TLE cases [54]. The identification of a lesion potentially responsible for seizures is one of the most important presurgical findings and dictates management and surgical prognosis. Lesional TLE is associated with much more favorable surgical outcome than nonlesional TLE, and outcome is particularly good for certain well-circumscribed lesions such as low-grade neoplasms or cavernomas [15, 16] (Fig. 38.2). It is important to recognize, however, that MR abnormality may not be involved in seizure onset and concordance with other findings must always be scrutinized [54, 55]. While many lesions, such as tumors and vascular malformations, are readily apparent on MRI, other epileptogenic lesions may be more subtle (e.g. FCD). A dedicated MRI protocol on a 3 T scanner is thus recommended as it has better grey-white matter contrast and signal-to-noise ratio than 1.5 T scanners. For this reason, 3-T MRI may diagnose occult dysplasia otherwise missed on 1.5 T MRI [56]. High-resolution volumetric T1, DWI and SWI sequences should be obtained in all patients. While Fluid-attenuated inversion recovery (FLAIR) sequences and T2-weighted imaging are useful sequences to demonstrate mesial temporal sclerosis or hippocampal atrophy, loss of internal architecture, and abnormal gray-white matter organization, these sequences may miss FCD in the unmyelinated brain [57]. Myelination occurs progressively and only starts to resemble that of the adult brain at about 18 months of age, rendering detection of lesions on T2-weighted images more challenging in infant and toddlers [58]. An institutional epilepsy protocol, with age-specific sequences (e.g., different sequences for above and below 2 years of age), will improve the detection of epileptogenic lesions [59]. For this reason, FLAIR and T2-WI can be performed in children with myelinated brains (over 2 years of age) and inversion recovery and DESTIR for unmyelinated brains (children under 2 years of age) [60]. Repeating MRI may be of value in some infants with non-lesional MRI as follow-up MRI may reveal malformations of cortical development once myelination progresses [6, 57] (Fig. 38.2). However, up to 50% of cases may present with normal neuroimaging [6]. It has been well-documented that normal "non-lesional" MRI harbor radiologically occult lesions, usually FCD that can be identified with quantitative post-processing techniques (e.g., voxel-based analysis, surface-based analysis, etc), and confirmed on pathology of surgical specimens [61–64].

The initial evaluations may be complemented with further testing to help localize the EZ—Interictal positron emission tomography (PET) scan, ictal single-photon emission computed tomography (SPECT), and interictal magnetoencephalography (MEG) can be beneficial and are generally recommended in patients with nonlesional (MRI-negative) epilepsy or suspected lesional TLE due to ill-defined lesions, such as FCD or tubers [65].

Interictal PET scan is another valuable tool in assessing EZ location by analyzing regional glucose metabolism in the brain with injection of radioactively labelled fluorodeoxyglucose (FDG). FDG-PET is particularly useful in cases of non-lesional MRI or when there is a discordance between MRI and scalp-EEG. On PET, a localized EZ manifests as a focal region of interictal hypometabolism, which may increase in the ictal period [15, 25, 66]. In TLE, temporal hypometabolism ipsilateral to EZ is associated with better seizure outcomes than bilateral or extensive hypometabolism [25]. FDG-PET has demonstrated particularly high sensitivity in localizing EZ for patients who have noncontributory EEG and MRI [6, 66]. However, because the area of hypometabolism usually extends beyond the EZ, PET cannot be used to delineate the margins of resection and cannot differentiate from primary EZ and secondary foci [66, 67].

Ictal single-photon emission computed tomography (SPECT) is an imaging modality capable of assessing cerebral perfusion during a seizure [25]. When combined with MRI using the Subtraction Ictal SPECT Coregistered to MRI (SISCOM), it may identify areas of hyperperfusion corresponding with focal seizure activity [68]. In mesial TLE, hyperperfusion is typically identified in the medial temporal region, along with the insula, putamen, thalamus, and cerebellum. Partial or complete resection of the most prominent hyperperfusion signal is associated with good seizure outcomes, even in MRI negative patients [6, 25]. However, ictal SPECT is resource intensive and requires trained personnel, along with adequate monitoring [25]. It may show multifocal hyperperfusion and inadvertently show areas of propagation rather than an extended EZ when there is rapid seizure propagation or infraclinical seizure onset and can be misleading—interpretation thus requires experience and expertise [69].

Interictal magnetoencephalography (MEG) selectively measures magnetic fields produced by cerebral electrical activity that is parallel or tangential to the cortex, such as those located at the bank of sulci, contrasting the perpendicular activity detected by EEG [70]. Compared to scalp EEG, MEG has the advantage of a high spatio-temporal resolution without signal deterioration as its signal readily passes through the meninges, skull and scalp [71]. When the position and orientation of interictal spike models are overlaid with the patient's own coregistered MRI (termed magnetic source imaging), spatial resolution is optimized, aiding in surgical planning for electrode implantation or resection [70, 72, 73]). MEG is primarily a useful tool for localization of interictal epileptic spikes and mapping the EZ during the presurgical workup of suspected TLE [6, 25, 70, 74, 75], particularly in cases where MRI, PET, SPECT or VEEG fail to sufficiently localize the EZ or provide discordant data. The identification of compact MEG dipole clusters is particularly useful to localie the EZ in MRI-negative cases, FCD- or TSC-related cases [72, 73]. In

TLE, MEG may help in lateralization for those patients with bilateral temporal epileptiform discharges or structural abnormalities [76]. Resection of a tight MEG cluster is associated with improved seizure outcome [74]. Tasked-based MEG has also shown promise for noninvasive functional mapping of eloquent cortex with direct measurement of neuronal activity offering better temporal resolution than fMRI which relies on neurovascular coupling [73].

Temporal lobe surgery potentially deals with eloquent cortex, which entails significant neurological risks with surgery. Therefore, it is important to localize eloquent temporal lobe function, especially language neocortices, as well as lateralize verbal and visuospatial memory preoperatively. First, a comprehensive neuropsychological evaluation determines neurocognitive performance parameters, assists in lateralizing language and predicts neuropsychological outcome following either surgery or continued seizures [6, 15]. This helps patients and families weigh the benefits and costs of surgery, compared with other potential treatment modalities [6, 11]. Such evaluation includes age-appropriate, standardized tests to assess intelligence, language, memory, attention, problem-solving, executive function, visuospatial and perceptual analysis and reasoning, academic skills, motor and sensory function, behavior, personality, emotional status, and adaptive functioning. Of particular importance during neuropsychological testing is the identification of preoperative memory impairments. Typically, children with left (or dominant) TLE present more severe verbal memory dysfunction, while nonverbal dysfunction is worse in children with right (non-dominant) TLE [6]. However, TLE may also broadly affect working, episodic, semantic, and autobiographical memory [77].

Subsequently, language lateralization and motor localisation (important to assess in cases of temporal-plus epilepsy requiring possible frontal resection) may be determined noninvasively using functional MRI (fMRI). The fMRI uses blood oxygen level dependent (BOLD) technique and changes in deoxy and oxyhemoglobin to map functional brain regions. MR sequences taken during tasks capture areas of increase oxygenated blood flow to functional cortical areas correlating to the tasks [78]. In most cases, fMRI correlates well with both Wada test (intracarotid sodium amobarbitol test) and invasive electrocortical stimulation mapping in its ability to lateralize language [79]. In addition to lateralizing language, fMRI may also identify patients at higher risk of postoperative memory decline. As a general rule, resection of a language-dominant medial temporal lobe (hippocampus) will result in memory decline in approximately 30% of patients with intact verbal memory preoperatively [80–85]. However, this modality requires multiple task repetitions for functional mapping procedures, making its use impossible with certain patients, such as younger children below the age of 8 and those with cognitive impairment (full-scale IQ < 80) [6, 15]. Instead, the intracarotid sodium amobarbital procedure may be performed as it requires less active patient participation [79]. With pretest teaching, emotional preparation, and simplified test items, most children over 8 years old can complete this test [6]. Wada memory asymmetry with better verbal memory performance after injection ipsilateral to the side of surgery than after contralateral injection are more likely to have a favorable verbal memory outcome following resection or ablation of the involved mesial temporal lobe [6].

When congruent noninvasive investigations identify a lesional TLE syndrome, and there is little concern for functional deficits, patients may proceed directly to definitive single phase resective or ablative surgical treatment. This scenario represents the most favorable surgical outcomes, particularly in the presence of a discrete radiological lesion (e.g., tumor or cavernoma) [15, 86, 87] (Fig. 38.1).

38.7 Invasive Investigation

Noninvasive workup fails to adequately identify an EZ in approximately a fifth of patients with suspected TLE, and invasive monitoring may be necessary. Indications for invasive investigation in patients with suspected TLE in whom further EZ mapping is required include suspected TLE patients with (1) non-lesional MRI, (2) lesional TLE but incongruent findings on noninvasive investigation, (3) TLE syndrome in whom lateralization is uncertain, such as when bilateral seizure onset is suspected, and (4) TLE syndrome, semiology, or lesion but suspected extra-limbic, extra-temporal or contralateral involvement requiring further mapping [88] (Fig. 38.2). Finally, invasive mapping of functional with invasive electrocorticography may be necessary if noninvasive testing does not adequately lateralize language or memory. For example, invasive functional mapping is recommended in patients in whom (1) Wernicke area is suspected to be involved early or (2) suspected frontotemporal epilepsy cases requiring motor mapping [26, 86].

The invasive workup aims to delineate the EZ by capturing ictal and interictal electrographic data through intracranial electrode implantation followed by prolonged EEG monitoring for days to weeks. Because electrode coverage is limited, an EZ location or network involvement must be hypothesized a priori, in order to place electrode contacts in areas of putative EZ and avoid placement in areas unlikely to contribute to the EZ or network [15, 25, 86]. Two different approaches are commonly used for intracranial electrode placement—the open approach involves implantation of subdural electrodes (SDE), grid and strip with or without depth electrodes through a craniotomy, whereas the Stereoelectroencephalography (SEEG) approach involves the stereotactic placement of depth electrodes through pinholes under angiographic conditions [88–90].

SDE placement through a craniotomy remains a good option for EZ delineation in neocortical regions, especially those involving or adjacent to eloquent cortex, such as cortical language areas. This technique allows continuous coverage over large cortical areas and is well-suited to carry out cortical stimulation to map eloquent cortex, such as Wernickes area. In TLE, additional depth electrodes can be placed perpendicular into the amygdala and hippocampus through the second temporal gyrus [91, 92]. However, this technique does not readily allow for coverage of contralateral hemisphere and is limited in its sampling of ipsilateral depth of sulci or deep structures, such as the anterior cingulate for example.

SEEG involves the precise stereotactic implantation of depth electrodes through small incisions and 2–3 mm burr holes guided by neurovascular imaging using a

stereotactic frame, frameless neuronavigation, or a stereotactic robot [93–96]. Compared to SDE, SEEG allows better mapping of 3D epileptogenic networks, along with easier access to deep regions such as depth of sulci, periventricular region, cingulate gyrus, insula, and mesial temporal lobe. SEEG should be favored over SDE in patients with prior craniotomy or suspected bilateral TLE requiring bi-hemispheric coverage. By avoiding craniotomy, SEEG is associated with decreased operative pain, shorter recovery time, and a lower rate of serious adverse events than SDE (1.3% vs. 3.4%, respectively). Furthermore, SEEG removal is a minor procedure that does not require return to the operating room, which is necessary with SDE for grid explantation. Therefore, timing of definitive surgical treatment remains up to the treating multidisciplinary team [88–90]. The main limitation of SEEG is the risk for sampling bias if areas of EZ are not sampled and that it may be less ideal for language mapping compared to SDE.

38.8 Functional Anatomy

Noninvasive workups, occasionally supplemented by invasive monitoring, will identify candidates for surgical treatment of epilepsy. To understand the techniques and risks of surgery for TLE, intricate knowledge of the anatomy of the temporal lobe is essential [97].

The temporal lobe lies beneath the sylvian fissure (Fig. 38.3). It is limited anteriorly and inferiorly by the sphenoid and temporal bones. There are well defined

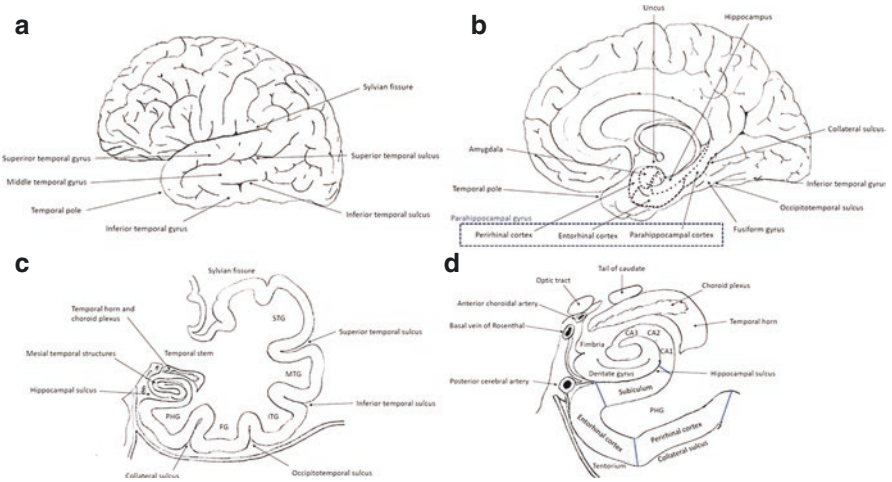

Fig. 38.3 Surgical anatomy of the temporal lobe: sagittal view of the lateral surface (**a**); sagittal view of medial and inferior surfaces emphasizing mesial temporal structures (**b**); coronal view highlighting gyri and sulci (**c**); coronal view of mesial temporal structures (**d**). STG: superior temporal gyrus. *MTG* middle temporal gyrus, *ITG* inferior temporal gyrus, *FG* fusiform gyrus, *PHG* parahippocampal gyrus. CA1–CA2–CA3: zones of Ammon's horn

lateral and medial posterior limits. On its lateral surface posteriorly, it is separated from the occipital lobe by the lateral parietotemporal line, which connects the preoccipital notch and the parietooccipital sulcus, and from the parietal lobe by the occipitotemporal line, which connects the most posterior limit of the sylvian fissure and the lateral parietotemporal line. Functionally, the temporal lobe is connected to the other cerebral lobes, insula, and basal ganglia by the temporal stem.

There are four surfaces to the temporal lobe: superior, lateral, inferior, and medial. The superior surface is directly under the sylvian fissure and is made up of three parts. The planum polare is the most anterior, followed posteriorly by the anterior transverse temporal gyrus, also known as Heschl's gyrus, and the planum temporale, itself consisting of the middle and posterior transverse temporal gyri. The lateral surface is composed of three gyri and two parallel sulci: the superior temporal sulcus separates the superior temporal gyrus from the middle temporal gyrus, and the inferior temporal sulcus separates the middle temporal gyrus from the inferior temporal gyrus. The inferior temporal gyrus is separated from the fusiform gyrus by the occipitotemporal sulcus, which marks the beginning of the inferior surface. Medially, the fusiform gyrus is separated from the parahippocampal gyrus by the collateral sulcus. The rhinal sulcus borders the medial edge of the parahippocampal gyrus and separates it from the medial surface. This surface is further divided into three segments; the anterior segment extends from the anterior edge of the uncus to its posterior limit, the middle segment follows and ends at the quadrigeminal plate, the posterior segment reaches the calcarine point where the parietooccipital and calcarine sulci meet. The temporal horn and atrium of the lateral ventricle are located within the medial temporal lobe.

The anterior medial temporal surface consists of the uncus and the entorhinal cortex. The uncus is further separated into an anterior and a posterior segment, which join medially at the apex of the uncus. The anterior segment faces the internal carotid artery (ICA) and the proximal middle cereberal artery (MCA) in the carotid cistern. It is part of the parahippocampal gyrus and is made up of two gyri: the semilunar gyrus, located superiorly, and the ambient gyrus. The posterior segment of the uncus faces the posterior cerebral artery (PCA) and anterior choroidal artery (AChA) in the crural cistern, as well as the anterior portion of the cerebral peduncle. It has a superior and an inferior part, separated by the uncal sulcus. The latter is formed by the entorhinal area, which is important in afferent and efferent connections to the hippocampus. The anterior medial temporal surface is bordered laterally by the anterior part of the temporal horn. This part is limited posteriorly by the most common entry point of the AChA into the temporal horn, known as the inferior choroidal point, just behind the hippocampal head. The amygdala lies anteriorly and is separated from the hippocampal head by the uncal recess. It forms the lateral aspect of the anterior segment of the uncus and parallels the semilunar gyrus. The amygdala composes the anterior wall and anterior part of the roof of the temporal horn. Lateral to the hippocampal head is the collateral eminence, which forms the floor of the temporal horn.

The middle medial temporal surface is composed of the fimbria of the fornix, which lies above the dentate gyrus, and the parahippocampal gyrus located

inferiorly (Fig. 38.3). The fimbriodentate and hippocampal sulci separate the dentate gyrus from the fimbria and the parahippocampal gyrus, respectively. At this level, the subiculum rests on the superior surface of the parahippocampal gyrus. The middle medial temporal lobe is bordered laterally by the posterior part of the temporal horn, which begins at the inferior choroidal point and extends to the atrium. In this part of the temporal horn, a cleft between the thalamus superiorly and the fimbria of the fornix inferiorly serves as an attachment site for the choroid plexus. This is known as the choroidal fissure. Opening this fissure allows access to the medial surface of the temporal lobe, as well as the perimesencephalic and ambient cisterns. The body of the hippocampus forms the medial wall, adjacent to the choroid plexus, whereas the collateral eminence continues to form the floor of this part of the temporal horn. Clinically, this serves as an important landmark to determine the medial limit of the neocortical removal in temporal lobe surgery. The roof and lateral walls of the lateral temporal horn are composed of a layer of tapetal fibers, covered by optic radiations forming Meyer's loop. Only the most anterior part of the lateral wall of the temporal horn is devoid of optic radiations. Damage to this structure causes upper contralateral quadrantanopia.

The posterior end of the parahippocampal gyrus forms the posterior medial temporal surface and is divided into the isthmus of the cingulate gyrus superiorly and the lingual gyrus inferiorly. Above, the fimbria of the fornix runs posteriorly and wraps around the posterior portion of the pulvinar as it becomes the crus of the fornix. Just below the splenium of the corpus callosum, the hippocampal tail blends into the fasciolar gyrus. The quadrigeminal cistern marks the medial border of this surface. The lateral border of the posterior medial temporal lobe is formed by the atrium of the lateral ventricle. The floor of the atrium is formed by the posterior end of the collateral sulcus and the intraventricular portion of the tail of the hippocampus. The anterior wall is divided into a lateral part formed by the pulvinar and a medial part formed by the crus of the fornix. The medial wall is also separated into a superior prominence formed by the callosal fibers of the forceps major and an inferior prominence formed by the calcarine sulcus. Finally, the lateral wall of the atrium is formed by the optic radiations.

The mesial temporal structures present widespread afferences and efferences. The hippocampus, formed from the dentate gyrus and the four cornu ammonis zones (CA 1–4) of the pyramidal layer, is a central component of the mesial temporal lobe and the Papez circuit. The hippocampus receives input from the entorhinal cortex, which is itself supplied by inputs from the perirhinal and parahippocampal cortices, amygdala, piriform cortex, insula, basal forebrain, frontal cortex, thalamus, brainstem, and basal ganglia. The Papez circuit is completed by projections from the subiculum to the fornix, mammillary bodies and mammillothalamic tract, anterior thalamic nuclei, and cingulum. Some projections also return to the entorhinal cortex. Many of these structures subsequently project to the cerebral cortex [32].

The PCA, ICA, and AChA all contribute to the arterial supply of the medial temporal lobe, whereas the MCA supports the remaining neocortical surfaces through various branches. Venous drainage of the temporal lobe is highly variable. Typically, lateral neocortical surfaces either drain into the superficial sylvian vein (SSV) or

into the tentorial sinuses. Medial temporal structures drain towards the deep middle cerebral vein, which eventually joins the vein of Galen.

38.9 Surgical Treatment: Options, Goals, and Outcome

The goal of surgery for TLE is to optimize quality of life by achieving seizure freedom with as little neurological sequelae as possible [15]. Anterior temporal lobectomy results in seizure freedom in approximately 60–70% of patients with drug-resistant TLE [1, 8, 11, 14]. Evidence supports early referral and surgery to avoid significant disability brought about by sustained exposure to damaging seizures [1, 11]. In very select cases, surgery may be performed in TLE patients prior to meeting "drug-resistant" criteria. In patients with TLE associated with developmental tumors, the well-known poor natural history and high rate of seizure freedom (80%) with resection may warrant early surgery in some cases, keeping in mind patient characteristics (e.g., lower risk of permanent deficit) and patient preferences (e.g., desire to reduce or wean antiepileptic medications, etc.). Alternatively, patients may choose clinical-radiological follow-up and any evidence of radiological tumor progression (increased size, increased enhancement) may lead to surgery despite controlled seizures [36–39] (Fig. 38.2).

Seizure freedom is a critical goal in epilepsy surgery as it is the most important predictor of quality of life [10, 41, 45, 98]. Nevertheless, surgery is also associated with improved neuropsychological outcomes. It is well established that for various neuropsychological outcome domains, including cognitive, memory, language, executive function, social, behavioural, and quality of life outcomes, most pediatric patients remained stable or improved post-surgery [11]. Seizure freedom is quite consistently associated with better neuropsychological outcome, and lower presurgical baseline scores predicted positive postoperative cognitive outcome [11]. It is important to recognize that left temporal surgery can be detrimental to language and verbal memory outcomes, although these patients often perform more poorly even before surgery [11, 99]. The complexity of assessing postoperative IQ must be emphasized and may be related to factors other than surgery, namely neurodevelopmental trajectory, change in AEDs, seizure recurrence, school attendance, and the psychosocial demands of rigorous treatment [11]. Other studies also support the fact that postoperative neuropsychological outcomes depend on language and memory cortex localization, underlying pathology, and age at seizure onset, with older age at seizure onset being associated with worse outcome, rather than on surgery itself [100].

When counselling patients for the benefits and risks of epilepsy surgery, it is important to manage expectations and provide patients and families with as accurate a picture as possible of the expected benefits. Several patient characteristics have been identified as improving the likelihood of seizure freedom following temporal lobectomy. Lesional epilepsy (e.g. abnormal MRI findings) and lack of generalized seizures are positive predictors of postoperative seizure freedom [1], while residual

or distant epileptogenic tissue is associated with persistent or recurrent seizures, supporting the importance of careful patient selection and EZ delineation with preoperative workup and complete resection during surgery [41]. Multiple seizure types and preoperative developmental delay are also associated with worse outcomes [101]. These factors are important to discuss with patients and families when choosing a treatment option.

Importantly, modern surgical options extend far beyond temporal lobectomy—The surgical armamentarium now includes minimally invasive procedures such as magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (LITT), neuromodulation techniques, namely deep brain stimulation (DBS), and closed-loop responsive neurostimulation (RNS), as well as multiple hippocampal transection (MHT) in addition to well-reported subpial transection (MST) [15, 102]. Treatment selection depends on results of preoperative investigations, provider expertise and patient preference (Fig. 38.2; Table 38.1).

38.10 Resective Surgical Approaches for Resection

There are two main resective surgical approaches for temporal lobectomy: anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH) through a craniotomy (Figs. 38.4 and 38.5). Extent of resection is case-specific and depends on results of preoperative investigations, including EZ, and localization of eloquent cortex, which should be preserved. Studies have shown that adequate volume resection focused on complete resection of EZ is more important than maximal volume resection in establishing surgical success [100].

38.10.1 Anterior Temporal Lobectomy: Indications and Technique

ATL is the most commonly performed surgical approach and includes removal of the anterior hippocampus, amygdala, temporal pole, and anterolateral temporal cortex [57, 103]. Therefore, it is preferred if lateral temporal epileptogenicity is suspected together with mesial temporal lobe EZ, as is most often the case with pediatric patients [21, 103].

38.10.1.1 Technique

Temporal lobe exposure involves common initial steps regardless of the selected surgical approach. Patient is positioned supine with head elevated and turned to the side opposite the affected temporal lobe. A question mark incision is made,

Table 38.1 Summary of indications, advantages, and disadvantages for each surgical option

Surgical options	Indications	Advantages	Disadvantages
Anterior temporal lobectomy	– Unilateral TLE with mesial and lateral temporal epileptogenicity	– Gold standard – Better seizure outcome than selective amygdalohippocampectomy—especially in pediatric patients (controversial)	– Possible worse neuropsychological outcome than selective amygdalohippocampectomy (controversial)
Selective amygdalohippocampectomy	– Unilateral TLE restricted to mesial temporal lobe – No lateral temporal and extratemporal disease	– Theoretically reduced postoperative cognitive decline (controversial)	– Potentially worse seizure outcomes than anterior temporal lobectomy in children – More frequent reoperation rate
Lesionectomy	– Lesional TLE	– Excellent seizure outcomes	– Risk of failure if extra-lesional brain involved in epileptogenic zone
Laser interstitial thermal therapy	– Deep-seated epileptogenic lesion (tumor, hippocampal sclerosis, periventricular heterotopia) – Patient or provider prefers minimally invasive option	– Minimally invasive (avoids craniotomy, reduces hospital stay and periprocedural pain) – Better contextual memory outcomes, especially naming and recognition – Resection remains possible after failed LITT	– Slightly worse seizure outcomes than resection – Risks of transient and permanent neurological deficit, and hemorrhage
Multiple hippocampal transections	– Language-dominant mTLE – Also possible in non-dominant mTLE – Preserved preoperative verbal memory – Nonlesional TLE	– May preserve verbal memory (especially if good baseline function) – May be combined with multiple subpial transection or lateral resection when necessary	– Uncertain efficacy and safety – Few studies, especially of pediatric cases

Deep brain stimulation	– Bilateral TLE – Unilateral TLE unamenable to resection or ablation (e.g. previous contralateral procedure, potential for significant memory loss)	– Possible improvement in mood and cognition	– Mostly studied in adults – Palliative procedure – May exacerbate or induce new seizures – Risks of paresthesia, implant site pain or infection, and lead misplacement
Responsive neurostimulation	– Bilateral TLE – Unilateral TLE unamenable to resection or ablation (e.g. previous contralateral procedure, potential for significant memory loss)	– Allows long-term data collection – Prolonged battery life compared to DBS – Closed-loop technology – Possible improvement in mood and cognition	– Mostly studied in adults – Replacement requires intracranial access – Risks of infection, hemorrhage, and lead damage – Not yet magnetic resonance imaging compatible

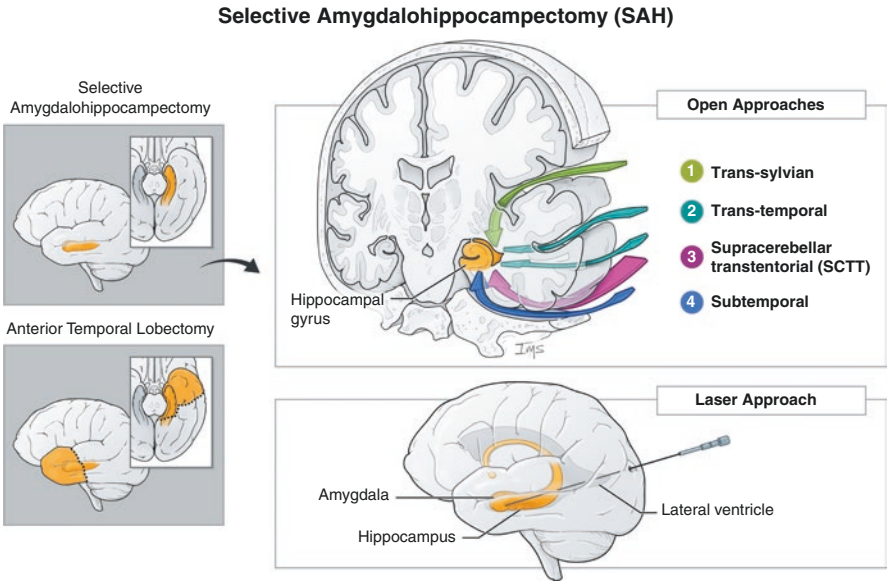

Fig. 38.4 SAH illustration: comparison of ATL and SAH (left); transsylvian, transtemporal, supracerebellar transtentorial, and subtemporal approaches (right top); LITT approach (right bottom)

avoiding the superficial temporal artery and frontal branch of the facial nerve (Fig. 38.5a). The scalp flap and temporalis muscle are then reflected anteriorly (Fig. 38.5b), and a pterional craniotomy is performed (Fig. 38.5c). Adequate exposure is of utmost importance and craniotomy may be tailored to the specific surgical goals. Dural opening exposes the anterior temporal lobe, usually with the middle temporal gyrus forming the center of the field (Fig. 38.5d). Neuronavigation may be used at any time to help in localization (Fig. 38.5e) [57, 103].

Once the temporal lobe is exposed, the lateral temporal neocortex is removed en bloc. En bloc resection is preferable for gross pathological identification and orientation to pathological anatomy. Resection is performed lateral to the collateral sulcus and begins with bipolar coagulation along the inferior broder of the superior temporal gyrus, extending from the temporal pole anteriorly to 3–4.5 cm posteriorly on the left (dominant) side, and 4.5–6 cm posteriorly on the right (nondominant) side, or to the vein of Labbé (Fig. 38.5f–h). This reduces the risk of postoperative language deficit. Importantly, venous anatomy should be preserved. The pia mater and draining veins are coagulated and cut prior to lifting out the specimen to avoid avulsion and bleeding. The superior temporal gyrus, which is more commonly associated with language function, is typically preserved in the dominant temporal lobe [57, 103].

The lateral corticectomy is deepened 3–3.5 cm inferiorly and laterally towards the tentorial edge until the temporal stem is transected and the temporal horn of the

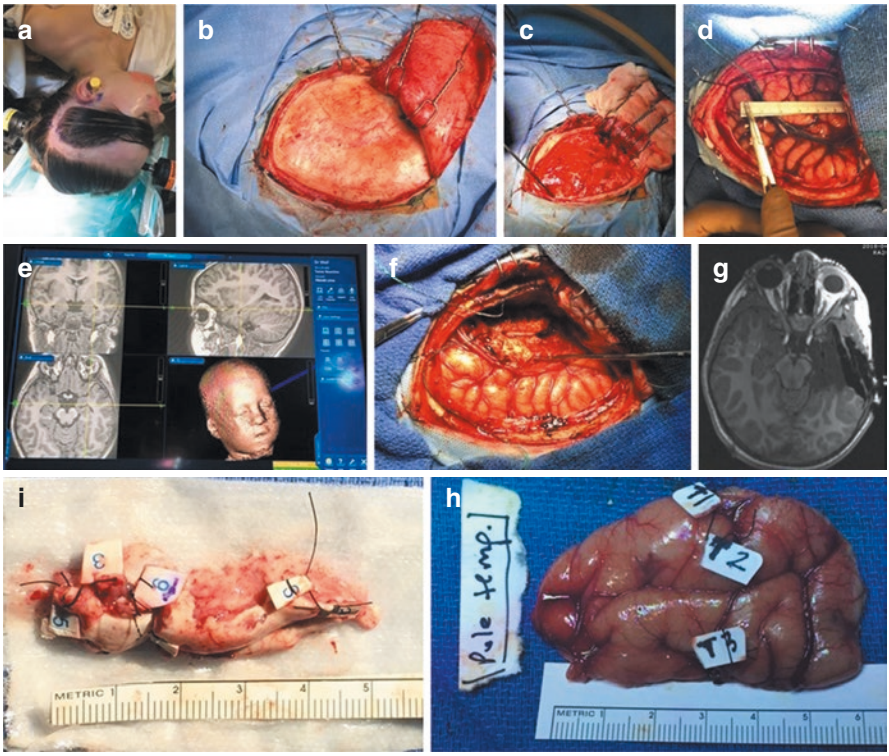

Fig. 38.5 Intraoperative images illustrating steps in an anterior temporal lobectomy in a patient with left medio-lateral TLE and FCD involving the superior temporal gyrus: patient positioning (**a**); incision and skin flap retraction (**b**); frontotemporal craniotomy exposing dura (**c**); dural opening and planning of lateral corticectomy (**d**); intraoperative neuronavigation (**e**); post-lateral temporal corticectomy and parahippocampal gyrus resection (**f**); intraoperative MRI showing resection cavity (**g**); lateral temporal corticectomy specimen (**h**); medial temporal resection specimen (**i**)

lateral ventricle is identified. This direction avoids critical sylvian vessels and the basal ganglionic region, which could be encountered should the dissection be carried superiorly. The temporal horn is opened widely to reveal the choroid plexus, which serves as an important landmark. The amygdala can be identified as a bulky gray matter structure. The choroid plexus is retracted rostrally towards the surgeon (as the view is perpendicular and the head is inverted), and the choroidal fissure is opened by splitting the fimbria, providing access to the mesial temporal structures. The head of the hippocampus is then disconnected from the uncal recess anteriorly and inferiorly, removing part of the amygdala. Posteriorly, the tail of the hippocampus is disconnected from the choroidal fissure toward the tentorium. Anteriorly, dissection is performed superolateral to the amygdala in an arbitrary line separating the amygdala from the basal ganglia. The amygdala and uncus are disconnected until the arachnoid layer covering the carotid cistern is encountered. When the third

cranial nerve and PCA are visualized through the arachnoid membrane, the inferior portion of the apex and the posteromedial surface of the amygdala has been removed. When the MCA is visualized, the superior part of the amygdala has been removed (Fig. 38.5i). The entire disconnection is performed subpially using either microinstruments and controllable suction or an ultrasonic aspirator on low settings. This protects the neighboring critical neurovascular structures [57, 103].

38.10.1.2 Intra-operative Electrocorticography

Intraoperative electrocorticography (ECoG) involves placing electrodes on the temporal neocortex or depth electrodes in the medial structures (amygdala, hippocampus) during resective temporal surgery [104, 105]. Intraoperative ECoG may be used to help define the borders of resection of the EZ in patients undergoing a single-stage 'tailored' ATL or temporal lesionectomy. Because of the nature of the technique, which involves a short 15–30-minute window of recording during resective surgery under general anesthesia, there are several limitations. The main limitation is that unless spontaneous ictal activity is recorded by chance, the iECoG invariably records interictal activity, i.e. the irritative zone instead of the seizure onset zone (SOZ) [106–109]. The recorded irritative zone may in fact be related to spread to non-epileptic surrounding areas or result from surgical manipulation, and its resection may theoretically increase risk without seizure benefit [110, 111]. High-frequency oscillations (HFOs)—a type of recorded cerebral electrographic activity attributed to field potentials formed by abnormal synchronous bursting of pyramidal cells—have been used as a biomarker for epileptic tissue in many centers during iECoG. HFOs, which are commonly observed in the form of ripples (80–250 Hz) and fast ripples (250–500 Hz), are more specific to epileptogenic tissue and more tightly linked to seizures than spikes, and thus more representative of the SOZ. They often overlap with interictal spikes, and are often smaller than the irritative zone, and are particularly useful for identifying EZ in tumor-related and FCD-related DRE [112]. Their removal, particularly of fast ripples which are more likely to be pathogenic, is associated with improved seizure outcome in children [113].

Intraoperative ECoG may be performed prior to the planned resection, to further delineate the irritative zone, or after resection, to measure residual epileptiform activity [107]. It must be noted that the impact of iECoG on outcome is controversial, with conflicting evidence both suggesting improved seizure outcome and other studies showing no benefit in TLE [114, 115]. A RCT trial is underway to compare results of resection between interictal spike-based and HFO-based iECoG tailored resection in DRE [109, 116]. Despite uncertainty regarding its role in pediatric TLE surgery, iECoG has been shown to be useful, particularly in cases of lesional TLE due to FCD, cavernomas, tubers or low-grade neoplasms to help define resection

borders in single-stage surgery [117]. In FCD-related TLE, for example, MRI and other noninvasive tests may not adequately define the extent of the lesion or EZ (particularly in infants and toddlers), and single-stage iECoG-guided resection may help avoid invasive monitoring [104]. For a patient with a lateral temporal tumor, iECoG of mesial structures or of peri-lesional temporal cortex may help map the EZ and guide resection. Cases of HS with dual pathology may also benefit from iECoG to delineate "tailored" lateral cortical resection during ATL. This technique can improve the completeness of lesionectomy, as specimens of post-resection tissue with interictal spiking on iECoG often show lesion (FCD or tumor) [104]. However, it is important to recognize that chasing interictal spikes beyond the preoperatively 'planned' resection may increase risk to eloquent tissue and increase neurological complications, albeit most are transient [104]. By contrast, HFOs (particularly fast ripple) detected on iECoG may "limit" the extent of resection, thereby avoiding unnecessary neurological risks while optimizing seizure outcome [109].

Additional limitations include the impact of anesthesia on recordings, with some agents suppressing epileptic activity (e.g. Propofol) and other agents (e.g. Etomidate) provoking epileptic activity.

Finally, awake resection may be used in older children and adolescents capable of cooperating in whom eloquent language function is believed to be involved or adjacent to an epileptogenic lesion or the EZ. This method can be useful in language-dominant TLE [101, 119]

38.10.2 Open Selective Amygdalohippocampectomy: Indications, Technique, and Approaches

SAH is an alternative surgical approach that preserves lateral temporal neocortex and underlying white matter [100]. Therefore, it is considered when preoperative findings are restricted to the mesial temporal lobe, such as medial temporal sclerosis [101], in the absence of lateral temporal or extratemporal involvement. Four different access routes to the mesial temporal structures may be used.

The transcortical approach (Fig. 38.4) is similar to the previously described technique, but the temporal horn and mesial temporal structures are reached either through the middle temporal gyrus or the inferior temporal gyrus, avoiding most of the functional lateral neocortex of the superior temporal gyrus. With this approach, early disconnection of the amygdala and hippocampus is possible, and the surrounding vasculature, as well as cerebral peduncle are protected. Neuronavigation has increased the safety of this procedure [57, 103]. The disadvantage is approach-related damage to the lateral temporal lobe, resulting in disconnection of basal lateral temporal lobe.

The transsylvian approach (Fig. 38.4) involves opening of the sylvian fissure to enter the temporal horn at the base of the superior temporal gyrus and through the anterior temporal stem. The amygdalohippocampal complex may then be removed en bloc using subpial dissection. While this technique leaves the lateral temporal neocortex untouched, it also exposes the MCA branches and anterior insula. This increases the risks of vascular and retraction injury, which may result in stroke and language deficit [118]. Therefore, extensive surgical experience is necessary to master this procedure [57, 103]. The temporal stem is transgressed with this approach, which may be associated with neurocognitive deficits [120].

The subtemporal approach (Fig. 38.4) also avoids temporal lobe intrusion, while minimizing the risk to the MCA and preserving the temporal stem. Using a smaller craniotomy, the anterior temporal horn is accessed through the collateral sulcus and fusiform gyrus, allowing resection of the uncus and amygdala anteriorly, as well as hippocampus and parahippocampal gyrus posteriorly. This approach requires brain relaxation with hyperventilation, hyperosmolar therapy, and lumbar corticospinal fluid (CSF) drainage to avoid retraction of the neocortex [57, 103].

Finally, the supracerebellar transtentorial (SCTT) approach (Fig. 38.4), in which an SAH or a postero-mesial lesion is resected from below through a sub-occipital craniotomy and trans-tentorial route is as effective as other open approaches with possible a reduced rate of visual field deficit and avoids retraction or transgression of lateral temporal cortex (transtemporal approach), or temporal stem (transsylvian approach) [121–123].

While studies are lacking to compare these different approaches, there is some evidence that the transcortical approach is preferable to the transsylvian approach. The subtemporal approach preserves IQ but may negatively affect verbal memory and language [57, 100, 103].

38.10.2.1 Comparison of Anterior Temporal Lobectomy and Selective Amygdalohippocampectomy

While improved seizure outcomes with ATL over SAH have been suggested in large meta-analyses, a recent systematic review and network meta-analysis of 28 articles by Jain et al. found no difference in seizure-free outcomes between the two procedures, although both were superior to medical management [100, 124]. In the pediatric literature, however, there is more evidence that SAH is associated with significantly worse seizure control rates and more frequent reoperation rates than ATL [9]. The worse seizure outcome with SAH is likely related to the non-resection of pathological lateral temporal neocortical structures, which may more readily be MRI-negative in young children who are also at greater risk of dual pathology, or more extensive resection of mesial structures due to larger exposure [15, 57].

While SAH has been associated with the theoretical advantage of reduced postoperative cognitive decline by sparing lateral temporal structures, this has not

clearly been shown and the benefit of seizure reduction or cure on neurodevelopment and cognitive outcome cannot be understated [9].

38.10.3 Lesionectomy

Medically refractory TLE may be caused by low-grade tumors and vascular lesions within the lateral temporal neocortex or mesial temporal structures [1, 125, 126]. However, in some cases resection of the lesion only is often insufficient as it may be surrounded by normal-appearing epileptogenic tissue such as gliosis or type III focal cortical dysplasia. Hence, intraoperative electrocorticography may a useful adjunct to identify surrounding epileptogenic tissue and guide resection, increasing chances of seizure freedom [57, 125, 127].

In children with refractory lesional mTLE, the transsylvian-trancisternal selective lesionectomy is an appropriate approach. This technique involves microdissection of the sylvian fissure to open the interpeduncular and ambient cisterns. This exposes the mesial temporal structures, allowing resection of mesial temporal lesions [125, 126]. However, tumors of the mesial temporal lobe present further challenges. In amygdalo-uncal tumors, resection must carefully avoid the basal ganglia above, which may be difficult to distinguish from the amygdala. In the uncal region, diffuse infiltrative tumors may breach or obliterate the subpial plane and put the carotid artery, which is anterior to the uncus, and third nerve, which is medial, at risk. Similarly, caution is necessary when resecting tumors of the hippocampus that may be close to the choroid plexus, AChA, PCA, draining veins and the cerebral peduncle. In such cases, the surgeon must keep in mind that the ultimate goal is seizure control with preservation of neurological function. Therefore, a subtotal resection or resection of mesial temporal structures may sometimes be preferrable [57, 125].

38.11 Alternatives to Standard Resective Surgery

38.11.1 Minimally Invasive Ablation: Laser Interstitial Thermal Therapy and Radiofrequency Ablation

Magnetic resonance-guided laser interstitial thermal therapy (LITT) and radiofrequency ablation (RFA) are minimally invasive thermo-ablative procedures that destroy epileptogenic zones by creating heat through a probe (LITT) or electrode (RFA) [128]. Whereas LITT utilises a diode laser, which is transported via optical fibers and generates heat by the absorption of photons in the tissue, RFA establishes a current flow between two electrodes for heat induction [129–131].

Both LITT and RFA are minimally invasive alternative that may be used to perform selective amygdalo-hippocampal ablation as a less invasive treatment option. They can also be used to treat other deep-seated epileptogenic foci within the temporal lobe, such as periventricular temporal heterotopias (Figs. 38.1 and 38.4). For mTLE, LITT involves placement of a fiber optic laser probe using a longitudinal approach across the long axis of the hippocampus and into the amygdala and uncus (Figs. 38.2 and 38.4). This technique, in which ablation is performed with real-time magnetic resonance thermography, results in slightly less favorable seizure outcomes than those reported with temporal lobectomy [132–134].

The slightly lower success rate than open SAH and ATL may be related to incomplete ablation of certain mesial structures, notably the amygdala [63, 64, 128, 134]. It has been shown that a laser probe trajectory that targets more mesial, anterior, and inferior structures of the temporal lobe—including the amygdala, hippocampal head, parahippocampal gyrus, entorhinal cortex, and perirhinal cortex—are associated with higher rates of Engel I outcomes than those with more postero-lateral trajectory that ablate more posterior hippocampus at the expense of these anteromedial structures. Rhinal cortices are known to be highly epileptogenic and intensely interconnected within the limbic network [134].

Immediate benefits of LITT and RFA include avoiding craniotomy, avoiding intensive care admission, reduced hospital stay and periprocedural pain. LITT also significantly reduces the risk of upper quadrantanopia, from 52–100% in standard resective surgery for mTLE to 8–20% [135]. Better contextual verbal memory outcomes, especially better naming and object recognition have been observed with LITT compared to open SAH, whereas noncontextual memory may decline [136–138]. Although considered minimally invasive, LITT and RFA are not without risks. Transient and persistent neurological deficits may occur, most commonly upper quadrantanopia, as well as deficits seen with open SAH, such as affective disorders, cranial nerve palsies, as well as language and memory deficits, particularly for nonlesional dominant-hemisphere mTLE. Postoperative hemorrhage is possible but rarely symptomatic. Overall complication rate is comparable to that of surgery and other stereotactic procedures [133, 134].

38.11.2 Multiple Hippocampal Transections and Multiple Subpial Transection

In patients with language-dominant mTLE and preserved verbal memory, the risk of decline in verbal memory is significant following resective or ablative surgery [102, 127, 139]. An evolving alternative is MHT, a procedure in which the horizontal hippocampal circuits involved in seizure propagation are selectively transected to disrupt seizure activity while preserving vertical fibers involved in memory [102, 139].

This technique has been used in cases involving the dominant and non-dominant hemisphere, as well as lesional and normal imaging [102, 127] with comparable seizure outcome and favorable memory outcome, albeit with limited data [102, 127, 139].

This procedure may preserve verbal memory in patients of all age groups, including children, with good baseline scores while achieving reasonable seizure outcomes [102, 139]. When lateral temporal neocortical involvement is suspected, MHT may be combined with the similar MST technique or lesionectomy, resulting in long-term seizure outcomes comparable to ATL and favorable cognitive outcomes [127].

38.12 Neuromodulation

38.12.1 Vagus Nerve Stimulation (VNS)

Left VNS is a well-established adjunctive treatment often considered in patients with drug-resistant TLE who are not eligible for, or refuse resective surgery, or have persistent debilitating seizures after maximal unilateral temporal lobe resection. Numerous trials have shown that VNS is associated with a 50% reduction in seizure frequency from baseline in 50% of treated patients, although higher seizure control rates have been reported with longer follow-up. The main benefit of VNS over other neuromodulation technologies are its non-invasive nature, as it does not require placement of intracranial electrodes. The most common adverse event is stimulation-induced hoarseness; however, cough, pain, infection, and extremely rare instances of asystole have been reported [140–142].

38.12.2 Deep Brain Stimulation

DBS is a promising treatment modality that has shown efficacy in decreasing seizure frequency in patients with refractory epilepsy who are not good candidates for resective surgery [143, 144]. In TLE, this represents a significant portion of patients including those who present bilateral or nonlesional TLE, as well as potential for significant verbal memory loss after amygdalohippocampectomy [143–145].

DBS involves insertion of depth electrodes that act as an implantable electrical current delivery system producing continuous or predefined intermittent stimulation, termed open-loop stimulation. This stimulation disrupts targeted pathological networks by reducing neuronal activity [32, 146, 147]. In mTLE treatment, DBS has targeted the hippocampus and amygdala, either unilaterally or bilaterally [32]. Except for a study reporting a 15% seizure reduction in four patients treated with

left hippocampal DBS [148], amygdala-hippocampal stimulation in these patients has been shown to produce at least 50% reduction in seizure frequency, with some nonlesional mesial TLE patients becoming seizure free [149–152]. For example, in a prospective, randomized double-blind trial, hippocampal DBS was found to reduce seizures in 88% of patients, with 50% of the treatment group achieving seizure freedom [153].

However, DBS targeting the anterior nucleus of thalamus (ANT) has also proven useful in treating partial and secondarily generalized seizures [143]. A recent randomized controlled trial provided Class IV evidence that ANT DBS led to a 69% 5-year reduction in seizure frequency, as well as significant improvement in quality of life that were sustained at 10-year follow-up [144, 154]. Like other neurostimulation approaches, responder rates increased over time [144, 147]. Further trials including pediatric patients are required to assess efficacy and safety in this population, as well as clarify patient selection criteria [147].

The risks of DBS include a small chance of exacerbating seizures [155, 156], intracranial hemorrhage, implant site pain or infection, as well as paresthesias [143, 144]. Other complications such as incorrect lead placement or lead migration may be more frequent in pediatric populations due to growth of the head and body [32, 147]. However, the increasing use of near-infrared spectroscopy and intraoperative MRI will likely increase accuracy of lead placement and reduce complications [157, 158].

38.12.3 Responsive Neurostimulation

RNS was approved in adults for treatment of focal epilepsy in 2013 and has since been used off-label in children at certain epilepsy centers [15, 32, 147, 159]. It represents an interesting option for treatment and/or long-term data collection in patients with either bilateral mesial TLE or unilateral TLE unamenable to resection or ablation, such as those who have had a previous contralateral procedure, allowing for an eventual resection in a small number of patients [15, 160, 161].

RNS involves placement of a neurostimulator in the skull under the scalp, connected to intracranial implants and electrodes via a small craniectomy (Fig. 38.6). This implantable system terminates seizures by recognizing unique preictal ECoG patterns and responding with a high-frequency stimulation impulse to the EZ. This is termed closed-loop stimulation [32, 147, 162, 159]. Additionally, RNS may work by altering the plasticity of targeted neural networks [147, 163]. There is robust data showing that RNS is effective at improving seizure control in patients with unilateral or bilateral mTLE and TLE with neocortical or eloquent cortex seizure [162, 164–169]. Meaningful improvement in quality of life has also been reported in nearly half of patients undergoing RNS [165, 168, 170]. While data supporting its

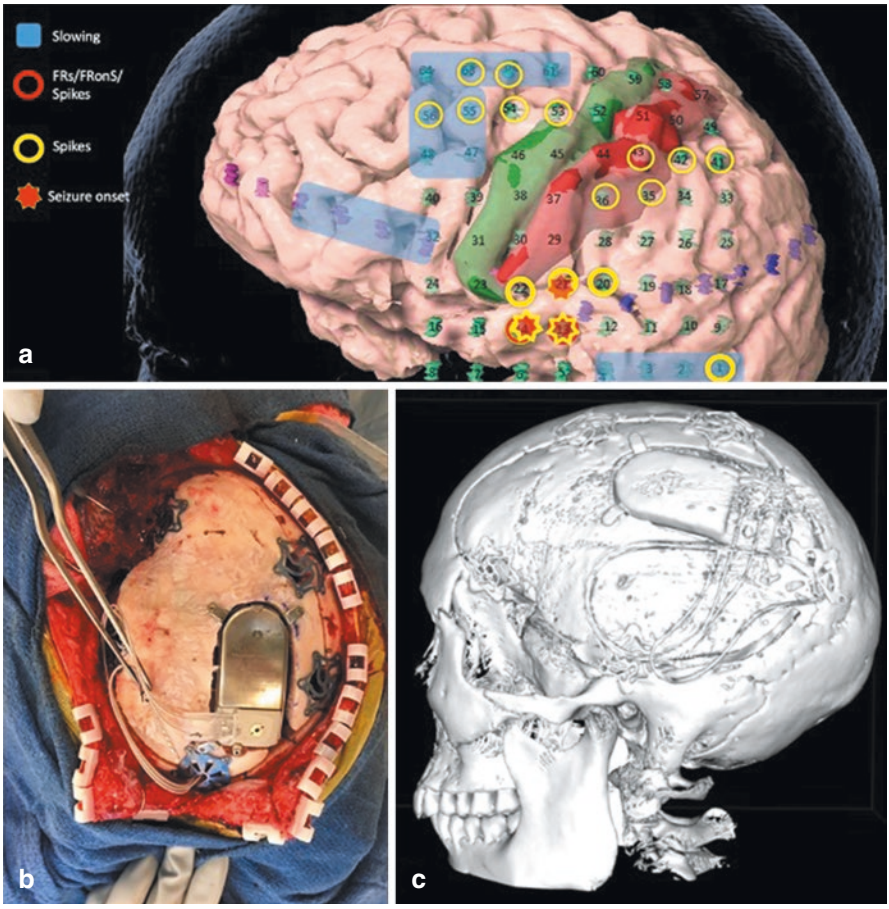

Fig. 38.6 RNS for treatment of TLE: mapping (**a**); intraoperative image (**b**); 3-D reconstruction (**c**)

use in children is more limited, a recent report demonstrated its efficacy: a 16-year-old girl with left temporal neocortical EZ and daily seizures treated with RNS showed only weekly auras at 6-month follow-up [171]. RNS may also result in improvements in mood and cognition [170, 172].

The main drawbacks of RNS, beyond inherent surgical risks of infection, hemorrhage, and lead damage [162, 164, 169], are that—contrary to DBS and vagus nerve stimulation (VNS)—system replacement requires access to the skull [32]. Because the stimulator is in the skull, RNS is usually not placed in children under the age of 3 years. Of note, the present RNS system is not MRI compatible [147, 173].

38.13 Conclusions

Surgery for pediatric drug-resistant TLE is a highly rewarding intervention as it significantly improves seizure control and quality of life in well-selected candidates compared to continued medical therapy. Potential surgical candidates should be referred to a comprehensive pediatric epilepsy center early for surgical evaluation. A high index of suspicion is warranted in children with TLE as good surgical candidates may present with misleading 'non-localized' or non-lateralized' clinico-electrographic presentation. Patients with nonlesional TLE or lesional TLE in whom the EZ is inadequately mapped noninvasively (e.g. discordant noninvasive data) or involves eloquent language pathways may benefit from invasive monitoring to delineate the EZ, map resection borders and eloquent cortex. There are many surgical options and surgical approaches that should be tailored to each patient's needs. Surgical resection or ablation of the epileptogenic focus is prioritized when it can be done with no or acceptable morbidity. Tumor-related TLE can usually undergo lesionectomy with or without intraoperative ECoG, leading to excellent seizure outcome. Lesional TLE due to malformations of cortical development are more challenging, but usually undergo lesionectomy or ATL, which may be tailored using intraoperative ECoG. SAH can be carried out in classic mTLE cases, usually seen in older adolescents, and LITT should be considered as a minimally invasive alternative to open SAH when it is available. However, overall success rate is lower in pediatric patients undergoing SAH than adults due to high rate of dual pathology affecting both mesial temporal structures and lateral temporal neocortex. Patients with bitemporal epilepsy or temporal lobe epilepsy involving eloquent structures in whom permanent language or memory deficits (e.g., older patients) are expected may be candidates for neuromodulation, such as DBS or RNS.

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Chapter 39
Extratemporal Lobe Epilepsy

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39.1 Introduction

Extratemporal epilepsy can be managed well with surgical treatment; but proper patient selection, evaluation, and discussion of expected outcomes and risks are critical in this challenging situation. Despite optimized medical treatment, approximately one third of all pediatric patients with epilepsy continue to have seizures, meaning they have medically resistant epilepsy [1, 2]. The most effective treatment for intractable extratemporal epilepsy is a focal cortical resection with excision of the epileptogenic zone (the area of ictal onset and initial seizure propagation). Surgery for extratemporal epilepsy represents a challenge requiring a rigorous preoperative workup often culminating in a technically demanding operative procedure. It is the most common type of epilepsy surgery performed in children. Although anteromesial temporal lobectomy for temporal lobe epilepsy is known to carry a reasonably low morbidity, the resections necessary for extratemporal seizure foci typically involve larger areas of cortex, which often may either encompass or abut functionally significant regions of the brain.

The surgical plan, which should ideally be devised by a multidisciplinary team in the setting of a comprehensive epilepsy center, is based on a multitude of factors and includes a consideration of pathological substrate, neuroimaging data, electroencephalography (EEG)/neurophysiological information, functional mapping data, and the specific risk–benefit profile of the individual patient. Published rates of seizure freedom after surgery for extratemporal epilepsy vary between 30 and 80%, compared with more than 80% for temporal lobe epilepsy [3].

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However, the treatment goals are the same: the reduction or elimination of seizures with minimal morbidity, as well as the preservation or improvement of neurocognitive function. Several published studies have demonstrated both the safety and efficacy of extratemporal epilepsy surgery in children [1].

39.2 Considerations in Pediatric Extratemporal Epilepsy Surgery

There is a growing body of literature on extratemporal epilepsy surgery in children. This patient population warrants special consideration for several reasons. First, the pathological substrate differs in the adult and pediatric populations. The most common cause for intractable partial epilepsy in adults is hippocampal sclerosis, classically treated by anterior temporal lobectomy with amygdalohippocampectomy. In children, however, the predominance of extratemporal origin epilepsy is related to developmental brain abnormalities (cortical dysplasia, tuberous sclerosis complex, Sturge-Weber syndrome) and low-grade cortical tumors (gangliogliomas, DNETs, oligodendrogliomas, astrocytomas) [2, 3] (Table 39.1).

Second, the treating physician must take into account the developmental implications of intervention in an affected child with a still developing nervous system. Although the developing brain is very sensitive to the detrimental effects of recurrent seizures, with potentially permanent neuropsychological and cognitive sequelae, the plasticity of that developing brain also lends itself to better functional recovery after cortical resections that may involve eloquent areas [5, 6].

Nevertheless, it is now increasingly appreciated that uncontrolled epilepsy in childhood can have a detrimental effect on a child's intelligence and cognitive abilities and, moreover, that epilepsy surgery performed in childhood may play a critical role in enhancing development and overall quality of life. Finally, because medically refractory partial seizures are unlikely to remit when an adequate response is

Table 39.1 The most common underlying pathologies in children undergoing surgery for extratemporal lobe epilepsy [4]

Pathology	%
Cortical dysplasia	42
Tumor	20
Atrophy/stroke	10
Gliosis/normal pathology	6
Tuberous sclerosis complex	5
Hypothalamic hamartoma	3.6
Sturge Weber syndrome	2.9
Rasmussen syndrome	2.7
Vascular (AVM, cavernoma)	1.5

not achieved with the first two major antiepileptic medications, early surgery is now often advocated for children at many centers [7].

39.3 Pre-surgical Evaluation of Extratemporal Epilepsy

The most important part of a pre-surgical evaluation is to identify the epileptogenic zone or the area of abnormal cerebral tissue that is responsible for the seizures and to determine its relation with the eloquent cortex. Before now, this identification was only based on the ictal and interictal EEGs. High-definition MRI has been an important advance, especially 3 and 7 T MRI that have made it possible to identify very small lesions during this pre-surgical evaluation. Identifying the pathological substrate, seizure frequency and the prognosis for psychomotor development are primordial in the work-up evaluation. The family history and the family members' description of the seizures help to identify the type of seizure while frequency must be documented through careful neurological examination. Often the neurological examination is what allows us to locate the focus of the seizures [8].

Because of the pathological complexity of extratemporal epilepsy, patients who are being considered for surgery are best evaluated in a comprehensive epilepsy center by a multidisciplinary team of epilepsy neurologists, epilepsy surgeons, neuropsychologists, neuroradiologists, psychiatrists, and social workers. Typically, the preoperative evaluation consists of a comprehensive battery of tests designed to localize the epileptogenic zone. A thorough understanding of the potential strengths and limitations of each of these aspects is critical for appropriate patient selection and satisfactory surgical outcomes.

Routine structural imaging with magnetic resonance imaging (MRI) together with scalp video-EEG (VEEG) and the neuro-psychological evaluation constitute the most basic requirements of any preoperative epilepsy evaluation. However, other noninvasive techniques are now also commonly used to locate the ictal onset zone and functionally map eloquent cortex. These include positron emission tomography (PET), single photon emission computed tomography (SPECT), and magnetoencephalography (MEG).

39.3.1 History and Examination

The initial evaluation of extratemporal epilepsy should include a comprehensive neurologic history and examination. The existence of an acquired or genetic etiology for the partial epilepsy should be determined. The presence of a symptomatic neurologic disorder may suggest the lateralization and localization of the epileptogenic zone and the potential treatment options for the partial seizure disorder. The ictal semiology, or intra-seizure symptoms, including the presence of an aura or

postictal deficit, seizure type(s), seizure frequency, and disabling effect of the seizure disorder, should be analyzed.

39.3.2 Video EEG (VEEG)

Video-EEG is essential for documenting seizure manifestations. Ictal patterns are more often regional than localized in childhood epilepsies, and children display a wide variety of artifacts that can confound EEG interpretation. There is a close relationship between ictal and interictal electrographic findings, but less than half of all interictal spikes are detected at the scalp. A recording or registry of one or more seizures is very important in confirming the epilepsy diagnosis in a child as well as to help lateralize and localize the epileptogenic area. The most important factor of the Video-EEG is identifying the irritative zone and the interictal spikes, as well as the ictal area or area that is triggering the seizures. Generally, several seizures are registered and their symptoms are analyzed together with the ictal EEG registry. The ideal is to be able to locate both the interictal zone and the ictal zone during the Video-EEG. However, this ideal is very difficult to achieve in children with refractory epilepsy, even in tumoral pathologies, since their interictal activity can be quite widespread or it may not be possible to lateralize the seizure onset. These are the most significant differences in epilepsy between adults and children.

In extratemporal epilepsy, detecting epileptiform activity from deeper brain regions, which include a large portion of the extratemporal cortex, has its limitations. Scalp EEG may not show any interictal abnormality in these cases. What is more, early ictal changes may not be detectable until seizure activity has spread to the brain convexity [9]. The most difficult areas for scalp EEG detection of interictal and ictal discharges include the mesial frontal cortex, the orbitofrontal cortex (which can be semiologically indistinguishable from temporal lobe seizures), and also small foci in the primary motor or sensory cortex, which can produce clinical seizures but remain undetected by scalp EEG because of the relatively restricted area of cortex involved. Ictal EEG changes may also be obscured by muscle artefacts that, not infrequently, occur simultaneously to EEG seizure onset in extratemporal lobe epilepsy [10].

39.3.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is the gold standard for detecting and defining structural pathology in epilepsy. This is very important, since lesional epilepsy has a much better outcome from surgery than cases without lesions. In foreign tissue lesions such as tumors, vascular MRI is the cornerstone of any search for structural neuropathology and obtaining a high-resolution epilepsy protocol MRI is crucial in all surgical candidates. Focal cortical dysplasia can be very difficult to detect on

routine 1.5 T MRI. High-resolution 3 T MRIs read by experienced neuroradiologists may reveal a subsequently pathologically confirmed abnormality. Functional MRI (fMRI) is becoming more available in major epilepsy centers and can be helpful in the non-invasive mapping of eloquent cortex [11]. Cortical dysplasias may be MRI-invisible or may be visible as subtle differences in thickness in gray–white matter relationships, blurring of normal gray–white matter borders, or, more obvious and distinct, focal anomalies (Fig. 39.1). Typically, MRI sequences are loaded into intraoperative navigation platforms (e.g., Medtronic or Brain-Lab navigation systems) to help guide the surgery.

MRI sensitivity in detecting abnormalities depends on the techniques used, the pathological substrate/pathology, and the experience of the interpreting physician. The MR images should be assessed by epilepsy imaging experts who are already familiar with the patient's clinical and electroencephalography (EEG) findings. An optimal MRI technique for assessing the pathological substrate should include a variety of imaging sequences, including T1-weighted imaging (WI), T2WI, proton density, and fluid attenuation inversion recovery (FLAIR) sequences. These need to be acquired in at least two orthogonal planes covering the whole brain, using the minimum slice thickness. A three-dimensional T1 volume sequence with a slice thickness of 1.5 mm or less should be included because this sequence provides excellent gray/white matter contrast and can be reformatted into any orthogonal or nonorthogonal plane. The three-dimensional volume T1WI can also be subjected to additional postprocessing without the penalty of additional imaging time [12].

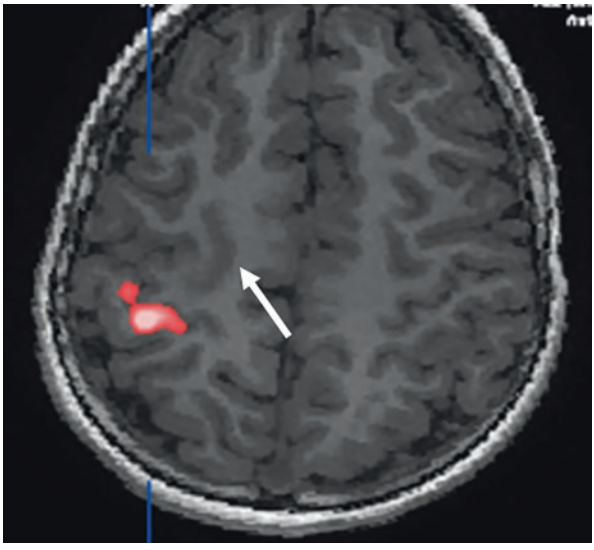

Fig. 39.1 3 T functional MRI showing blurring of normal gray–white matter borders (white arrow) indicative of a focal cortical dysplasia in the superior frontal sulcus close to the primary motor area of the hand (red zone)

Gadolinium does not improve the sensitivity of MRI for patients with epilepsy and should only be used to characterize selected intracerebral lesions, such as tumors. A systematic approach should be used to evaluate MRIs to optimize detection of subtle lesions and dual pathologies. While fMRI usually locates the primary motor cortex reliably, its dependablity in lateralization and localization of language areas depends on the subject's cooperation and the experience of the technician.

39.3.4 FDG-PET (Positron Emission Tomography)

Functional neuroimaging uses either metabolic or blood flow measurements to identify dysfunctional cortex, presenting the data in an anatomical view. The main utility of PET is to identify hypometabolism in patients who show no visible structural lesion on MRI. PET scanning is usually performed as an interictal test and looks for a baseline reduction in glucose metabolism using 2-[18F]Fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET). The sensitivity and specificity of PET varies according to the brain region producing the epilepsy. In temporal lobe epilepsy, there can be a close correlation between the areas of PET abnormality, the epileptogenic zone and surgical outcome. In extratemporal epilepsy, this technique provides contributory information less frequently. In clinical practice, co-registering PET information with the patient's MRI scan can help identify areas of abnormality previously missed when either investigation technique is used alone. Subtle gyral abnormalities produced by malformations of cortical development can become more evident [13].

FDG-PET scans are performed in the interictal period and can reveal hypometabolism in the epileptogenic lesion in many patients with a nonlesional MRI [14]. The pathophysiological mechanisms that result in this hypometabolism are not well understood. The extent of the hypometabolism on FDG-PET is usually larger than the actual underlying epileptogenic lesion (if present) or the epileptogenic zone identified on intracranial EEG. Therefore the decision regarding the extent of neocortical resection should be made not on the basis of FDG-PET alone, but in conjunction with information from MRI, EEG (including intracranial EEG if warranted), and other imaging modalities. Both the presence of an MRI lesion and the presence of hypometabolism have been shown to be independently predictive of a good surgical outcome with respect to seizures. A meta-analysis of 46 studies performed by Willman et al. showed that an ipsilateral PET hypometabolism had an 86% predictive value for good surgical outcome (defined as Engel class I or II) [15].

In children with tuberous sclerosis complex suffering from chronic refractory epilepsy, FDG-PET may complement MRI in helping to differentiate the epileptogenic tubers from clinically silent tubers. In addition, α-[11C]-methyl-L-tryptophan (AMT), a radiotracer that depicts the tryptophan metabolism, has shown promising results in preliminary clinical studies aimed at distinguishing between epileptogenic and electrically silent lesions in children with multiple tubers [16].

39.3.5 SPECT (Single-Positron Emission Computed Tomography)

In contrast to PET, this investigation is carried out in the ictal stage and so provides information on the ictal onset zone although, in common with PET, its greatest utility is in lesion-negative patients with focal epilepsy. Technetium 99-m is the radiotracer used to identify areas of increased cerebral blood flow or hyperperfusion. Testing has to be performed under ideal conditions. The tracer is injected within seconds of seizure onset. Injection and focal tracer uptake within 10 s of the start of the seizure is much more likely to identify the area of seizure onset than an injection 60 s later when spread of the seizure discharge makes the information much less meaningful. The seizure also has to be long enough because a very brief partial seizure of less than 10 s is unlikely to provide substantial information. SPECT coregistered to MRI imaging (SISCOM) improves the sensitivity of an ictal SPECT in locating the ictal onset zone and provides anatomical information on the location of the seizure focus. SISCOM may be especially useful in providing preoperative guidance for intracranial electrode placement in children with frontal lobe epilepsy because rapid seizure spread often results in erroneous clinical and electrophysiological interpretation of the focus site [17, 18].

Neither PET nor SPECT information alone can justify surgery in a particular brain area in lesion-negative epilepsy. It is better to contrast information from these analyses together with clinical and EEG information before determining the need for surgery. Also the technical and interpretational limitations of the SISCOM method need to be remembered since they can result in a false localization of the epileptogenic zone and misidentify areas of seizure propagation as seizure onset zones [19].

39.3.6 MEG (Magnetoencephalography)

Magnetoencephalography (MEG) has been reported to be a valuable noninvasive technique that can be used to locate both epileptogenic and eloquent cortices in children with extratemporal epilepsy who are being evaluated for surgical treatment. This technique measures the magnetic fields associated with the intracellular current flows within neurons. Source localization of epileptic spikes and evoked responses as determined by MEG are co-registered with magnetic resonance imaging (MRI) as magnetic source imaging (MSI). MEG is based on the physical phenomena generated by the electrical currents that accompany magnetic fields during the inter-ictal period. The orientation of the magnetic field relative to the electrical current is described as Orsted's "right-hand rule," which states that when the right thumb is pointing away from the hand, it will point in the direction of the electrical current, the surrounding magnetic flux will be aligned in the direction of the other

four right fingers. MEG uses highly sensitive biomagnetometers to detect extracranial magnetic fields produced by intracellular neuronal currents [20].

Although invasive study with subdural and or depth electrodes is felt to be superior in locating extratemporal ictal onset zones in children, other studies have shown the promise of MEG as a technique for locating the epileptogenic zone. The diagnosis of extratemporal lobe epilepsy may be hampered by poor electroclinical localization on scalp EEG caused by bilateral deep, distributed, or rapidly propagating epileptiform activities over the hemispheres. MEG locates epileptogenic zones better than an EEG because it has better spatial and temporal resolution than the latter [21, 22].

39.3.7 Neuropsychological Evaluation

The neuropsychological assessment of a child can take on different forms, depending on the theoretical approach taken by the neuropsychologist and the specific goals of the evaluation. Most neuropsychological evaluations involve gathering information from several domains of function including general cognitive ability, language, visual perception, motor, sensory, memory, attention, and executive functions (executive functions typically include regulation of behavior as well as planning, organization, and integrative problem-solving skills) as well as assessment of emotional, social, and adaptive function.

The neuropsychological examination may identify functional deficit areas that can pinpoint "where the lesion is" and whether there is any focal and/or multifocal dysfunction. The different focal epilepsies have specific neuropsychological profiles: frontal, temporal, parietal or occipital. The neuropsychological evaluation also identifies the patient's intellectual strengths and weaknesses so that an educational plan can be developed to optimize their education and help compensate for deficits; it may also predict the risk of postoperative deficits, which is especially important in determining the risk–benefit ratio for the surgery [23].

Neuropsychological testing done during the Wada test helps to determine cerebral dominance for language, memory, and visuospatial functions. Language or verbal memory deficits are suggestive of a dominant hemisphere dysfunction, visuospatial memory deficits suggest nondominant temporal dysfunction, and deficits in both suggest bi-temporal involvement [24].

39.4 Invasive EEG Studies

Nonlesional cases and patients in whom the epileptogenic zone is in close proximity to, or even overlaps, eloquent cortex, almost invariably require chronic invasive EEG recordings and detailed brain mapping by direct electrical stimulation. In general, EEG plays a critical role in locating the seizure onset and irritative zones. However, in extratemporal epilepsys, scalp EEG may not show any interictal

abnormality. What is more, early ictal changes may not be detectable until seizure activity has spread to the brain convexity [25]. One must remember that scalp EEG is poor at detecting epileptiform activity in the deeper brain regions that include a large portion of extratemporal cortex. There are no universal criteria for invasive EEG monitoring in pediatric patients. Invasive monitoring is often indicated for nonlesional cases and possible indications for invasive EEG recording include the following [26]:

1. The MRI does not show a cortical lesion in a location that is concordant with the electroclinical/functional hypothesis generated by the VEEG recordings (so-called MRI-negative cases).
2. The anatomical location of the MRI-identified lesion (and at times the location of a clearly hypometabolic focal area on PET) does not agree with the electro-clinical data. This can occur in cases with deeply seated brain lesions such as deep sulcal lesions.
3. There are two more anatomical lesions of which at least one does not agree with the electroclinical data, or both lesions are located within the same functional network, and it is unclear if one, or both, of them actually is/are epileptic.
4. The anatomo-electro-clinically identified location (MRI-negative or MRI-identificable lesion) involves potentially highly eloquent cortex.

39.4.1 Subdural or Depth Electrodes

There are two types of invasive electrodes: subdural and depth electrodes using stereoencephalography (SEEG). Subdural grid electrodes are most suitable for identifying "eloquent cortex" and differentiating these zones from the epileptic focus. Since grids require rather large craniotomies, only unilateral exploration is performed (Fig. 39.2). Subdural strips are often used when less crucial areas are investigated (together with grids or depth electrodes), and can be inserted bilaterally.

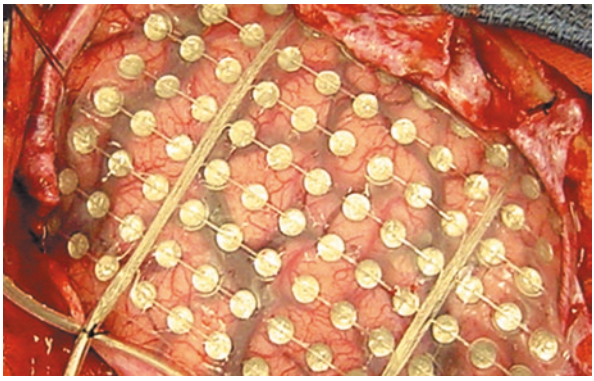

Fig. 39.2 Subdural electrodes

Depth electrodes contain up to 20 evenly spaced contacts. The EEG signal quality is usually better than that obtained with subdural electrodes and they obrain excellent recordings from deep structures, something which is more difficult with subdural contacts. They can be inserted bilaterally and into several lobes, either perpendicularly or laterally to the skull and do not require craniotomy (Fig. 39.3). Depth electrodes are easier to remove than subdural electrodes. The procedure may be performed at bedside without local or general anesthesia. However they can only provide a limited coverage of the lateral cortical surface, which makes cortical mapping difficult. Invasive EEG recording poses risks, like any invasive procedure. The overall reported complication rate of subdural electrodes (with grids) is up to 14% with permanent sequelae in about 2% of patients [26–28].

There has recently been a great increase in depth electrode use becuse the technique appears to offer excellent localization results and be significantly better tolerated and less invasive for patients. SEEG utilizes a strategy of depth electrodes that are placed either with conventional stereotactic techniques or with a surgical robot. Inherent to the concept of SEEG is the use of the depth electrode array to support or negate a carefully constructed hypothesis of the epileptogenic cortex network that is derived from a deliberate, exhaustive study of the preoperative work-up. Depth electrodes are limited in their field of reach to 2–3 mm, which means that SEEG strategies lack the "survey capacity" that arises when large grids and strips are placed over wide regions of cortex. However, they enable sampling from deep cortical regions that are difficult or impossible to sample with traditional grid-based strategies. Examples of such regions include the insula and cingulum, mesial structures that are being increasingly recognized and acknowledged as potentially important

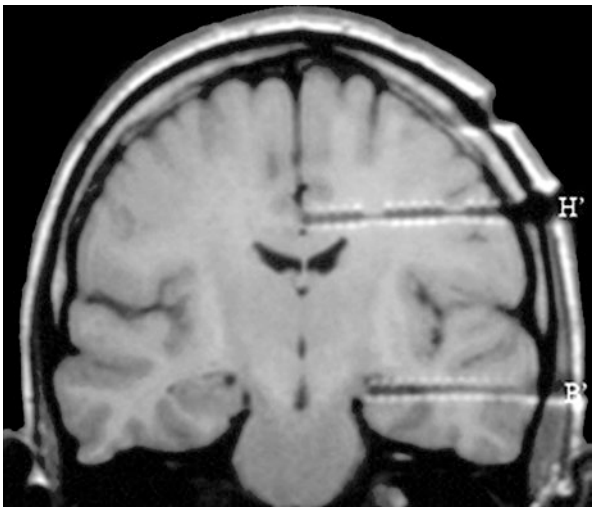

Fig. 39.3 Depth electrodes

inherently epileptogenic regions. Furthermore, SEEG allows bilateral sampling and sampling from noncontiguous cortical lobes. Many current discussions and some controversy surrounds the challenge of defining the appropriate role for grid-based investigation and SEEG to support contemporary approaches to refractory epilepsy. It is likely that each modality will have unique attributes, but the precise roles and indications for each approach have not yet been defined [27, 29].

The resection following a depth electrode investigation takes place at a later time and in a separate operative setting than their implantation. Depth electrode removal occurs after a suitable period of monitoring (usually 5–7 days) and is performed under a brief general anesthetic. In some centers, laser interstitial thermal therapy (LITT) is used at the time of anchor bolt removal to eliminate the newly identified epileptogenic cortex [30].

39.4.2 Functional Mapping

Precisely identifying the eloquent cortex essential to sensorimotor, language, and memory function, as well as defining the anatomical relationship between ictal foci and functional centers, is critical for surgical risk assessment and decision making in extratemporal epilepsy. Noninvasive imaging techniques, including functional MRI and DTI tractography provide accurate maps of the primary sensorimotor, language and visual cortex in children (Fig. 39.1).

Functional mapping may also be performed intraoperatively via direct cortical stimulation or extra-operatively via implanted subdural electrodes. Wada testing (intracarotid amobarbital test) is useful for establishing the laterality of language and memory function in cooperative children. Cortical mapping is performed with the application of very small currents through intracranial electrodes on the brain surface or within the brain to stimulate discrete cortical areas. This can be done either intraoperatively as an ‘awake’ operation or during the monitoring period in the epilepsy monitoring unit after electrode insertion. Stimulation protocols vary according to centers, the invasive electrode used, and the brain region/s being studied. Stereo-EEG stimulation of primary motor cortex usually involves 1 Hz stimulation, using a 1 ms pulse width and 1–3 mA current for 40 s. Extraoperative subdural EEG stimulation of the language areas is performed with a 50 Hz, 0.2 ms pulse width, 1–20 mA stimuli for 5 s. Stimulation of the primary cortex will produce twitching of the appropriate contralateral area whereas stimulation of the language areas will produce temporary aphasia. Information derived from stimulation is mapped to depict cortical functions in different brain regions. Where these ‘eloquent’ regions lie in relation to the ictal onset zone as revealed by intracranial electrodes will determine whether surgery is possible without substantial risk of major deficits or how the surgeon can tailor the extent and area of resection in the light of posible risks [31, 32].

The surgical resection is always planned according to the available information. Usually it is necessary to resect the cortex below the ictal onset electrodes in order to achieve seizure freedom unless doing so is likely to produce unacceptable deficits. The epileptic lesion zone, if well identified by imaging, is also resected as much as possible. Whether the irritative zones and the areas to which the electrical seizure spreads should also be resected has not been systematically studied and practice varies according to center.

39.5 Surgery

The goals of extratemporal epilepsy surgery in children are somewhat different from those in adults. In addition to controlling seizures, the goals of pediatric epilepsy surgery are to prevent the possible harmful consequences of uncontrolled seizures; to prevent continued interictal activity resulting in permanent cognitive, behavioral, and psychosocial problems; to prevent secondary epileptogenesis; and to avoid the adverse effects of antiepileptic drugs. However, despite the general acceptance of and expectations regarding the benefits of seizure control on the child's cognitive, behavioral, and psychological development, it is important to keep in mind that definitive data on this matter are still pending. Therefore, the primary goal of pediatric epilepsy surgery remains limited to the attainment of seizure freedom until further data are gathered to support the beneficial effects of surgery on the other domains of a child's life [33].

An extratemporal localization of the epilepticogenic focus in functional cortex (sensory, motor, or language) can constitute a possible contraindication for surgery because its removal may result in a permanent neurologic deficit. Other significant medical problems may also preclude the comprehensive presurgical evaluation and operative procedure. Age and developmental delay or psychiatric disease are not contraindications.

The major factors that potentially complicate surgical intervention of extratemporal epilepsy include seizure multifocality, the presence of nonlesional MRI-negative epilepsy, and the proximity of the epileptogenic zone to eloquent cortex. As a result, surgical strategies should consider a wide array of therapeutic options that must be tailored to the individual patient's risk–benefit profile.

When the comprehensive preoperative evaluation does not reveal an apparent localized seizure focus that can be approached surgically, the treating team of specialists is left with a dilemma regarding how to proceed. The options include either no surgery or the use of a palliative procedure, such as vagal nerve stimulation or corpus callosotomy, in the appropriate clinical setting. At our institution, selected patients who are suspected of having partial seizures but show no localizing data, have been offered bilateral depth electrode survey studies to lateralize and locate their seizures. The surgical process has two steps. First, depth electrodes are

implanted to locate the epileptogenic zone and, after two months, the focus is resected. This technique has been useful in both lesional and nonlesional cases and has led to successful resections in several patients once the ictal onset zone is located. For example, in our tuberous sclerosis complex cases, we have performed this technique successfully in patients with bilateral tubers; classically they were not considered epilepsy surgery candidates because their preoperative evaluations could not identify the exact epilepsy focus. If the bilateral depth eletrode study reveals a unilateral focus, this is then approached at a later date, with a classic two-stage procedure consisting of initial depth electrode placement followed by resection of the ictal focus in the second surgery.

39.5.1 Lesionectomy

Lesionectomy is the most common type of surgical resection in extratemporal epilepsy. In most cases, complete resection of the visible MRI lesion is necessary to achieve seizure freedom. However, in most patients, the area surrounding the lesion must also be resected for a successful outcome. The extent of perilesional resection is determined by the pathology of the lesion and also by the results of invasive ictal and interictal EEG recordings. Lesions that can produce epilepsy include areas of cortical dysplasia, tumors (low grade gliomas, dysembryoplastic neuroepithelial tumors), areas of old stroke or traumatic injury, and vascular malformations (cavernous malformations). In the majority of these lesions, excellent results can be achieved by complete removal of the lesion and some of the adjacent cortex. This peri-lesional resection can be directed by intraoperative electrocorticography. These specific techniques vary depending on the locations and types of lesion being removed. Cortical dysplasia is an exception to this rule. It is well recognized that resective surgery for cortical dysplasia has a lower success rate than surgery for other lesions like tumors. This is probably due to difficulties in defining the boundaries of the structural abnormality and the relatively frequent involvement of cortical dysplasia in eloquent areas that cannot be resected, so mapping the adjacent eloquent cortex will determine the extent of the cortical resection.

Modern neurosurgical operating rooms benefit from neuronavigation systems that can aid surgery with more precise resections. Neuronavigation has been found to be an extremely useful tool in epilepsy surgery. Based on preoperative MRI images, the neuronavigator provides the surgeon with precise strategic information helping to locate functional areas and their relationship with the area to be resected. Imaging of the three-dimensional reconstruction MRI (acquired with thin 1 mm slices) fused with functional imaging (mainly PET and SPECT) provide the surgeon with a three dimensional map of the brain to allow precise seizure focus resection in extratemporal epilepsy cases.

39.5.2 Multilobe Resections

Multilobe resections are also possible. For example, this can be done in patients with Sturge–Weber syndrome, or with cortical dysplasia, with the dysplasia removed as an addendum to one lobe resection. As expected, functional complications of multilobar resection are often related to the location of the resected area. In particular, removal of a cortical dysplasia in the motor, sensorial, language and/or visual areas is more likely to result in a permanent neurological deficit.

39.5.3 Hemispherectomy

The term 'hemispherectomy' is used here to cover a variety of operations in which one cerebral hemisphere is excised or disconnected from the other. These operations are carried out in children or adolescents with medically refractory seizures resulting from severe unilateral hemisphere damage. Nowadays these operations are only carried out to improve epilepsy control in a small group of conditions like Rasmussen's syndrome, hemimegalencephaly, Sturge–Weber syndrome, or post-stroke porencephaly with seizures that have become intractable to medication [34].

The entire hemisphere is removed in the classic procedure, but there are modifications including a functional hemispherectomy, perinsular hemispherotomy and vertical hemispherotomy in which the hemisphere is left in place but disconnected from the opposite hemisphere by sectioning pathways such as the corpus callosum or the corticospinal tract. The great majority of suitable candidates for hemispherectomy have a pre-operative hemiparesis, reflecting the severity of the hemispheric damage. This can be associated with other signs, such as hemianopia or hemisensory loss, and most patients have some degree of mental and psychomotor retardation.

Hemiparesis is not a contraindication for hemispherectomy. The pre-operative ability to perform gross finger movements, or of other major joints (e.g. shoulder, elbow, hip, knee) is not a contraindication to surgery. These movements are not usually worse after a hemispherectomy, nor is a pre-existing spastic gait, although there may be a transient worsening for weeks after the operation. Hemianopia is usually but not always complete in the cases being considered. Its absence should not be considered an absolute contra-indication to hemispherectomy.

If this operation is performed on the language dominant hemisphere, permanent aphasia may result unless language functions can be transferred to the other side of the brain by processes of cortical development. These processes are age-dependent. It is possible to carry out dominant hemispherectomy before the age of 5 years old without any impairment of language functions. Recovery of language after dominant hemispherectomy in children with later onset seizures (after the age of 5 years)

is, however, rarely complete although some transfer of language functions is possible up to the early teens [35, 36].

39.5.4 Corpus Callosotomy

Corpus callosotomy has been particularly helpful for controling atonic, "falling," seizures as well as for tonic seizures, and for generalized tonic–clonic seizures. While "falling" seizures may benefit, other seizure types may persist, so generally this should be thought of as a palliative rather than curative procedure. Focal seizures can become more severe after section, and in experimental models, kindling can occur more rapidly. It may be that this occurs because seizures were originating in one hemisphere and the homologous region in the opposite hemisphere was helping to control, limit, or stop the actual seizure progression [37, 38].

After callosal sectioning an acute disconnection syndrome may occur presenting akinetic mutism, incontinence, apraxia, or the alien hand syndrome. It is thought that this is more likely if the callosotomy is complete. This is why many surgeons prefer to do an anterior 2/3 section first. If necessary the posterior third can be sectioned later resulting in a lower likelihood of adverse postoperative effects. However, in addition to the amount of callosal fibers actually resected, the presure from the spatula on the brain might explain the acute effects of the callosotomy [39].

39.5.5 Vagal Nerve Stimulation (VNS)

Vagal nerve stimulation is a palliative treatment for refractory epilepsy and was approved by the US Drug and Food Administration in 1997. According to these studies, VNS significantly reduces seizure frequency in about 70% of cases and sporadic cases are reported to be seizure free [40]. The improvement in seizure control seems to increase with time and to persist at long-term follow-up, particularly for children implanted under 6 years of age [41]. Some authors advocate the use of vagal nerve implantation as soon as possible in selected patients to achieve behavioral and neuropsychological improvements and a better quality of life [42]. There is also evidence that VNS may be effective in improving cognitive deficits independently of controlling seizure activity [43]. Due to the heterogeneity of the studied populations, there are no clear relationships between device efficacy and the patient's clinical characteristics, including gender, age at seizure onset, age at implantation, type of genetic mutation, duration of VNS treatment, infantile spasm, or autism features. Although the precise mechanism of action of vagal nerve

stimulation is still unknown, there seems to be a reduction in cortical excitability due to a direct effect of the interference in GABA receptor density.

Placing a VNS device is a low-risk procedure. Infection may occur at the incision site and the reported rate is between 0 and 8%. Other complications include vocal cord paralysis, which is usually transient. Significant or permanent injury to the vagus nerve was rare (<4%). Rarely asystole may occur in the operating room (0.1%). Lead fracture or dislodgement from the device and battery failure can occur unrelated to the surgical procedure. In the long run, patients may complain of voice alteration and hoarseness (19–29%), local paresthesias, throat or neck pain (12%), and cough (6%). Dyspnea may be seen (3%), as well as headaches [44].

39.6 Complications

The reported complications of extratemporal epilepsy surgery include cerebrospinal fluid (CSF) leakage or positive CSF cultures, usually in the absence of clinically evident meningitis. Studies of the pathological changes seen in cortex underlying subdural arrays have revealed focal, transient aseptic meningitis in many patients. Other reported complications include transient neurological deficit, edema, epidural or subdural hematoma, and stroke. As in other surgical modalities, complication rates tend to decrease with increasing surgical experience. Class 2 data indicate that dexamethasone may reduce cerebral swelling in children with implanted subdural grid electrode arrays. However, this corticosteroid can also decrease the posibility of seizures, lengthening the extraoperative monitoring periods required to locate the ictal focus [45, 46].

39.7 Conclusions

Extratemporal epilepsy in children represent a real challenge in the field of epilepsy surgery. Identifying certain pathologies can be dificult. Our understanding of the relationship between these lesions and the epileptogenic zone is still incomplete and the affected area often includes functional cortex. Our ability to manage these patients has dramatically improved with non invasive techniques like high resolution MRI, PET, ictal SPECT, and MEG as well as invasive methods employing subdural electrodes, depth electodes and cortical brain mapping. There is also a growing understanding of the predictive value of ictal EEG patterns in planning surgical resection. The future of surgery for extratemporal epilepsy in children is promising, although there are still many issues to be addressed so we can provide optimal care for these challenging patients. More than any other patient population, children require the coordinated attentions of epilepsy experts from multiple disciplines including clinical neurology, structural and metabolic imaging, neurophysiology, and experienced surgeons with stereotactic systems at their disposal.

39.8 Illustrative Case

This case illustrates the contribution of the different imaging modalities, and the surgical planning.

Case Studied

We evaluated a 12-year-old girl with a history of epilepsy since age 2. Her seizures consisted of stereotyped hypermotor movements of the left upper extremity with no alteration of awareness, occasionally followed by secondary generalized tonic–clonic seizures. Seizures occurred up to 20 times per day, mostly during sleep. Her epilepsy remained intractable despite treatment with different antiepileptic medications. The EEG showed no definite localization of the seizure onset, although late ictal and postictal periods produced bifrontal rhythmic delta activity. The presurgical MRI showed cortical and subcortical signal abnormalities in the right frontal lobe (Figs. 39.4 and 39.5). The interictal FDG-PET revealed a hypometabolism in the right frontal lobe (Fig. 39.6) and the ictal SPECT demonstrated hyperperfusion in the right middle frontal gyrus (Figs. 39.7 and 39.8).The patient underwent right frontal lobectomy, and at the 4-year follow-up she is totally seizure free and going to school (Fig. 39.9 Post surgical MRI).

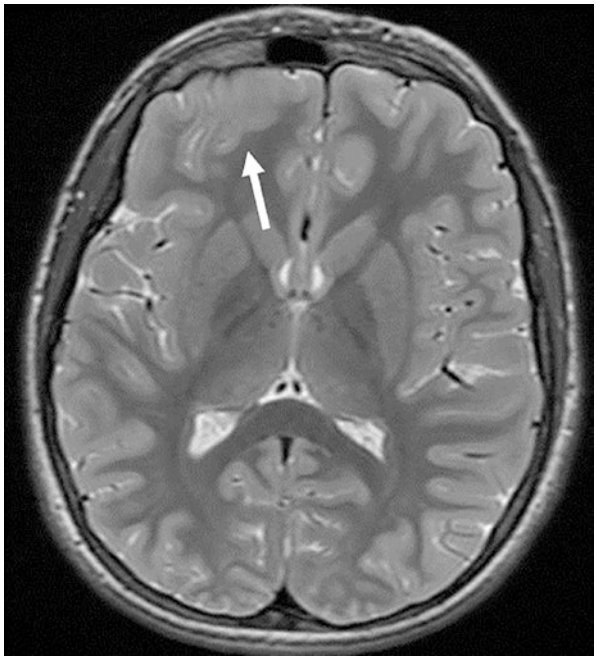

Fig. 39.4 A presurgical MRI showing cortical and subcortical abnormalities on axial T2

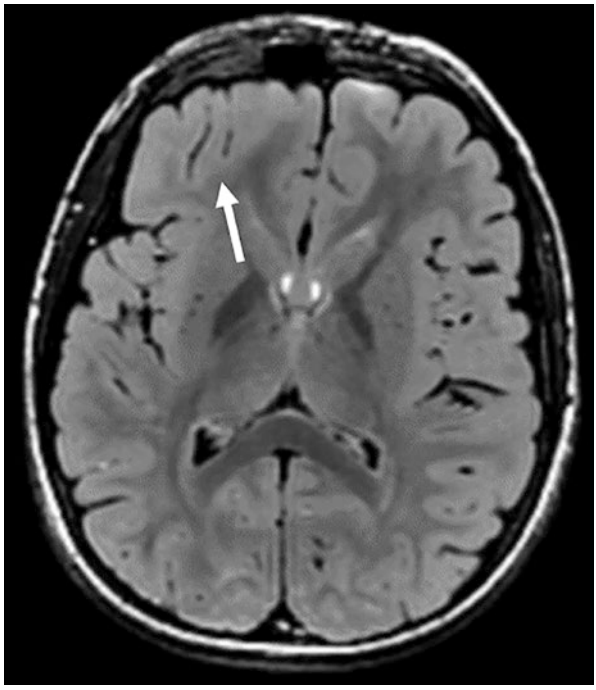

Fig. 39.5 FLAIR (fast fluid-attenuated inversion recovery images) MRI illustrates right frontal cortical dysplasia (white arrow)

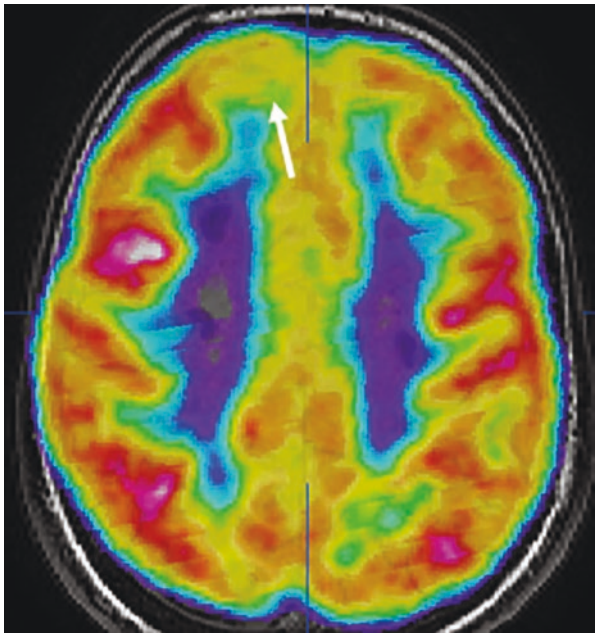

Fig. 39.6 Hypometabolism in the right frontal lobe on the FDG-PET (white arrow)

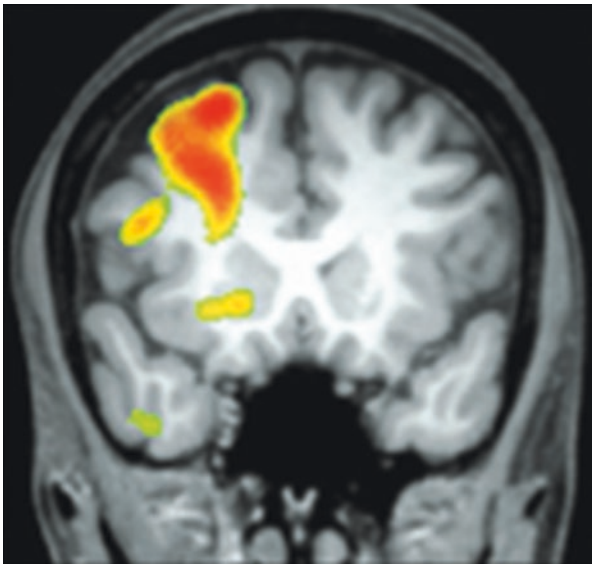

Fig. 39.7 Ictal SPECT co-registered to MRI with marked hyperperfusion in the right middle frontal gyrus

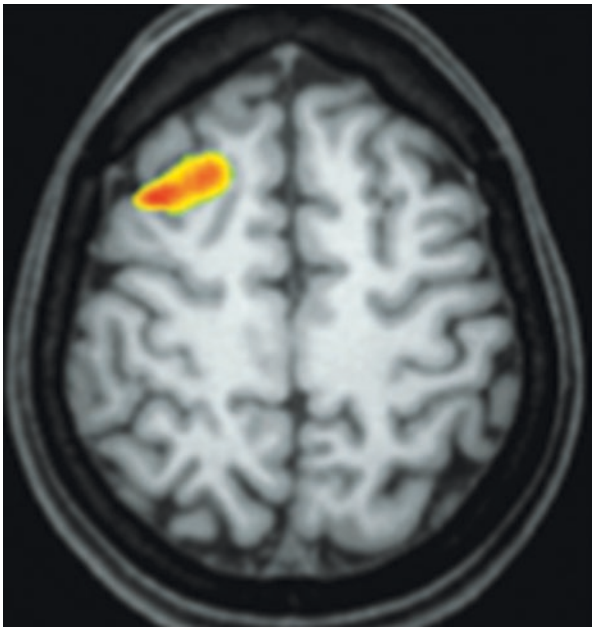

Fig. 39.8 Coronal view SPECT showed the area of hyperperfusion. This area was included in the resection

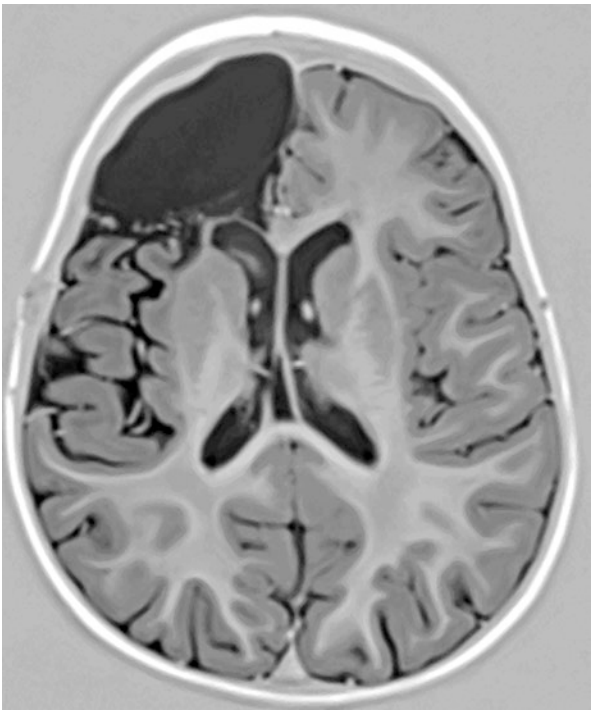

Fig. 39.9 Post surgical MRI shows the extent of the right frontal lobectomy. The patient is seizure free

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Chapter 40
Hemispherectomy

Carrie R. Muh

40.1 Hemispherectomy

Hemispherectomy and hemispherotomy are the surgical removal or disconnection of one cerebral hemisphere of the brain to treat hemispheric epilepsy. Dr. Walter Dandy published the first documented hemispherectomies in 1928 [1]. These consisted of removal of essentially the entire right hemisphere in patients who presented with tumors that were causing left sided paralysis. The patients all survived the surgery, and one survived for three and a half years after surgery. Dandy noted that the plegia in these cases was complete in the arm and leg but only partial in the face, and deep sensation and pain was often preserved in the plegic arm and leg.

At the annual meeting of the American Medical Association in 1938, Canadian neurosurgeon Kenneth McKenzie presented the case of a patient who underwent a right anatomic hemispherectomy for refractory epilepsy [2]. In 1950, the procedure became more widespread after South African neurosurgeon Rowland Krynauw published his experience using hemispherectomy to treat 12 patients with hemiplegia, epilepsy and cognitive deficits. His patients' seizures and mental status improved, some going years without seizures even off medications [3].

Those earliest hemispherectomies involved physically removing essentially the entire affected hemisphere as well as the choroid plexus, though in some reports, the hippocampus and gyrus rectus were left in place. The large resection cavity was left empty and in communication with the remainder of the ventricular system. These large anatomic hemispherectomies were found over time to lead to significant side

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effects such as obstructive hydrocephalus and superficial hemosiderosis, which at times were fatal [4].

The surgery was modified to remove less tissue and, over time, has largely been replaced with procedures such functional hemispherectomy or hemispherotomy. Since then, the surgery has continued to evolve and there are now multiple ways to perform the procedure through more minimally invasive routes, relying more on disconnection and less on removal of tissue. For many epilepsy neurosurgeons, the choice of surgical technique will depend on the patient's underlying pathology.

40.2 Patient Selection

As is true in most surgical procedures, choosing the correct patients is of the upmost importance for obtaining good outcomes after hemispherotomy or hemispherectomy. Because a large portion of cortex will be removed or disconnected, including a motor strip, sensory strip and occipital cortex, the surgery is generally only offered to patients who already have deficits due to a unilaterally abnormal hemisphere. Patients often have hemiplegia and a visual field deficit pre-operatively.

Not all patients with hemispheric epilepsies will be candidates for hemispherectomy or hemispherotomy, while those with certain pathologies will be more commonly considered for the surgery. Common pathologies that are amenable to hemispheric surgical treatment include: Rasmussen's encephalitis, Sturge Weber, peri-natal infarct, hemimegalencephaly, large multi-lobar cortical dysplasia (malformations of cortical development, MCD), infantile spasms, hemiconvulsion-hemiplegia-epilepsy syndrome (HHE), hemispheric traumatic brain injury (TBI) and other hemispheric injury, infarction or hemorrhage.

Each of these disorders has a different presentation, but all can lead to one grossly abnormal hemisphere from which drug-resistant seizures emanate and one essentially normal hemisphere which the patient relies upon for most of their function.

40.2.1 Rasmussen's Encephalitis

Rasmussen's encephalitis is characterized by a progressive, chronic inflammation of one cerebral hemisphere. The encephalitis leads to drug-resistant epilepsy as well as loss of function and neurologic deterioration. The affected hemisphere may look normal on initial imaging, but then begin to visibly atrophy on subsequent imaging (Fig. 40.1). Medications are initially used to treat the seizures, but invariably the seizures are resistant to medications. Children develop hemianopia, hemiparesis or hemiplegia, cognitive decline, speech difficulties if the dominant lobe is affected, and various changes in seizure semiology over time. Patients often begin with simple focal motor seizures, then progress to secondary generalized tonic clonic seizures, complex focal seizures, and somatosensory seizures [5].

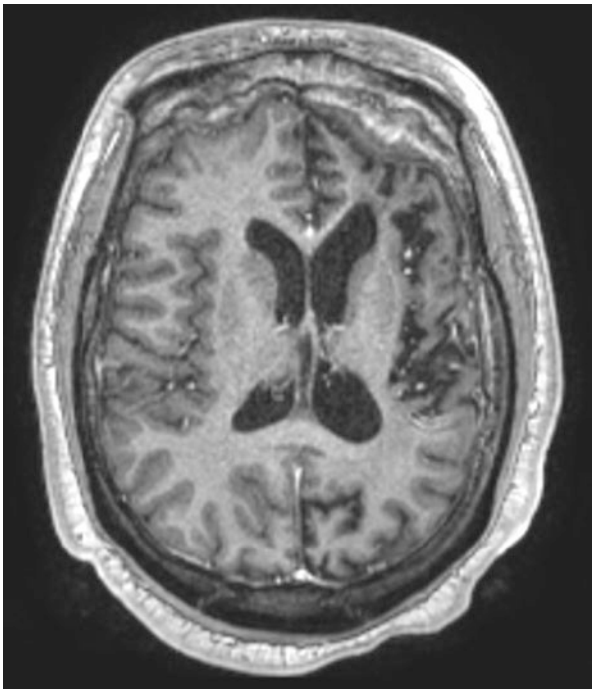

Fig. 40.1 Axial MRI displaying left hemispheric atrophy due to Rasmussen's encephalitis

More than two thirds of patients with Rasmussen's encephalitis develop epilesia partialis continua, often in the early acute stage of their disease process [6]. The underlying cause of the inflammation is unknown and may be initially treated with immunotherapy to slow the neurological deficits, though this has not been shown to have a benefit in controlling their seizures [7, 8]. Hemispheric disconnection or resection surgery may be curative in controlling seizures and stopping progression of the disease for these patients [8, 9].

40.2.2 Sturge Weber

Sturge Weber is a rare neurocutaneous syndrome characterized by hemispheric pial angiomatosis and a cutaneous facial angioma, also called a port wine stain, along the distribution of the trigeminal nerve branches. The facial port wine stain is ipsilateral to the pial angiomatosis in most patients, but can be bilateral. Patients often have ocular symptoms, such as visual field deficits [10].

Computed tomography (CT) scan will demonstrate cortical and subcortical calcification which is often visible as a parallel "tram-track" lines, while magnetic resonance imaging (MRI) shows volume loss, leptomeningeal enhancement and, often, flow voids or dilated parenchymal veins (Fig. 40.2). The syndrome leads to the development of hypertrophic pial vasculature, and patients often do not have

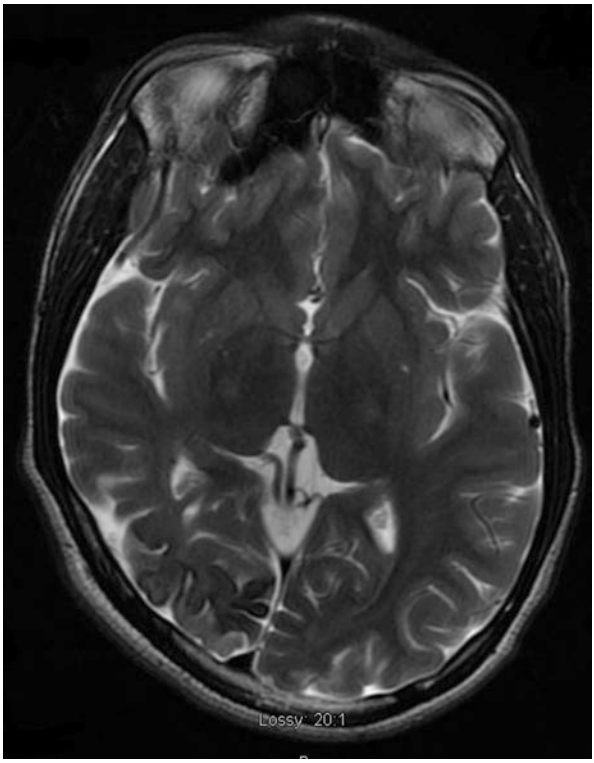

Fig. 40.2 Axial MRI showing right hemispheric volume loss and occipital cortical calcifications common with Sturge Weber

typical venous sinuses or superficial cortical venous drainage. This abnormal venous pattern can lead to venous stasis and retrograde venous flow toward the ventricles. The surrounding parenchyma can become hypoxic, leading to brain injury and subsequent seizure activity, developmental delay, hemiparesis and optic nerve atrophy. The seizures are usually the first neurologic symptom and most patients with Sturge Weber develop epilepsy in the first year of life [10, 11].

Most patients' seizures are medically intractable, and hemiplegia or loss of developmental milestones may develop after significant seizure activity. Hemispherectomy may be considered early in these patients to preserve their ability to develop cognitively [12].

40.2.3 Peri-Natal Infarcts and Vascular Insults

Perinatal vascular injuries are those that occur during the latter half of pregnancy or within the first several weeks of a newborn's life. One in 3500–4000 newborns will suffer an ischemic stroke, and others suffer hemorrhages in the perinatal period [13, 14]. These injuries include perinatal ischemic stroke, hemorrhagic stroke, venous

infarcts, dural venous sinus thrombosis and thromboembolic events. About 40–50% of infants with perinatal stroke will have normal neurologic development, but 50–60% will have significant deficits or die from the vascular injury [14]. Children with symptomatic perinatal infarcts or hemorrhages may develop contralateral hemiplegia or hemiparesis, language difficulties, learning disabilities or cognitive delays, and behavioral difficulties, in addition to epilepsy. Many of these children are diagnosed with cerebral palsy.

Imaging will show evolution over time, initially showing ischemic or hemorrhagic changes as a neonate. Later, an area of encephalomalacia and often a porencephalic cyst will develop in the region of vascular damage (Fig. 40.3a, b).

40.2.4 Hemimegalencephaly

Hemimegalencephaly is a rare congenital abnormality where one cerebral hemisphere is hypertrophic. This leads to developmental delays, contralateral hemiparesis and refractory epilepsy. Seizures generally begin early in infancy, often with infantile spasms. The baby's cranium may appear asymmetrically enlarged on the affected side. Hemimegalencephaly affects 1–3 in 1000 children with epilepsy. Hemimegalencephaly may occur as part of a genetic or neurocutaneous syndrome, such as tuberous sclerosis or neurofibromatosis I, and may be inherited, though in about half of patients, there is no known syndrome or familial history [15].

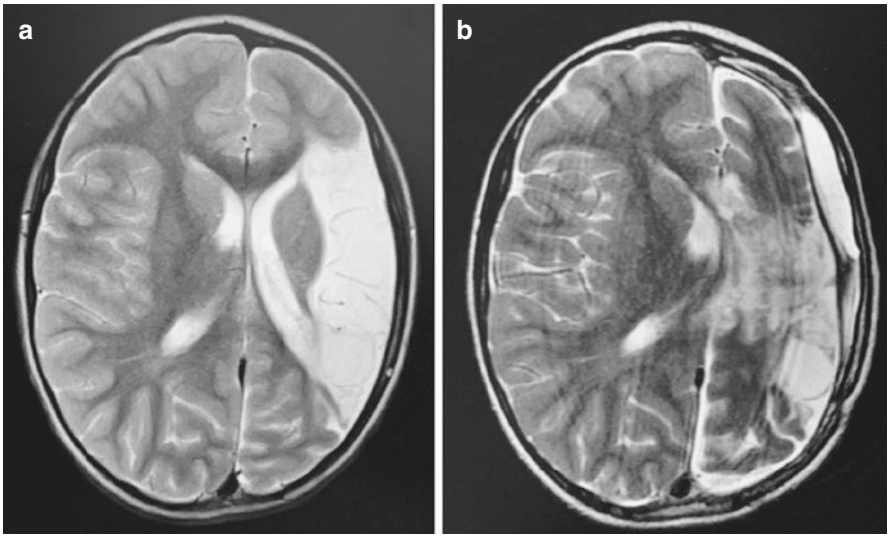

Fig. 40.3 (**a**) Axial MRI of a patient with a left perinatal infarct; (**b**) Axial MRI of that same patient after undergoing functional hemispherectomy

The brain tissue on the affected side shows hamartomatous overgrowth with dysplastic tissue, loss of cortical lamination, gliosis, heterotopia and often balloon cells [16]. Imaging shows an enlarged hemisphere with thickened cortex, indistinct grey-white differentiation, abnormal gyration with pachygyria and/or polymicrogyria or agyria, heterotopias, and often an ipsilateral ventriculomegaly or colpocephaly [15, 17].

Patients with hemimegalencephaly generally have contralateral hemiparesis and may have a visual field deficit due to the malformed hemisphere. The seizures may be quite severe and medically refractory, so early hemispherectomy as a baby is often the recommended treatment. Removal or disconnection of the affected hemisphere can significantly improve the child's neurologic development in addition to controlling their seizures (Fig. 40.4a, b).

40.2.5 Malformations of Cortical Development (MCD)

MCDs include a wide range of disorders with abnormal cortical organization. The cortex is not arranged in the normal manner, leading to pathologic, uncontrolled electrical activity between malpositioned or atypical neurons. MCDs include hemimegalencephaly, polymicrogyria, tuberous sclerosis complex, lissencephaly, schizencephaly, heterotopia and focal cortical dysplasia [18].

Focal cortical dysplasia (FCD) may be the most common cause of intractable epilepsy in children [19]. FCDs are localized regions of cortical abnormality that

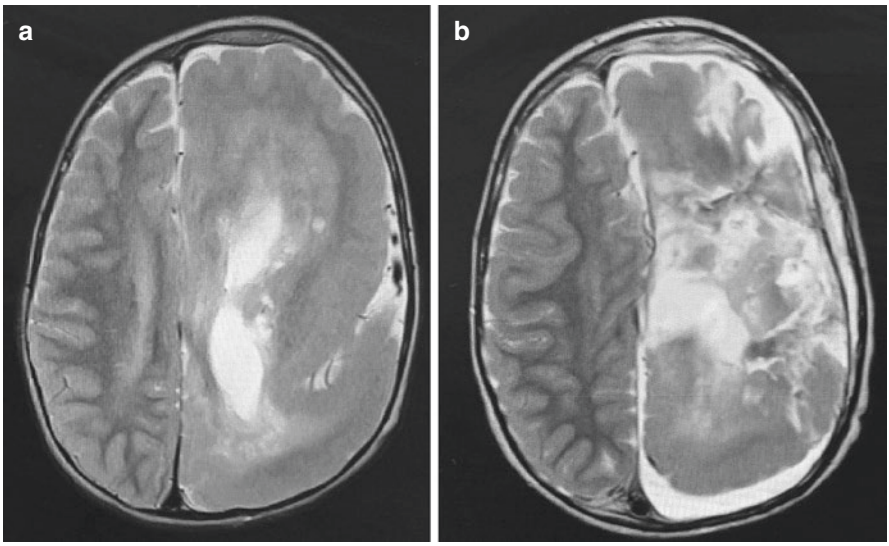

Fig. 40.4 (**a**) Axial MRI showing left hemimegalencephaly; (**b**) Axial MRI of that same patient after undergoing functional hemispherectomy

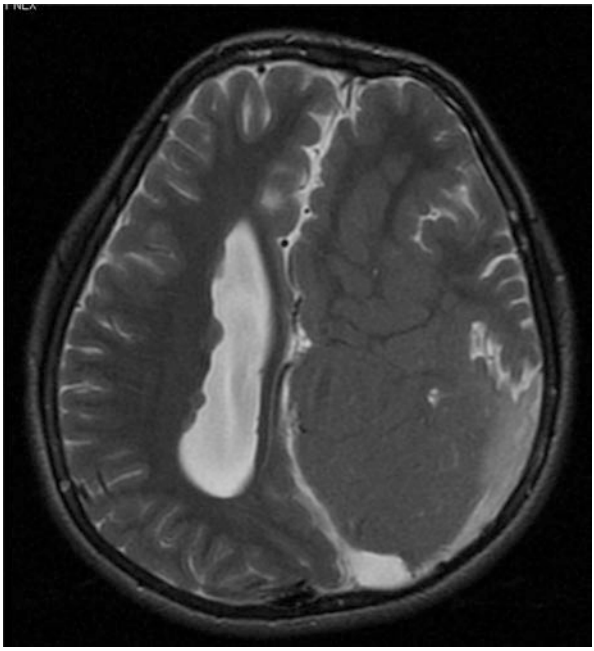

Fig. 40.5 Axial MRI reveals diffuse left hemispheric cortical dysplasia

often appear on MRI as focal cortical thickening with blurring of the grey-white junction. Some cortical dysplasias are very localized, while others are larger and more diffuse, and may involve multiple lobes or most of a hemisphere (Fig. 40.5). Patients with intractable epilepsy due to large cortical dysplasias involving multiple lobes may benefit from hemispherectomy, often with some improvement in developmental outcome in addition to decrease in seizures [20].

40.2.6 Infantile Spasms

Infantile spasms are short, stereotypical jerks or spasms of an infant's arms, often with forward thrusting of the head and a jackknife movement with the knees pulled up. They each may last only a second or two, but can happen in clusters of dozens at a time and can occur up to 100 times in a day. EEG reveals hypsarrhythmia, a disorganized high voltage pattern. This syndrome is often called West syndrome, after Dr. William West who published a letter to the Lancet describing his own infant son's spasms and developmental delay in 1841 [21].

Babies with infantile spasms generally develop their seizures between 4 and 8 months old, though they can develop in the neonatal period as well. Many babies respond to adrenocorticotropic hormone (ACTH), vigabatrin, or rarely pyridoxine (vitamin B6), while others are medically refractory. A ketogenic diet can be helpful for some. For those infants with infantile spasms who are medically refractory and

have cortical abnormalities on their MRI, including perinatal infarct or dysplasia, hemispherectomy can be a profoundly beneficial treatment [22].

40.2.7 Hemiconvulsion-Hemiplegia-Epilepsy Syndrome (HHE)

HHE syndrome was described Dr. Henri Gastaut in 1957 and 1959 when he described 150 patients with a pattern beginning with febrile seizures in childhood, generally under age 4 years [23]. The seizures involve prolonged hemiconvulsions followed by flaccid hemiplegia, which may transition to spastic hemiparesis. The children often have a seizure-free interval of months to years, then develop chronic epileptic seizures, often focal onset. Imaging shows unilateral edema initially, followed by diffuse atrophy throughout the affected hemisphere [24].

40.2.8 Other Hemispheric Injury, Infarction or Hemorrhage

Any injury to a large portion of the brain, including severe traumatic brain injury (TBI), meningitis, stroke or intraparenchymal hemorrhage can lead to hemispheric epilepsy. Patients with hemispheric abnormalities and medically refractory seizures should be referred to an Epilepsy Center to be considered for hemispherotomy or hemispherectomy.

40.3 Pre-operative Evaluation

Any patient with epileptic seizures that are significantly impacting their quality of life, and cannot be controlled after trying two to three appropriate anti-epileptic medications, should be referred to a comprehensive Epilepsy Center. There, an experienced team can determine if they are a candidate for surgery.

It can be argued that the most vital factor in predicting a successful surgical outcome is appropriate patient selection. Before offering a hemispheric epilepsy surgery to a patient, it is mandatory that the patient undergo a detailed assessment by a multidisciplinary epilepsy team. The patient must be seen by an epileptologist, and a thorough history and examination is necessary.

It is important to understand the patient's seizure frequency, seizure semiology, age of onset, family history, risk factors for epilepsy including genetic or metabolic disorders, and prior medical therapies. The presence and extent of

contralateral hemiparesis, visual field deficits, and developmental delays should be determined.

Presurgical evaluation seeks to determine the patient's seizure type and location of onset. The patient will be admitted to an epilepsy monitoring unit (EMU) and undergo several days of video-recorded inpatient electroencephalography (video EEG) monitoring so that the epileptologists can study the seizure semiology.

The EEG can demonstrate if the patient's seizure activity is exclusively, or mostly, beginning in one hemisphere. If the contralateral hemisphere also has frequent seizure onset, then a hemispherectomy may not be the best option for that child. If location of seizure onset cannot be determined confidently with a scalp video EEG, then intracranial EEG with depth electrodes (stereoEEG) or subdural grids may be beneficial.

In addition to EEG, the patient needs intracranial imaging. Patients who are likely to benefit from hemispherectomy generally have one grossly abnormal appearing hemisphere on MRI. Most of the diagnoses listed above have stereotypical abnormalities apparent on MRI. Vascular imaging with contrasted MRI or magnetic resonance angiography (MRA) may be helpful for planning of surgery.

For those patients, where the seizure onset is not clearly coming from most of one hemisphere, functional imaging such as positron emission tomography (PET) or single-photon emission computerized tomography (SPECT) can be useful in localizing areas of seizure onset. PET uses radiolabeled glucose to highlight brain metabolism which may demonstrate regions of interictal hypometabolism. An ictal SPECT involves the injection of a radiolabeled tracer during a seizure; the tracer binds in the brain rapidly and remains stable for several hours, so the imaging will reveal the intracranial circulation as it was during the seizure. Epileptogenic zones often demonstrate increased circulation during the seizure [25].

For patients who have abnormalities in their dominant hemisphere, or where there is concern for bilateral abnormalities, a Wada test may be conducted. Also known as an intracarotid sodium amobarbital procedure (ISAP), the Wada test involves the injection of a short-acting barbiturate to essentially sedate one hemisphere at a time. Questioning performed during this anesthetic can reveal if the patient's language or memory would be affected by removal or disconnection of either hemisphere. However, because this test requires patient cooperation in a relatively stressful environment, it is rarely performed on children or other patients with developmental delays.

A detailed neuropsychological evaluation is performed prior to hemispherectomy or hemispherotomy. This assessment can aid in determination of learning difficulties and cognitive delays, and can provide the treating physicians a better understanding of the child's degree of disability.

A physical examination is obviously imperative as well. Most patients with hemispheric epilepsy have some degree of hemiparesis or hemiplegia and hemianopia due to their underlying cortical pathology. These patients will be unlikely to

suffer significant additional weakness or visual deficits from hemispheric epilepsy surgery, as much of their remaining function may have already migrated to the good hemisphere. Patients who have full strength or normal visual fields, however, would be at risk for significant post-operative neurologic deficits with a hemispheric disconnection.

For some patients, the connections with the occipital lobe and posterior temporal lobe should be preserved so as not to cause a hemianopia, while for other patients, the seizures would continue at an unacceptable level without a complete disconnection, so visual field cut may be a deficit the patient and family are willing to trade for a better chance at seizure control. Likewise, if a patient has a progressive neurologic condition that will eventually lead to severe loss of function, a hemispherectomy may be an appropriate option even if it will likely cause some deficits, since it may slow or prevent further neurologic and cognitive deterioration over time. Each patient and family needs to have a good understanding of the risks of the surgery being offered to them, as well as their expected neurologic condition post-operatively.

Once the patient has undergone this systematic, detailed evaluation and a hemispherectomy has been recommended by a multidisciplinary team, then the neurosurgeon must determine the best surgical approach to achieve that goal.

40.4 Surgical Options for Hemispherectomy or Hemispherotomy

40.4.1 Anatomic Hemispherectomy

The initial hemispherectomies by Dandy, McKenzie and Krynauw in the first half of the twentieth century consisted of removal of the entire cerebral hemisphere. Though the surgery was drastic, it became popular as it allowed surgeons to control seizures in 70–80% of previously intractable patients. The mortality rate of 6–10% was acceptable for the era [26].

In 1966, however, Oppenheimer and Griffith published an article on persistent intracranial bleeding after anatomic hemispherectomy. This surgery had been performed in 17 patients with “infantile hemiplegia with fits”, four of whom did well for several years after surgery, but then developed headaches, deteriorated neurologically, and died. The necropsy of three of them showed that they had had “repeated bouts of bleeding” within the cranial cavity [4]. They had suffered from obstructive hydrocephalus, granular ependymitis and superficial hemosiderosis. Further papers on this topic over the next few decades corroborated this description of the chronic superficial hemosiderosis that lines the cortex along the resection cavity, which leads to obstructive hydrocephalus and may be fatal. This form of surgery therefore fell out of favor due to the almost 25% risk of delayed mortality [4].

40.4.2 Operative Notes

For an anatomic hemispherectomy, a patient is placed supine with the ipsilateral shoulder elevated and rotated. The head is in Mayfield pins and is rotated so that the head is almost lateral. A large craniotomy is made, generally through a question-mark-shaped incision extending from midline just behind the hairline back to the occipital region and then down to the zygoma. The temporal fascia is left connected to the scalp to preserve the facial nerve. The temporalis muscle is incised anteriorly and the inferior blood supply to the muscle is kept intact. The intracranial anatomy may be displaced in disorders such as hemimegalencephaly, so a detailed review of the pre-operative MRI will help the surgeon determine the location and size of the craniotomy. A large craniotomy flap is made followed by a large dural opening, permitting exposure of the sagittal sinus and the Sylvian fissure, with access to the anterior skull base.

When performing an anatomic hemispherectomy, hemostasis and control of blood loss is critical. The middle cerebral artery (MCA) can be visualized at the Sylvian fissure. The MCA can be dissected free then tied off and divided proximal to its bifurcation, distal to the perforating vessels. This will decrease blood loss from the cortical resection while preserving blood supply to the basal ganglia via perforating branches. Because the cortical tissue will be removed with this surgery, more vessels can be taken than in the more minimal disconnection procedures.

While some surgeons remove the hemisphere en bloc, this can be perilous with anomalies such as hemimegalencephaly, leading to traction on the basal ganglia and brainstem, so significant experience is needed to perform this safely. Frequently, removing the tissue via multiple smaller lobectomies is safer.

The lateral ventricle can be entered and opened along its lateral aspect to dissect the insular tissue and expose the deep midline structures. A temporal lobectomy can then be performed. This will provide additional working space and visualization of the deeper cerebral vessels.

The corpus callosum can be exposed through the open lateral ventricle. A complete callosotomy is performed, making sure to visualize the genu and splenium. The ipsilateral and contralateral anterior cerebral arteries (ACA) can be well visualized; it is imperative that the contralateral ACA be preserved, while the ipsilateral ACA should be tied off and divided distal to the anterior communicating artery (Acomm). The frontal lobe is dissected free completely from the falx to the Sylvian fissure.

Attention is then turned posteriorly, and the posterior cerebral artery (PCA) is tied off and divided. The multiple posterior bridging veins are coagulated and divided, the posterobasal white matter is divided, and the parietal and occipital lobes can be dissected free.

The resection site should be closely inspected to ensure that there are no residual connections from the affected cerebral cortex to the remaining tissue. The lateral ventricle will be widely opened, so the visible choroid plexus may be coagulated to decrease risk of post-operative hydrocephalus, taking care not to injure the

choroidal arteries. A layer of Surgicel (Ethicon, Inc.) or other fibrin sheet is placed down over the resection cavity.

A plethora of techniques have been reported to fill the large resection cavity, from reduction duraplasty to an extradural Silastic breast prosthesis [27]. A water tight dural closure is required, as are multiple epidural tack-up sutures, both circumferentially and centrally. The bone, fascia and scalp are closed in the standard craniotomy fashion, and a subgaleal drain is often placed temporarily due to the large size of the incision.

40.4.3 Hemidecortication

Hemidecortication is quite similar to anatomic hemispherectomy, however the underlying white matter and ventricles are mostly preserved when the pathologic cerebral cortex is resected. This variation was introduced by Krynauw in 1950 and popularized by Ignelzi and Bucy when they published a review of 420 published cases in 1968 [28]. They described that the MCA was divided just lateral to the basal ganglia, the ACA was taken distal to Acomm and the PCA was taken just prior to entering the calcarine fissure. The cerebral cortex was then removed, leaving the white matter. The basal ganglia, thalamus and corpus callosum over the lateral ventricle were left intact. The temporal horn was opened with the temporal lobectomy, but the ventricle opening was often covered to maintain ventricle integrity. A septostomy was performed, connecting the two ventricles.

They noted a reported 6.6% mortality rate, which was acceptable in that era [28].

40.4.4 Functional Hemispherectomy and Variants

Rasmussen introduced a modified version of the hemispherectomy in 1973 [26, 29]. In this initial version of the functional hemispherectomy, he described resecting only the insular and temporal regions of the cortex and leaving behind the remainder of the cerebral hemisphere which was consider to be less epileptogenic tissue.

Rasmussen's initial functional hemispherectomy results were not as satisfying, as only 45% of patients became seizure free versus 59% of those who underwent anatomic hemispherectomy [30]. Therefore, the surgery was revised over the years. A 1982 lecture by Rasmussen described removal of the temporal lobe and insula with preservation of the frontal and occipital poles, but with complete sectioning of the white matter down to the pia, fully disconnecting the residual cortex from the remaining hemisphere and brainstem. This resulted in a "functional complete but anatomical subtotal hemispherectomy" [31].

A 1988 series of 14 patients who underwent this modified functional hemispherectomy by Rasmussen or Villemure reported no deaths or serious complications aside from one patient who developed dystonia after a shunt was placed for

hydrocephalus [30]. Four patients continued to have at least one seizure after surgery, three of whom had significant improvement in seizures and/or social function and IQ.

The techniques for functional hemispherectomies have been modified multiple times over the ensuing decades. Many of these variations have been referred to as "hemispherotomies" though they still involve significant tissue resection.

In the 1980s and 1990s, Peacock and Mathern at UCLA noted that the residual deep structures were considered the source of persistent seizures and the reason for failure for some functional hemispherectomies [32]. Therefore, they developed a modified lateral hemispherotomy in which the deep structures are removed with the overlying insula, but the frontal and occipital cortex are left in place. Surgically, they note that the MCA is ligated in the Sylvian fissure and the frontal-temporal-parietal operculum and insular are removed along with the caudate nucleus, thalamus, and basal ganglia. The remaining temporal lobe is resected, including the hippocampus, and part of the orbitofrontal cortex is removed. The frontal and occipital cortex are left in place but the white matter tracts are fully disconnected [32]. In the 96 patients operated on via this technique from 1988–2008, there were no deaths, no hemosiderosis, 3 re-operations for persistent seizures, and 31 patients developed hydrocephalus requiring a shunt placement [33].

In the 1990s, Schramm in Bonn, Germany described a hemispherical deafferentation which minimized the resected tissue [34]. Their version begins with a hippocampectomy, either with or without anterior temporal lobectomy. The lateral ventricle is then opened and the white matter of the frontal, temporal, parietal and occipital lobes is divided using a transventricular or transcortical approach. A transventricular callosotomy is performed. They note that various modifications can include insular resection or transsylvian deafferentation. In the 13 patients in their initial series, there were no deaths or severe complications, and one patient required a shunt [34].

Villemure in Lausanne, Switzerland described a periinsular hemispherotomy to again try to minimize risks while still resecting achieving the benefit of functional hemispherectomy [35]. This method again involves a large craniotomy with exposure of several cm of brain on each side of the Sylvian fissure, as the surgery is performed entirely through a supra-insular and infra-insular approach. As in previously described versions, there is resection of the frontal and parietal operculum, a transventricular callosotomy, frontobasal disconnection, and a temporal lobectomy including mesial structures. The insula is removed or disconnected. In a series of 43 children undergoing this technique, two had neurologic deterioration with hemorrhage distant from the surgical site and one developed hydrocephalus requiring a shunt. 34 children were free of disabling seizures (Engel I) and 3 children were almost seizure free, classified as Engle II [36].

Shimizu in Tokyo, Japan further modified the functional hemispherectomy to perform a similar resection and disconnection, but via an opercular cavity rather than periinsular. His published his series of 27 patients in 2000 showed that 18 were free of disabling seizures (Engel I), two were almost free of seizures (Engel II), six had worthwhile improvement in seizures (Engel III), and one had no worthwhile

improvement (Engel IV) [37]. There were no deaths, one patient with cerebral edema and neurologic deterioration, and five patients required shunting.

40.4.5 Disconnective Hemispherotomy

In recent years, surgeons have moved toward more minimal approaches that involve disconnecting more and resecting less.

In 2015, Chandra in New Delhi, India described the use of endoscopy to perform an endoscopic interhemispheric transcallosal hemispherotomy [38]. No lobectomy was performed. The surgery consisted of an interhemispheric complete corpus callosotomy, followed by anterior and middle disconnection by traveling from the genu to the anterior skull base down to the sphenoid, using neuronavigation and endoscopic guidance. The gyrus rectus is resected and the disconnection proceeds laterally. The hemisphere is divided lateral to the thalamus to the atrium of the ventricle. The temporal lobe and mesial temporal structures are disconnected. The endoscope is then brought posteriorly to disconnect the fornix.

Their series reported 11 patients who underwent endoscopic interhemispheric hemispherectomy. They reported no deaths or significant complications; two patients had prolonged fevers. Nine patients achieved Engel I outcomes and two patients with hemimegalencephaly had Engel II outcomes [38].

Technically, a complete endoscopic disconnection is easier in patients with perinatal infarcts than it is in patients with hemimegalencephaly, due to the anatomy and ability to visualize without significant retraction. Some other centers who have reported use of the endoscopic disconnection have done so only in patients with perinatal infarct and atrophy [39]. Postoperatively, complete disconnection can be evaluated with MRI with diffusion tensor imaging (DTI) to assess white matter and fiber tract disconnection.

More recently, MRI-guided laser ablation has been used to perform a hemispheric disconnection in a child with perinatal MCA infarct and encephalomalcia of the insula [40]. Stone at Boston Children's Hospital described the use of five fiber trajectories to maximize disconnection while minimizing brain passes. A pass entering the parietal lobe, traveling lateral to the occipital horn and up to the uncinate fasciculus disconnected the temporal stem; a trajectory from the occiput along the long axis of the hippocampus ablated the mesial temporal structures; a third pass travelled from the superior medial parietal lobe to the basal occipital region; the fourth achieved a partial callosotomy; and the fifth traveled through the frontal lobe, completing the callosotomy and disconnecting frontal tissue. The patient had worsening of her hemiparesis but was able to ambulate. She had a few seizures a few months post-operatively, but then remained seizure free for the last 11 months of follow up [40].

These newer hemispherotomy procedures are not widely used clinically at this time, but many centers are using more disconnection and less resection for appropriate patients.

40.5 Outcomes

Numerous studies have demonstrated the clinical benefit of hemispherectomy or hemispherotomy in correctly selected patients. In a large number of published series, 50–93% of patients with a wide range of pathologies are seizure free after hemispheric disconnection or removal [11, 20, 41–44].

Mortality rate is very low with modern surgical techniques, generally 1% or less [11, 34, 35, 37]. Hemiparesis is unchanged in the majority of patients, 66%, is worse post-operatively in 18% of patients, and is actually better in 15% of patients [20]. Behavior issues often improve after surgery, and many patients see a significant cognitive improvement, including improvement in language [42].

20% of patients or more will have peri-operative complications including intracranial hemorrhage, infection, infarction, hydrocephalus or hygroma [20, 44]. Some series report up to a 73% rate of complications if minor complications such as a transient post-op fever are included, but even leaving out these mild, transient issues, up to one third may have chronic hydrocephalus or hygroma requiring CSF diversion post-operatively [41]. With functional hemispherectomy, patients no longer develop superficial hemosiderosis as they do after anatomic hemispherectomy, though generally 3–15% of patients develop hydrocephalus requiring a shunt [11, 34, 35, 37].

As with many resective surgeries, the rates of Engel class I results are highest at 3 months postoperatively (80–90%) but decrease over the next several years (70–80% at 1 year, 50–77% at 5 years and more) in many studies [11, 25, 45].

Functional hemispherectomy and disconnective hemispherotomy involve a smaller surgery, with less risk of hydrocephalus and bleeding than with anatomic hemispherectomy, but many series report cases requiring reoperation to complete the disconnection [42].

With any of these approaches, it is imperative to achieve a complete disconnection, including a complete callosotomy as well as frontobasal disconnection and disconnection of the mesial temporal structures. The more minimally-invasive the surgical approach used, the more technically challenging the surgical disconnection can become. Postoperative seizure recurrence or persistence should be evaluated with MRI with diffusion tensor imaging to evaluate residual fiber tracts, and reoperation for completion of the disconnection or conversion to an anatomic hemispherectomy may need to be considered.

40.6 Clinical Pearls

Patient selection is vital to achieve good outcomes, and surgical decisions for these complex patients must be made with a multidisciplinary epilepsy team.

The family and patient need to have a good understanding of the risks of hemispheric disconnection, including hemianopia, hemiplegia and hydrocephalus.

For the correctly selected patient, a hemispherotomy utilizing more disconnection and less resection may be as effective as a larger hemispherectomy with lower surgical morbidity.

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Chapter 41
Deep Brain Stimulation for Pediatric Movement Disorders

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41.1 Introduction

Deep brain stimulation (DBS) is a reversible technique of functional neurosurgery that is applied for the symptomatic treatment of hypokinetic (Parkinson's disease) and hyperkinetic movement disorders (tremor, dystonia, myoclonus, dyskinesias and Tourette syndrome) [1], as well as neuropsychiatric disorders.

DBS was developed initially in 1960s as a technique to treat neuropathic pain, without notably good results, while movement disorders, especially parkinsonian and essential tremors, were treated around that time by lesions in various targets of the basal ganglia. Levodopa and the complications of ablative surgery sent DBS to oblivion until 1987, when the effect of high frequency stimulation mimicking a lesion allowed thalamic stimulation to treat tremor safely [2]. Afterwards, different targets have been explored and indications have expanded.

DBS obtained CE marking as a treatment for essential tremor in 1993, for Parkinson's disease in 1998, for dystonia in 2003, for obsessive-compulsive disorder in 2009, and for epilepsy in 2010. The FDA approved DBS for essential tremor in 1997, for Parkinson's disease in 2002, for dystonia in 2003, for obsessive-compulsive disorder in 2009, and for epilepsy in 2018. There are clinical trials for

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chronic pain, major depression, Tourette syndrome, epilepsy, obesity, anorexia and Alzheimer's disease.

DBS in children has been applied predominantly for the treatment of dystonia [3, 4], although it has also been applied to other hyperkinetic movement disorders (chorea, tardive dyskinesias, etc.) [5]. Considering this fact, this chapter will refer first and foremost to dystonia.

Dystonia is defined as "a movement disorder produced by a simultaneous and sustained tonic contraction of agonist and antagonist muscles causing abnormal postures, repetitive and twisted movements, weakness, and osteo-articular deformities" [6].

Pallidotomy had previously demonstrated its effectiveness for tardive dyskinesias in Parkinson's disease and for dystonia [7–9], but the long-term decrease in efficacy [10] led to the application of deep brain stimulation techniques. However, pallidotomy continues to play a role in selected cases [11, 12].

Without treatment, dystonia is associated with serious complications such as skeletal deformities, language difficulties (dysarthria or anarthria, dysphonia or aphonia), feeding difficulties (dysphagia, malnutrition), respiratory problems, sleep disorders, pain and a high degree of dependency for all activities of everyday life. It should be noted that, in most cases, cognitive functions are preserved, being the patients aware of their situation [1].

41.2 Basal Ganglia Anatomy

Dystonia has traditionally been considered a disease of the basal ganglia and thalamus, though more recently it has been emphasized that dystonia arises as a consequence of disruptions across a much broader whole-brain network, including regions of the cerebral cortex, brainstem and cerebellum. The input nuclei of the basal ganglia, the caudate, and putamen, receive excitatory input from almost all cortical areas. The main output nuclei are the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticularis (SNpr). The GPi sends inhibitory outputs to pallidal receiving areas of the motor thalamus and brainstem nuclei [13]. A schematic representation appears in Fig. 41.1.

41.3 Classification of Dystonia in the Pediatric Age

A new classification scheme for dystonia was proposed in 2013 by Albanese et al. [6]. The diagnosis of dystonia was divided into two main axes: (1) the clinical features and (2) etiology. See Table 41.1.

This classification of Albanese is an evolution of the classical and etiogical division of dystonia into primary and secondary dystonia. Currently, the term "primary dystonia" is used as an etiological descriptor for genetic or idiopathic cases in which dystonia is isolated and there is no consistent pathologic change. While the term "secondary dystonia" may indicate non-isolated dystonia, a defined pathology or

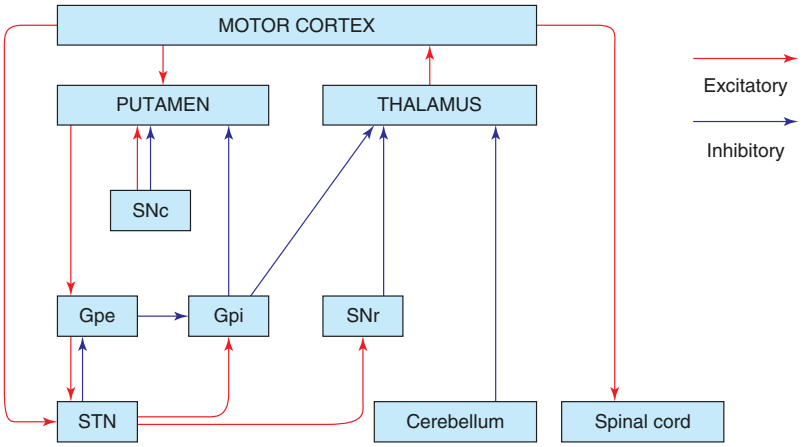

Fig. 41.1 Schematic representation of the connections of the basal ganglia, thalamus and cerebellum. Excitatory connections are represented by red arrows, inhibitory connections by blue arrows. Abbreviations: *GPe* Globus Pallidus Externa, *GPi* Globus Pallidus Interna, *SNc* Substantia Nigra Pars compacta, *SNr* Substantia Nigra Pars Reticulata, *STN* Subthalamic Nucleus. Modified from Lumsden et al. [13]

Table 41.1 Classification for dystonia

Axis I. Clinical characteristics	Axis II. Etiology
Clinical characteristics of dystonia	Nervous system pathology
Age at onset	Evidence of degeneration
• Infancy (birth to 2 years)	Evidence of structural (often static) lesions
• Childhood (3–12 years)	No evidence of degeneration or structural lesion
• Adolescence (13–20 years)	Inherited or acquired
• Early adulthood (21–40 years)	Inherited
• Late adulthood (>40 years)	• Autosomal dominant
Body distribution	• Autosomal recessive
• Focal	• X-linked recessive
• Segmental	• Mitochondrial
• Multifocal	Acquired
• Generalized (with or without leg involvement)	• Perinatal brain injury
• Hemidystonia	• Infection
Temporal pattern	• Drug
• Disease course	• Toxic
– Static	• Vascular
– Progressive	• Neoplastic
• Variability	• Brain injury
– Persistent	• Psychogenic
– Action-specific	Idiopathic
– Diurnal	• Sporadic
– Paroxysmal	• Familial
Associated features	
Isolated dystonia or combined with another movement disorder	
• Isolated dystonia	
• Combined dystonia occurrence of other neurological or systemic manifestations	
• List of co-occurring neurological manifestations	

Table 41.2 Genetic dystonia presenting in childhood

Symbol	Gene	New phenotypic designation	Additional information	Inheritance
DYT1	*TOR1A*	DYT-TOR1A	Early onset, generalized dystonia	AD
DYT3	*TAF1*	DYT-TAF1	Lubag	X-linked
DYT4	*TUBB4A*	DYT-TUBB4A	Whisper dystonia in adults H-ABC (hypomyelination with atrophy of basal ganglia and cerebellum) syndrome in children	AD sporadic
DYT5a	*GCH1*	DYT-THAP1	Dopa-sensitive dystonia	AD
DYT5b	*TH*	DYT-GNAL	Dopa-sensitive dystonia	AR
DYT6	*THAP1*	DYT-THAP1	Adolescent, mixed type dystonia	AD
DYT8	*PNKD*	DYT-MR1	Paroxysmal non-kinesigenic dyskinesia (PNKD)	AD
DYT10	*PRRT2*	DYT-PRRT2	Paroxysmal kinesigenic dyskinesia (PKD)	AD
DYT11	*SGCE*	DYT-SGCE	Myoclonus dystonia syndrome	AD
DYT12	*ATP1A3*	DYT-ATP1A3	Rapid-onset dystonia, parkinsonism	AD
DYT16	*PRKRA*	DYT- PRKRA	Young-onset dystonia-parkinsonism	AR
DYT18	*SLC2A1*	DYT-SLC2A1	Paroxysmal exertion-induced dyskinesia 2	AD
DYT24	*ANO3*	DYT-ANO3	Cranial-cervical dystonia, tremor	AD
DYT25	*GNAL*	DYT-GNAL	Adults, dystonia of cranial-cervical onset	AD
DYT 28	*KMT2B*	DYT-KMT2B	Early onset, generalized dystonia	AD

more generally a known etiology. The known genetic causes of dystonia presenting in childhood are summarized in Table 41.2.

Concepts relating to “pure dystonia” and “dystonia plus” syndromes are useful for clinical application, and they are based on phenomenology, not etiology. While etiology provides the organizational principle for “heredodegenerative” and most “secondary” categories. Secondary dystonia usually presents with evidence of structural lesions (bilirubin encephalopathy or kernicterus, inborn errors of metabolism like Lesch Nyhan or glutaric aciduria) or degeneration (abnormal iron deposition in Neurodegeneration with Brain Iron Accumulation disorders). Furthermore, this term could be associated with acquired causes of dystonia (perinatal brain injury, infection, neoplastic) [6, 14, 15].

Dystonia is usually a fluctuating state, and clinically the intensity varies. At its most extreme, periods of severe dystonia may be life-threatening and the most commonly used term to describe this condition is “status dystonicus”. Manji et al. described the condition as an increasingly frequent and severe episodes of generalized dystonia which require urgent hospital admission [16, 17].

41.4 Dystonia Assesment: The Burke-Fahn-Marsden Dystonia Rating Scale

The Burke-Fahn-Marsden Dystonia Rating Scale (BFM-DRS) [18] was introduced to assess generalized dystonia patients. It is composed of a motor part assessing dystonia and a part assessing the resulting disability. The motor subscale evaluates two clinical features of dystonia (severity and provoking factors) in eight body regions (eyes, mouth, neck, and the four limbs) and one functional area (speech and swallowing). Severity ranges from 0 (no dystonia) to 4 (severe dystonia). The provoking factors assess the situation under which dystonia occurs and range from 0 (no dystonia) to 4 (dystonia at rest). These two features, severity and provoking factors, are multiplied and then scores are summed, except for the eyes mouth and neck which are halved before summing as they are considered regions of lower weight. The resulting maximum total score on the BFM severity is 120. The BFMDRS section on disability assesses the effects of dystonia on ADL (speech, handwriting, feeding, eating/swallowing, hygiene, dressing, and walking), and the total maximum score is 30 [19]. A scheme of BFM-DRS is shown in Table 41.3.

Table 41.3 Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) scheme

Motor evaluation						
Area	Provoking factor		Severity		Weight	Result
1. Eyes	(0–4)		(0–4)		0.5	
2. Mouth					0.5	
3. Phonation/swallowing					1	
4. Neck					0.5	
5. Right arm					1	
6. Left arm					1	
7. Trunk					1	
8. Right leg					1	
9. Left leg					1	
					Total	/120
Disability evaluation						
Function	Language	Writing	Feeding	Swallowing	Hygiene	Walking
Severity	(0–4)	(0–4)	(0–4)	(0–4)	(0–4)	(0–6)
					Total	/30

41.5 Treatment of Dystonia

The medical treatment of generalized dystonia is ineffective in most cases [20]. In patients with dystonia and parkinsonism (e.g. mutations in the Parkin gene), or in those with primary defects in dopaminergic synthesis (e.g. Segawa disease), dystonia can be dopa-sensitive and improve significantly with levodopa. In the remaining dystonias, anticholinergic drugs, dopamine antagonists, baclofen or benzodiazepines commonly produce minimal clinical benefits and great side effects. Botulinum toxin is useful only in focal dystonia. However, different from adults in whom dystonia is usually focal or segmental, in children dystonia is more frequently generalized and could be rapidly progressive [21]. The intrathecal baclofen pump can improve muscle tone, but not motor function, and consequently has a palliative indication in "secondary dystonia" [22].

Bilateral DBS is the treatment of choice in "primary dystonia" refractory to medical treatment and has also been applied in other secondary dystonia with partial clinical improvement [23]. Status dystonicus (SD), a medical emergency that could result of heterogeneous conditions with nonuniform underlying physiology, is potentially reversible. DBS is considered the most efficient therapeutic approach and should be proposed early in its treatment of SD [24, 25].

41.6 Efficacy of DBS in Dystonia

Across all patients reviewed by Hale et al. BFMDRS-M scores improved 43.8 ± 36 after surgery with 45% of individuals achieving ≥50% improvement, while BFMDRS-D improved by 43.7 ± 31 with 45% achieving ≥50% improvement [20]. As we have discussed previously, the efficacy of DBS will depend on the etiology of dystonia:

A. Primary dystonia (DYT-TOR1A, DYT-SCGE or without identifiable genetic cause):

   The efficacy of DBS in generalized idiopathic dystonia has been demonstrated in various centers worldwide [26–29]. Patients with primary dystonia are more likely to experience >50% improvement in BFMDRS-M scores after surgery compared to patients with other causes of dystonia. Improvement ranges from 63 ± 31% [30]. There is a better prognosis in pediatric patients and young adults, with a short time of evolution, who have not developed osteo-articular deformities, and in dystonia with a greater phasic component than in those with severe tonic postures. Patients with mutations in the *TOR1A* gene [31] and *SGCE* gene [32], also called myoclonic dystonia, have the best prognosis. The motor improvement of dystonia is associated with an improvement in functional

Table 41.4 Efficacy of DBS based on the etiology

Primary dystonia		32–94%
	DYT-1(TorsinA)	60% [31]
	DYT-11 or myoclonus dystonia (SGCE+)	61–93%/30–60% [32]
Secondary dystonias		10–25%
	Infantile cerebral palsy	28.5% [40]
	PKAN	24–80% [41]

capacity for activities of daily life and a better quality of life. Cognitive functions are not modified by DBS [33].

B. Secondary dystonia

Patients with secondary dystonia obtain less benefit from surgery than those with primary dystonia [34]. In patients with secondary dystonia, the improvement in the BFMDRS scale would be 10–25%, but sustained over time [35–37] and preventing the appearance of contractures, which is why they are also considered candidates for surgery. The benefit of surgery seems to be conditioned by the structural integrity of the basal ganglia [38].

Patients with dystonia secondary to infantile cerebral palsy (PCI) require special mention. PCI is the most common cause of dystonia in children. About 10% of patients with PCI present a dyskinetic form. Early improvement of muscle tone and dystonic postures could prevent progression towards fixed contractures and dependency [39, 40].

Secondary dystonia caused by neurometabolic diseases has also been treated with DBS. Among them, pantothenate kinase deficiency (the most frequent NBIA disorder) shows an improvement of 24–80% [41, 42].

In some cases, a patient could present a complex movement disorder, with dystonia that could be associated with choreoathetosis. Chorea-Acanthocytosis or GNAO1-related encephalopathy are two examples that have demonstrated good response to GPi-DBS [43, 44].

In both primary and secondary dystonias efficacy correlates inversely with the duration of the disease [45–47].

Table 41.4 summarizes the efficacy of DBS based on the etiology.

41.7 Cost Benefit

There are several published literature that have analyzed the costs and benefits of DBS for patients with dystonia and have shown that, despite the high cost of this therapy, it represents a gain in QUALY (quality-adjusted life-year) [48, 49].

41.8 The Importance of Patient Selection

Appropriate patient selection will be based on a multidisciplinary evaluation including pediatric neurologists, neurosurgeons, rehabilitators and neuropsychologists. All of these members should be familiar with understanding when during the course of each illness it is appropriate to consider the use of DBS.

Patients referred for DBS surgery for treatment of dystonia should undergo a detailed history of illness and physical examination to determine the dystonia type and possible etiology. As mentioned, DBS is most often indicated in the treatment of isolated dystonias or "primary dystonias". In this group, profound improvements in the severity of dystonia have been reported, maintaining the beneficial effect for several years. On the other hand, symptomatic or "secondary dystonia" is known to be less responsive to DBS, the reasons for which remain unclear. A special mention is required for status dystonicus, due to different etiological conditions, where outcomes improved in recent years, potentially as a consequence of increasing use of DBS [13, 17].

In recent years, some progress has been made in the patient selection process. Somatosensory Evoked Potentials (SEPs) and Central Motor Conduction Times (CMCT) have been recently studied as predictors of the outcome from Deep Brain Stimulation (DBS). Accordingly, better outcome was seen in those children with normal versus abnormal CMCT or normal versus abnormal SEPs. These associations were independent of dystonia etiology and cranial MRI findings; therefore, they can exceedingly contribute to patient selection in "secondary dystonia" [50].

Reasonable expectations on the part of the patient and their family regarding the outcome from DBS treatment should be discusses and must cover the less positive results reported for dysphonia and dysarthria and the development of tolerance to DBS in some cases. In the case of neurodegenerative "secondary dystonias" (e.g. NBIA) it is also essential to remark on the possible loss of beneficial effect secondary to the evolution of the disease [42, 51].

The features of dystonia should be monitored before DBS using the most appropriate among the available dystonia scales (BFMDRS).

General preoperative screening of cognition in patients with dystonia to evaluate baseline cognitive status and monitor for possible postoperative changes is recommended, although, the current evidence suggests that Gpi DBS does not cause cognitive decline in primary dystonia [52]. Similarly, assessment of quality of life (QoL) is crucial to determine the impact of the surgery on Activities of daily living [19].

Once a dystonia patient has been properly evaluated and screened for DBS, it is important to counsel the patient on the degree of expected improvement in symptoms with DBS treatment. Patients with primary generalized dystonia generally have the best outcome, with improvements of 50–70% as measured by the BFMDRS

movement score commonly achieved. In the contrary, secondary dystonia typically responds more modestly (10–20%), although this level of improvement can be clinically significant.

Patients and parents additionally need to understand that the benefits of DBS will take time to accrue, considering that a number of visits may be required to optimize DBS programming.

41.9 Surgical Technique

Deep brain stimulation (DBS) surgery in dystonic patients basically consists in placing two brain electrodes usually at the dorsal and posterior part of the Globus Pallidus internus (GPi), a neurostimulator and two connecting cables between the pallidal electrodes and the neurostimulator [53]. The subthalamic nucleus (STN) has also been postulated as a stimulation target isolated [54, 55] or combined with the GPi [56].

In adult patients this surgery is usually performed in two stages: placement of the brain electrodes with the patient awake under local anesthesia during the first stage, and the neurostimulator and the connecting cables with the patient under general anesthesia on the second one. In our pediatric patients, we prefer to perform it under general anesthesia in a single stage and monitor the electrode placement using intraoperative neurophysiological techniques [57, 58]. However, there are hospitals that also operate pediatric patients awake [59].

The surgical technique for placing the electrodes at the level of the GPi has evolved enormously in recent years and there is great variability between surgeons and hospitals. However, in all cases it is based on stereotaxic principles.

Stereotaxic coordinates based on the Schaltenbrand-Wahren [60] and Talairach [61] atlas were initially used to locate the GPi. At present, direct MRI localization is preferable [53]. The target is chosen on an axial slice at the level of the anterior commissure (AC) at the junction between the two posterior quarters of the GPi. The software automatically calculates x, y and z coordinates. See Fig. 41.2a, b. The electrode direction is planned in the anterolateral direction as vertical as possible avoiding vessels, sulci and ventricles. Finally, it is confirmed that the position of the contacts is included in the GPi and that the tip of the electrode or its projection touches the lateral border of the optic tract in the three planes [57].

A stereotaxic framework (such as Leksell®), a neuronavigation-based guidance system (Nexframe®), a robotic arm (Neuromate® or Rosa®) [55, 62], a 3D printed disposable frame (STarFix®) [63] or a MR-guided system (Clearpoint®) [64] can be used to execute the trajectory. All these systems are based on stereotaxic coordinates. Some of these stereotaxic systems are shown in Fig. 41.2c–g.

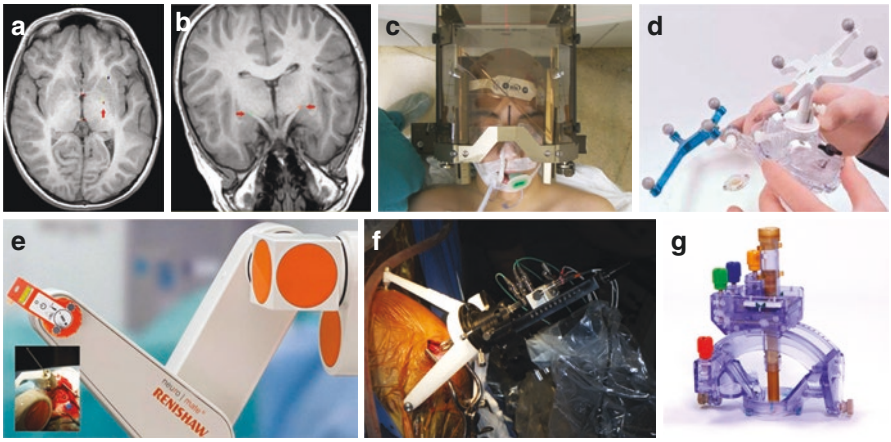

Fig. 41.2 Target location and systems for electrodes insertion: (**a**) GPi target chosen on an axial slice at the level of the (AC) commissure at the junction between the two posterior quarters of the GPi. (**b**) The trajectory ends at the lateral border of the optic tract. (**c**) Leksell® stereotaxic frame. (**d**) Nexframe® neuronavigation guided system. (**e**) Neuromate® stereotaxic robot. (**f**) STarFix® and (**g**) Clearpoint® system

41.10 Neurostimulation

The electrophysiological basis of this treatment is still unknown. High-frequency electrical stimulation through implanted electrodes mimics the effects of lesioning procedures previously employed (thalamotomies, pallidotomies or subthalamotomies), suggesting the inhibition of the circuit of neurons that with their abnormal functioning contribute to the movement disorder. On the contrary, low-frequency stimulation provokes fiber activation [65].

Different mechanisms of action that would combine inhibitory and excitatory processes have been proposed: jamming of a feedback loop, activation of inhibitory structures included in a more complex network, blockade of membrane ion channels, depolarization blockade, synaptic exhaustion, induction of early genes, changes in local blood flow, neuroplasticity, among others [65].

These different mechanisms vary in importance depending on the pathology to be treated and the target stimulated and it is probable that some are more involved in the acute effects and others in the long term changes, close to neuroplasticity [65].

This modulation of neuronal activity does not generate irreversible anatomic lesions in the stimulation zones, but rather produces a reversible clinical effect and the patient could return to his baseline clinical situation in the event of system disconnection. This disconnection should be performed progressively to avoid a "rebound effect".

On the contrary, fiber bundles are consistently activated at low or high frequencies. The hypothetical mechanisms envisioned should therefore be compatible and

even produce these observed effects, to be acceptable as hypotheses. The mechanism could be either one or a combination of several causes: jamming of a feedback loop, activation of inhibitory structures included in a more complex network, blockade of membrane ion channels, depolarization blockade, synaptic exhaustion, induction of early genes, changes in local blood flow, neuroplasticity, etc. It is probable that some are more involved in the acute effects and others in the long-term changes, close to neuroplasticity.

Commercial neurostimulation systems allow to choose different stimulation modalities: monopolar or bipolar between different contacts located at different levels or orientations (Directional stimulation [66]) and to regulate the amplitude, the duration and the frequency of the electrical stimulus.

41.11 Early Postoperative Management and Initial Deep Brain Stimulation Programming

At least a 3–5-day in-hospital stay after DBS implantation is recommended for wound healing and effective postoperative pain management. When to start DBS programming to check benefits and side effects from stimulation settings varies in different centers from 2 days to 1 month [67]. The initial programming process begins with the review of the preoperative and intraoperative data. Checking electrodes placement post-operatively using MRI protocols is strongly advised.

Currently, certain software (e.g. SureTune® Medtronic) provide patient-specific visualization of lead location and simulated 3-dimensional volume of tissue activation helping make decisions on how to start programming the DBS therapy.

Regarding dystonia, there is a considerable heterogeneity of patients' features and stimulation settings. It must be pointed out that dystonia requires a prolonged period of stimulation in order to appreciate a symptomatic benefit, in contrast to rigidity and tremor. This is indeed also the case of tonic component of dystonia, while the phasic component may improve early after stimulation [68].

At our center, DBS in-patient stimulation begins 48 h after surgery on electrodes 0 or 1 in monopolar configuration with standard parameters: 1.5 V 60 μs 130 Hz that are maintained until the first revision 1 month later. A wide range of stimulation parameters has been shown to be effective for GPi DBS in dystonia and these initial parameters may vary from center to center. Many dystonic patients benefit from the insertional trauma-related effect in the immediate postoperative period; therefore, it is not possible to assess with certainty the effect of the parameters programmed at that time.

After 3–4 weeks, each electrode can be tested in monopolar configuration to map motor and visual stimulation-related adverse effects up to 3–4 V using pulse width of 60 μs and rate of 130 Hz. The main goal is to determine the thresholds for side effects (muscle pulling, involuntary movement, visual phosphenes, paresthesia,

confusion, malaise, nausea, etc.) for each contact with stepwise increase of amplitude (0.5 V).

Regarding adverse effects resulting from the position of the DBS lead,

1. if the DBS lead is too ventral, electrical current will spread to the internal capsule, causing tonic muscular contraction, and to the optic tract, causing phosphenes
2. if the DBS lead is too posterior, electrical current will spread to the internal capsule, causing tonic muscle contraction
3. when DBS leads are too anterior or too lateral, most often symptomatic benefits are lost and large volumes of stimulation may be required to extend the field posteriorly and medially to reach the appropriate targets.

If there are no adverse effects, the patient is followed every 2–4 weeks or until the best parameters are found. In general, it is advised to keep the medical treatment unchanged for 1–3 months postoperatively. If there is a clear general improvement, the same stimulation is maintained, and medications are carefully reduced. After the first programming, routine follow-up at 4–12 weeks and subsequently every 6 months are recommended. It seems reasonable to assess the benefit 6 months after surgery, with annual evaluations [68].

In case of adverse effects, the stimulation is moved one electrode dorsally or double monopolar stimulation is considered. If the results are still unsatisfactory, patients may be trialed with bipolar stimulation. The process may be repeated until the patient presents a considerable improvement of dystonia in absence of side effects. It is safer to give the opportunity to switch back to the previous setting in case of side effects or worsening of dystonia (setting one of the stimulation group with the previous stimulation parameters). It is important to emphasize that impedances should be checked in every visit.

41.12 Long-Term Management of DBS in Dystonia

Beneficial effects of Gpi DBS will be sustained up to 10 years after electrode implant in “primary dystonia”. In contrast, it may be difficult to predict the extent and duration of improvement for “secondary dystonia”.

Programming strategies for long-term management of DBS in dystonia are not uniform and are guided by the needs of individual patients. In the event of reoccurrence of dystonic symptoms in the long term, device-related complication and reprogramming should be considered.

Failures to stimulation, especially in patients with “primary dystonia”, should not be consent without further evaluation of the individual case. Electrodes that are

placed suboptimally should be revised. In some cases, with partial response, alternative targets for chronic stimulation might be considered.

Adverse events should be systematically recorded over the long-term follow-up. It is considered mandatory to monitor proper function of the neurostimulation device at each visit. The battery life of the stimulator must be taken into account to prevent sudden cessation of stimulation, particularly in severe segmental/axial or generalized dystonia with swallowing and respiratory symptoms related to dystonia [51].

41.13 Adverse Events

DBS is a safe technique considering that adverse events are infrequent and, allmost all of them, reversible [69]. Complications may arise in 14–50% of cases [29], as a result of adverse events derived from the stimulation system ("hardware-related") or from the stimulation itself.

Adverse events arising from the stimulation system/prosthesis can be intraoperative (hemorrhage, electrode malposition) or postoperative (infections, skin erosions, system disconnections, electrode migration, cable fracture, and neurostimulator failure/deprogramming) [51, 70, 71]. A large number of these problems will require surgical intervention.

Table 41.5 summarizes the complications related to the prosthesis.

Concerning adverse events derived from stimulation, they may be due to inadequate programming or to the appearance of secondary effects (mainly capsular) when trying to achieve therapeutic stimulation intensities in improperly positioned electrodes It is necessary to highlight that the adverse effects derived from stimulation are always reversible. In this regard, speech abnormalities (dysarthria, dysphonia, and stuttering) and parkinsonian motor sign (gait abnormalities, hypokinesia and micrographia) are the most common stimulation-related adverse events resulting from current spreading to the internal capsule or stimulation of the ventral contacts in Gpi stimulation, respectively. In each instance, these adverse events can be significantly reduced by decreasing the intensity of stimulation or by switching to dorsal contacts [68].

Table 41.5 "Hardware-related" complications

Infection	10.3%
Intracranial hemorrhage	0.8%
Fractures, malfunction, migration, extension cable tension	18.7%
Stimulation shutdown	3.4%

41.14 Special Characteristics in Pediatric Patients

Children with dystonia have specific needs derived from their young age [59]. For this reason, it is particularly important to develop this program within a specifically pediatric multidisciplinary unit [1].

We perform direct targeting of the GPi on the preoperative MRI and we have realized that using this method the x coordinate is 2–4 mm more medial than in most published series [45, 57, 72].

Nutritional status should be examined to prevent skin ulceration and infection specially in younger patients. In fact, in younger children with a poor nutritional state who require DBS surgery due to the severity of the disease, subfascial placement of the neurostimulator should be considered [57].

Brain growth following electrode implantation may also result in relative retraction of contact positions compared to the original target position. Brain growth has been previously modeled suggesting a relative retraction of brain electrodes of between 5 and 10 mm between 4 and 18 years, mostly occurring before 5 years of age and to a lesser extent between 5 and 7 years [73].

The third point is the use of general anesthesia in pediatric patients. In adult patients, the surgery is usually performed with the patient awake, if the severity of the dystonia allows it. Although some authors also operate on pediatric patients while the patients are awake [59], we prefer to do it under general anesthesia. Intraoperative neurophysiological tests can be useful to determine the proximity of the electrode to the internal capsule and the secondary effect threshold [57]. Intraoperative imaging (MRI [64] or CT [74]) are highly recommendable in asleep DBS surgery.

Finally, the young age of most patients and the high voltage required for the treatment of dystonia, makes advisable the use of rechargeable neurostimulators in these patients [75] to prevent numerous replacements and its potential complications and financial cost along patient's lifetime.

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Chapter 42
Deep Brain Stimulation in the Management of Neuropsychiatric Conditions in Children

DBS in Paediatric Neuropsychiatric Diseases

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Abbreviations

AB	aggressive behaviour and self-harm
ALIC	anterior limb of the internal capsule
BNST	bed nucleus of stria terminalis
cg25	Broadman's area 25
CM	centromedian nucleus of the thalamus
DBS	deep brain stimulation
ED	eating disorder
GPi	globus pallidus internus [am = anteromedial, pv = posteroventral]
GTS	Gilles de la Tourette syndrome

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ITP	inferior thalamic peduncle
NAc	nucleus accumbens
OCD	obsessive compulsive disorder
pHyp	posterior hypothalamus
slMFB	superolateral branch of the medial forebrain bundle
STN	subthalamic nucleus
TRD	treatment resistant depression
VC/VS	ventral internal capsule/ventral striatum

42.1 Introduction

Psychiatric disorders remain refractory to treatment for a significant number of patients despite significant advances in pharmacological and non-pharmacological management strategies. Neurosurgery has provided an alternative option for patients with refractory psychiatric indications, where ablative therapy, including anterior cingulotomy, capsulotomy, limbic leucotomy were proven to be highly effective [1]. More recently, the advantages conferred by non-destructive, reversible and adjustable deep brain stimulation (DBS) therapy has favoured it over ablative procedures as the first choice option in most neurosurgical units worldwide.

Psychosurgery has had a highly controversial background, stemming from historical misuse and technological abuse in diverse patient populations with lack of ethical and regulatory oversight for ambiguous indications associated with considerable morbidity [2]. Because of that, current approach to neuromodulation with DBS in psychiatry has had to largely follow a structured ethical and regulatory route whilst advances in neuroimaging, stereotactic methods and neurosurgical tools have reduced the surgical risks.

Nonetheless, DBS therapy at present remains investigational for most psychiatric conditions with a lack of large-scale controlled studies to assess its efficacy and outcomes. At least partly this is related to the heterogenous symptoms and complex anatomy and biology of psychiatric disorders which make such studies difficult. This is even more evident in the paediatric population, where the stakes are significantly higher and where modulating the developing brain raises additional concerns. This chapter sets out to delineate the current evidence for DBS use in psychiatric conditions, highlighting the work done thus far in the paediatric population.

42.2 Scientific Evidences

A comprehensive review of the literature has recently detailed the state of art of potential applications of DBS in the management of complex neuropsychiatric conditions in adults and children [3]. Out of over seventy peer-reviewed studies reported so far, only 11 included patients under the age of 18 years. Among paediatric patients, the indications for surgery included GTS, AB and ED (Table 42.1)

Table 42.1 Deep brain stimulation for neuropsychiatric disorders in children

Author/Year	Study design	No. of patients	Age, years at surgery (range)	Indication	DBS target (s)	Uni/ Bilateral	Results (% improvement, mean)	Follow-up (mean, months)
Servello et al. (2009)	Observational, open label	35	17–57	GTS	Thalamus; GPi-pv; ALIC/NAc	Bilateral	50.3% (YGTSS)	3–24
Motlagh et al. (2013)	Open-label prospective	8	16–48	GTS	Thalamus, Gpi-am, GPi-pv	Bilateral	45% (YGTSS)	69
Nair et al. (2014)	Observational cohort	4	15–43	GTS	GPi-am	Bilateral	82.1% (YGTSS)	42.5
Sachdev et al. (2014)	Observational cohort	17	17–51	GTS	GPi-am	Bilateral	44.8% (YGTSS)	24.1
Johnson et al. (2019)	Multicentric, retrospective	110	14–61	GTS	CM, GPi-am, GPi-pv, NAc/ALIC	Bilateral	46.7% (YGTSS)	33.7
Martinez-Ramirez et al. (2019)	Multicentric, prospective	185	13–58	GTS	CM, GPi-am, GPi-pv, NAc/ALIC	Bilateral	45.1% (YGTSS)	12
Zhang et al. (2013)	Observational cohort	6	13–17	Anorexia	NAc	Bilateral	+28% (BMI 12.2 to 15.6)	1
Wu et al. (2012)	Observational cohort	4	16–17	Anorexia	NAc	Bilateral	+65%, (BMI 11.9 to 19.6)	38
Torres et al. (2013)	Observational cohort study	6	17–48	AB/DRE	pHyp	Bilateral	47% (ICAP); 30% reduction in DRE	6–82
Benedetti-Isaac et al. (2015)	Observational cohort study	9	16–33	AB/DRE	pHyp	Bilateral	65% (OAS); 89.6% seizure reduction	2–48
Tambirajoo & Furlanetti et al. (2020)	Observational cohort study	4	11–16	Lesch-Nyhan	amGPi/pmGPi	Bilateral	60.5% (BPI-frequency) 64% (BPI-severity)	22–98

GTS Gilles de la Tourette Syndrome, *GPi* globus pallidus internus, *am* anteromedial, *pv* posteroventral, *cm* centromedian nucleus of the Thalamus, *ALIC* anterior limb of the internal capsule, *NAc* Nucleus Accumbens, *YGTSS* Yale Global Tic Severity Scale, *AB* aggressive behaviour and self-harm, *OAS* Overt Aggression Scale, *pHyp* posterior hypothalamus, *DRE* drug resistant epilepsy, *ICAP* Inventory for Client and Agency Planning (maladaptative behaviour index), *N/A* not available, *BPI* Behaviour Problems Inventory

[4–14]. Despite of the large number of published works on the management of TRD and OCD with DBS among adult patients, consistent studies evaluating this approach in children are still lacking. The various brain targets approached for the treatment of the psychiatric conditions in children included the GPi, the ALIC or (VC/VS), the NAc, different nuclei of the Thalamus and the pHyp. The main findings and evidences available in favour or against DBS in the management of psychiatric conditions in patients under 18 years of age are discussed below.

42.2.1 Gilles de la Tourette Syndrome

42.2.1.1 Background

GTS is characterised by motor and vocal tics with a disease onset usually occurring before 18 years of age [15]. The onset of tic symptoms often begins in childhood, reaches a peak during the prepubertal period before gradually decreasing in the adolescence. Approximately 75% of children with GTS will experience a significant improvement in their symptoms by adulthood [15]. Children with severe and debilitating symptoms often have impaired quality of life (QoL) which is complicated by the presence of other psychiatric co-morbidities such as attention deficit/hyperactive disorder (ADHD), OCD, anxiety, depression and AB [16].

42.2.1.2 Surgical Management

Vanderwalle et al. 1999 reported the first three cases of DBS for GTS, using the centromedian nucleus—substantia periventricularis—nucleus ventro-oralis internus complex (CM-Spv-Voi) target, which was based on the stereotactic target used for ablative procedures introduced by Hassler and Dieckmann [17]. Multiple targets are currently in use including the dorsomedial nucleus of the thalamus, ventral anterior and ventrolateral motor part of thalamus, GPi (anteromedial part [am] and posteroventrolateral part [pl]), NAc and the ALIC. A pooled analysis of studies demonstrated that DBS for GTS had the highest efficiency amongst the psychiatric diseases [18].

Most of the studies for DBS in GTS have been conducted in adults with moderate to good clinical outcomes [19–26]. The first case series in 1999 of 3 patients aged 28–45 years had a 70–90% reduction in tic frequency and intensity over a follow up of 1–5 years [17]. A systematic review and meta-analysis of 57 studies involving 156 cases with a median age of 30.0 years ± 9.8 years (15–60 years) demonstrated a 52.68% reduction in the Yale Global Tic Severity Scale (YGTSS) scores [27]. No significant difference was seen in score reduction between the

different targets used. Overall vocal tic control was better than motor control [27]. Another long term study of post-DBS clinical outcomes in 110 patients in 13 centres demonstrated a median time of 13 months to achieve a 40% improvement in tics associated with a significant improvement in obsessive-compulsive behaviour with no appreciable differences across brain targets [8]. A prospective DBS database and registry of 185 patients in 31 centres with a mean age of 29 years (13–58 years) showed significant improvements in YGTCC score, motor and phonic tics [9]. There was a 35.4% incidence of adverse events (AE), with 3% rate of infections and 6% rate of dysarthria [9]. Another study reported on 15% risk of apathy exclusively seen with thalamic stimulation [28].

42.2.1.3 DBS for GTS in Paediatric Patients

The European Society for the study of Tourette Syndrome (ESSTS) initial guidelines in 2011 recommended that DBS should be reserved for resistant disease with well managed co-morbidities, an age limit of above 25 years, with the operation to be carried out in an experienced multi-disciplinary unit [21]. The updated guidelines in 2014 removed the 25-year-old age limit but recommended that ethical review should be sought for patients aged less than 18 years with careful and robust data collection [29]. A meta-analysis specifically looking at safety and efficacy of DBS in 58 children and young adults (mean age 17.9 ± 2.7 years, range 12–21 years) demonstrated an average of 57.5% ± 24.6% improvement in the YGTSS across the studies [30]. The presence of co-morbid depression correlated negatively with outcome and 25% experienced side effects, the majority of which were classed minor in nature. A single case report of a 15-year-old patient with extremely refractory GTS with associated OCD demonstrated an 81% improvement in YGTCC score and complete resolution of the OCD symptoms at 1 year after stimulation of ALIC/bed nucleus of stria terminalis (BNST), emphasising that young age should not be a contraindication for stimulation therapy in well selected patients [31]. Nevertheless, the application of DBS for OCD in the paediatric population is sparsely reported, since many children with OCD can spontaneously remit as they grow up [32, 33]. Also, the combination of pharmacotherapy and cognitive behavioural therapy can achieve remission rates as high as 50% [32, 33].

In the field of neuropsychiatric disorders, GTS represents the largest experience in terms of application of DBS as a treatment option in children. Since the first published case report over 20 years ago, there is now some evidence to support DBS as an effective and safe option for the treatment of medically refractory GTS in selected children and young adults. However, GTS is associated with high remission rates by early adulthood unlike movement disorders such as primary dystonia. Therefore, arguments for use of DBS in children for diseases that will have an eventual decrease in severity will need to include a rationale for possible persistence and for marked disability during symptomatic periods [34]. Uncontrolled GTS, especially if

associated with other comorbidities such as OCD, in a child may hinder social and educational development, irrespective of possible remission later in childhood and DBS offers the possibility of symptom control during this critical time [34]. However, the risk-benefit ratio of DBS needs to be considered in the light of symptom severity and adverse effect of alternative treatment [28]. Large prospective studies with long-term follow-up are needed for a better understanding of the impact of neuromodulation at different targets on the course of the disease in children.

42.2.2 Eating Disorders

42.2.2.1 Background

Even though early treatment of adolescents with anorexia nervosa (AN) is successful in 30–60% of patients, management of patients with symptom duration of longer than 3 years is more challenging [35]. Outcomes are poor with a high mortality rate in those with an established disease despite the best available psychological treatments [36]. Patients with severe AN are extremely aversive to eating and weight gain with pathologically rewarding behaviours of food restriction and other weight-loss behaviours [37]. AN has a strong association as a comorbidity with other psychiatric disorders and has shown improvement in outcomes after DBS for concomitant OCD or TRD [37, 38].

42.2.2.2 Surgical Management

Blomstedt et al. (2017) reported a female patient with TRD and AN who had DBS of BST with resultant subjective improvement in food and eating anxiety without any significant effects on the BMI [39]. Another paper reports of a female patient with refractory OCD and AN who underwent VC/VS-DBS with subjective improvement in AN symptoms with neuromodulation [40]. A single case report of a female patient with restrictive AN and chronic recurrent depression who underwent subgenual cingulate stimulation resulted in a BMI sustained above 19.1 for 2 years with no further interventions or hospitalisation required for the AN [41].

A pilot study looking at DBS in AN specifically was carried out in six patients using the subcallosal cingulate as the target [42]. Fifty per cent of patients maintained BMI greater than at baseline at 9 months with a similar number reporting improved QoL. One adverse event (Seizure) was attributed to metabolic disturbances [42]. A one-year follow-up open label trial of 16 patients (aged 20–60 years) with an average BMI of 13.83 and 88% incidence of co-morbid mood disorders, anxiety disorders or both demonstrated significant improvements in depression, anxiety and affective regulation with subcallosal cingulate stimulation [43]. Interestingly, significant changes in glucose metabolism in key AN-related

structures were noted at 6- and 12-months post stimulation. 44% had serious AEs related to the underlying illness and two patients requested device removal or deactivation during the study [43]. Another study of two adult patients with intractable AN who underwent stimulation of the NAc reported improved BMI at 1 year with no AE [44].

42.2.2.3 DBS for Eating Disorders in Children

Wu et al. specifically focused on the role of DBS in paediatric AN [11]. They undertook a study in four female patients aged 16–17 years with an average baseline BMI of 11.9, using the NAc as the target. Three patients had OCD and the fourth had generalised anxiety disorder. Significant increase in BMI was seen in all four patients with an average 65% increase in body weight after a mean follow-up of 38 months [11].

Despite the promising initial results, including in the paediatric age group, DBS in AN is high-risk and remains investigational with a current lack of consensus on the optimal target [38]. Severe chronic malnutrition leads to an increased risk of surgical complications and longer-term clinical outcomes are currently unknown. An ongoing longitudinal study is presently investigating the feasibility and efficacy of NAc-DBS in severe and enduring AN with a further aim to assess any subsequent neural changes and to develop an ethical gold standard to guide treatment applications [45]. What is already clear though is the need for multimodal therapy in this difficult to treat disorder where DBS's success will be highly dependent on other measures, including pre-surgical weight optimisation, psychological input and metabolic resuscitation.

On the other end of the eating disorders spectrum lies binge eating and obesity. To date, only few studies have reported the use of neuromodulation in the management of obesity with conflicting results. Pre-clinical and clinical studies have shown that neuromodulation of the lateral hypothalamic area (LHA) can result in weight loss [46–48]. Hamani et al. reported a loss of 12 kg in 5 months in a patient treated with LHA-DBS [48]. By turning off stimulation, the patient reverted to binging and weight gain [48]. However, Franco et al. showed LHA to be ineffective in improving anthropometric measures in a cohort of four obese patients with Prader-Willi Syndrome [49]. Four other case reports have investigated the role of neuromodulation of the NAc in the management of obesity (total of six patients) [50, 51]. Despite evidence of weight loss with NAc-DBS, one patient committed suicide and another decided to have the DBS system removed after 13 months [50]. Authors caution other groups regarding the high risk and complexity of these patients due to the associated psychiatric comorbidities, such as refractory depression, anxiety and personality disorders, and the need for well-designed studies, strict enrolment criteria and close psychiatric monitoring in trials addressing DBS management in morbidly obese patients [50].

In patients with refractory eating disorders, DBS appears to be feasible and of some advantage. Six clinical studies, including prospective trials, [42, 43, 52] reported on the safety and efficacy of DBS treatment of anorexia. Two other papers focused on or included paediatric patients in their analysis, showing a mean increase in BMI ranging from 28% to 65% with no additional risks compared to older patients with AN undergoing surgery [10, 11].

The mechanism of action of DBS in eating disorders is unclear and there remains scope for optimisation, an area worthy of further exploration given the high rate of morbidity and mortality associated with AN. Pre-clinical and clinical studies have shown that the mechanisms of reward and neural networks involved in eating disorders overlap, to some extent, at key structures along the fronto-striatal and mesolimbic pathways with circuits responsible for other neuropsychiatric disorders, such as depression, OCD and addiction [53, 54]. The ventral tegmental area sends mesolimbic and mesocortical dopaminergic projections to the NAc and to the prefrontal cortex via medial forebrain bundle [53, 54]. During the last decades, different structures of this network, such as slMFB, ALIC, NAc and cg25, have been targeted using ablative or neuromodulation techniques in the management of various neuropsychiatric conditions [53]. Therefore, further understanding of the underlying mechanisms of the diseases will allow a more personalized treatment, choosing the correct target for the correct individual patient.

42.2.3 Aggressive Behaviour and Self-Harm

42.2.3.1 Background

Self-harm behaviour is usually caused by perinatal insults, brain malformations and/or genetic syndromes, and is usually associated with mental and cognitive impairment, hyperkinesia, destructiveness of objects and aggressiveness [12, 13]. This dramatic condition is often refractory to medical treatment, precludes proper care and makes the use of restraining measures necessary in order to avoid harm to the patient and carers.

42.2.3.2 Surgical Management

Historically, stereotactic surgical procedures have been employed in an attempt to alleviate these symptoms, such as cingulotomy, amygdalotomy, dorsomedial thalamotomy and, [13] also the posteromedial hypothalamotomy as proposed by Sano et al. [55] Lesion of the pHyp was shown to be effective, to some extent, in 95% of the patients, with results considered “satisfactory” in up to 84% of the cases [55]. More recently, three groups reported on the use of bilateral DBS of the pHyp in a total of 22 patients with self-harm behaviour, refractory epilepsy and severe

cognitive impairment [12, 13, 56]. Franzini et al. reported an overall 65% improvement of the Overt Aggression Scale (OAS) and 50% improvement of epilepsy in two out of seven adult patients.

The ethical consideration on surgery for behavioural disorders limit the widespread application. Nonetheless the current evidence does suggest clinical benefit in carefully selected patients, including children, with severe self-harm refractory behaviour such as in Lesch-Nyhan syndrome [57].

42.2.3.3 DBS for Aggressive Behaviour and Self-Harm in Children

Torres et al. (2013) and Benedetti-Isaac et al. (2015) also included paediatric patients in their series, reporting dramatic behavioural improvement in eight out of ten patients with long-term follow-up (mean, 44 months) [12, 13]. Tambirajoo et al. 2020 recently published the long-term clinical outcomes and connectivity profiles in four children undergoing GPi-DBS for Lesch-Nyhan syndrome [58]. Bilateral DBS of the posteroventral (motor) and anteromedial (cognitive/behavioural) GPi using four electrodes led to clinical improvement of self-harm behaviour and motor control, which was not only dependent on the position of the active contacts within the GPi itself, but also strongly correlated with specific connectivity patterns between the basal ganglia and distant cortical brain regions. These findings shed light on the underlying mechanisms of DBS in the treatment of this complex condition and, in line with the literature, indicate a potential benefit of DBS in the management of drug-refractory aggressive behaviour in selected cases.

42.2.4 Autism Spectrum Disorder

ASD consists of a group of neurodevelopmental conditions altering cognitive and behavioural function, with an estimated prevalence of 1% worldwide [59]. The DSM-5 defines autism spectrum with high functioning patients capable of living on their own at one end, and those with severe symptoms at the other. Core to the definition of ASD are: (1) early-onset difficulties in social interaction and communication, (2) repetitive, restricted behaviours and interests [60]. Patients in the low functioning end of the ASD spectrum very often present with self-injurious behaviour, poor social interaction and other potentially life-threatening psychiatric features [59, 61]. Although medical management may improve some of these symptoms, a considerable subset of the patients turns out to be refractory to conservative treatment. Recently, reports have emerged on the use of DBS as an adjuvant tool in the management of a total of four severe refractory ASD patients, mainly as an attempt to decrease aggressivity and self-harm [62–64]. The basolateral nucleus of the amygdale (BLn) was targeted in two patients, [63, 64] the GPi in one patient and both the GPi and the ALIC in the other [62]. The authors concluded that

neuromodulation of the BLn may be an effective adjuvant tool for the management of self-harm behaviour and aggression, whereas the GPi or ALIC could be a target for the treatment of OCD-like symptoms in these patients. Nevertheless, clearly further long-term controlled trials are needed to better understand the role of surgical management in ASD.

42.3 Complications

The rates of serious surgical complications of DBS for psychiatric diseases are low, and in general comparable to those seen with DBS for movement disorders [28]. The most serious reported AE in psychiatric patients submitted to DBS were intracranial haemorrhage and suicide/suicidality. However, since psychiatric patients are usually younger, the risk of intracranial haemorrhage is expected to be lower [28]. On the other hand, Saleh et al. (2015) has shown higher suicidality rate (5.9%), increased in not only patients with TRD but also those with OCD and GTS [28] OCD patients had a high rate of postoperative mood changes [28]. Hardware related complications and infection occurred in 14.3% and 7.7% of the patients with higher infection rates in the GTS group. Of particular relevance to the paediatric patients, the infection risks tend to be higher compared to the adult patients. We recently reported a surgical site infection rate of around 10% in 129 patients undergoing DBS for dystonia with a mean age of 10.8 y (range 3.0–18.75) at a mean follow up of 3.3y (range 0.5–10.3). However, the DBS infection rate was 4.7% in the under 7-year-old cases [65]. Specific strategies are therefore required to reduce and manage these risks.

42.4 Perspectives and Challenges

A number of ethical considerations arise when considering DBS in psychiatric conditions. The selection of potential participants is important for optimising efficacy and safety. Although limited standardised criteria exist at present, [29] selection criteria should include patients who are physically, emotionally and cognitively capable of understanding and undergoing surgery [66]. This is particularly important in the children and will require specific frameworks and pathways. The presence of a stable social environment and the family members is also imperative. Informed consent can be challenging but with the inherent risks that DBS surgery carries, it is crucial that a comprehensive informed consent is obtained. As DBS procedures are often considered as “last resort” options, desperation on a patient or carer’s part can undermine the informed consent process due to possibly unreasonable high expectations clouding the appreciation of the various treatment options

and alternatives [67]. Pre-surgical expectation management and goal setting are therefore critical to achieve good patient satisfaction, both at the short and long term, highly relevant to the paediatric patients and their carers [68].

Interest in neuromodulation in the management of neuropsychiatric disorders continues to grow and remains an area of active research. Three main factors have been expressed as potential causes of failure of important clinical trials evaluating DBS in the management of neuropsychiatric disorders, and should be addressed in future prospective studies: a) premature evaluation endpoints; b) variable surgical protocols and selection of ideal brain targets; c) heterogeneous patient selection and lack of biomarkers predictive of favourable outcome [69–71]. Although current data available may support surgical intervention for the treatment of some refractory psychiatric conditions in the paediatric population, large long-term randomised trials are rare and thus the threshold for surgical neuromodulation in a child must remain high. A multidisciplinary approach to assessment and treatment by an experienced team is paramount if surgery is being considered. High quality research to further explore the ideal brain targets for specific indications, incorporating the ethical concerns and the potential influence of DBS therapy on the developing brain and vice versa, is needed. Well-designed translational neuromodulation research and functional connectivity analysis using cutting-edge imaging technology might shed light on the brain networks involved, the plasticity of the developing brain and the underlying mechanisms of neuropsychiatric disorders in paediatric patients paving the way towards personalised neuromodulation [8, 70, 72–74].

42.5 Final Remarks

The application of DBS for psychiatric indications has progressed at a steady pace in the adult population and at a much slower pace in the paediatric population. Despite of its approved use as an adjuvant strategy in the management of OCD, and encouraging results reported in the treatment of GTS and TRD, DBS for psychiatric disorders in paediatric patients remains largely investigational. The stakes are much higher in children and adolescents. Future multidisciplinary studies in children should be done in a long-term trial setting with strict and robust criteria and conduct to minimise the effect of harm and maximise the data and evidence on efficacy and safety of DBS therapy. A move towards personalising DBS therapy and exploration of new stimulation techniques will provide new frontiers and possibilities in this growing field.

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Chapter 43
Spasticity

George Georgoulis

Spasticity is defined as a velocity-dependent resistance to passive movement of a joint and its associated musculature. Spasticity is characterized by hyperexcitability of the stretch reflex related to the loss of inhibitory influences from descending supraspinal structures. Spasticity should not be treated just because it is present because it may serve to compensate for loss of motor power. Spasticity should be treated only when excessive tone leads to functional disability and impaired locomotion, or contractures and deformities. Neurosurgical interventions should be considered when the harmful spasticity couldn't be controlled by physical therapy and medications.

The disorder from cerebral palsy (CP) encompasses a group of conditions that are permanent but not unchanging. Cerebral palsy involves disorders of movement, posture, or both, and of motor function. As in adults, spasticity in children can be either useful for function or detrimental. Efficient treatments are available for spasticity in children with cerebral palsy, including botulinum toxin injections, intrathecal baclofen, dorsal rhizotomies (Fig. 43.1). These treatments can be used in isolation or in combination with orthopedic surgery. Selection of the correct treatment is difficult in children because they are still developing, and their needs may change as they grow. To formulate a treatment plan, one must project into the future by extrapolating the extent and severity of musculoskeletal contractures and their harmful consequences as well as the positive effects of spontaneous psychomotor development.

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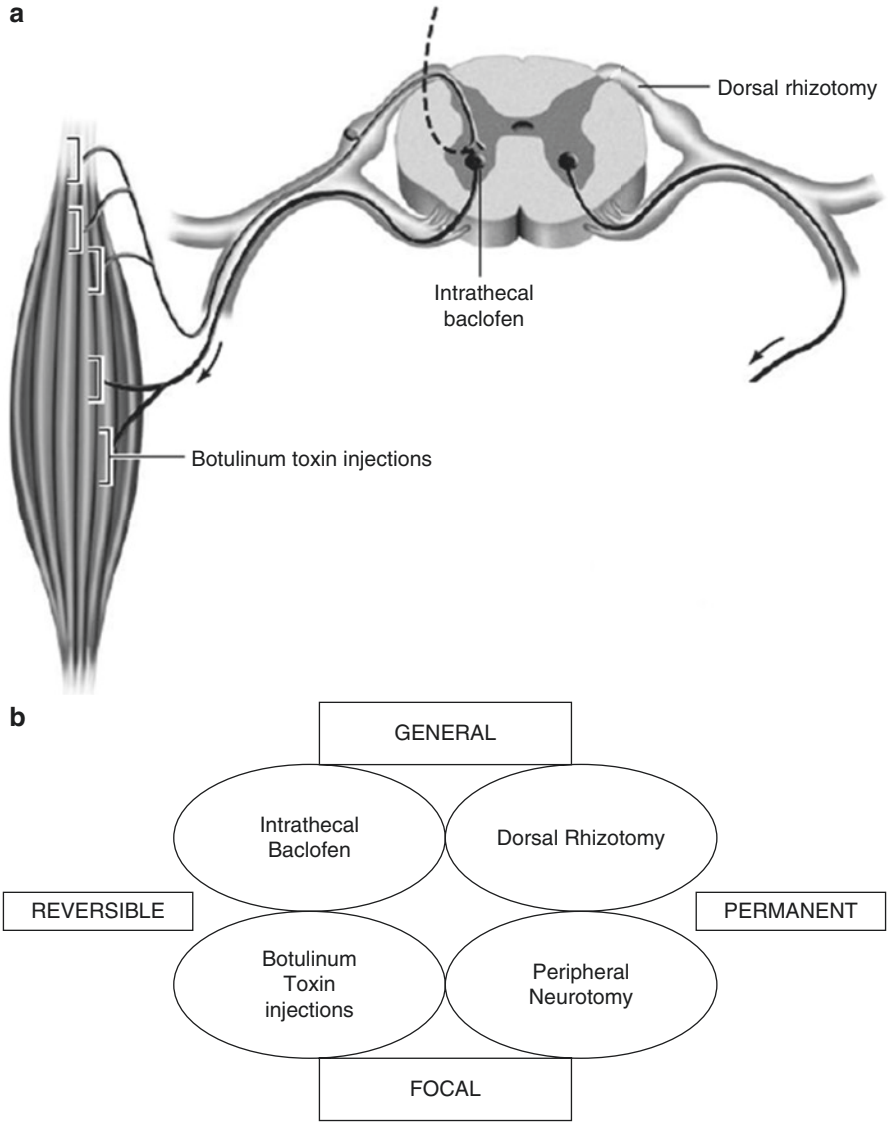

Fig. 43.1 (**a**) Methods for controlling spasticity, based on whether harmful spasticity is focal or general and whether effect is intended to be permanent or temporary. (**b**) Operative methods for reduction of spasticity for children and their anatomical targets

The first step in the evaluation process is to observe the child clinically to understand the child's function and disability. The second step is to measure range of motion (ROM) to detect contractures that will not respond to neurosurgical

treatment. The third step is to quantify the spasticity by using scales. The final step is to grade the child on the Gross Motor Function Measure and to observe the evolution of gross motor function with time. This assessment of a child with CP is crucial for decision-making.

Several effective neurosurgical treatments for spasticity can be used in children with cerebral palsy. For diffuse spasticity of the lower limbs, dorsal rhizotomy or intrathecal baclofen administration may be considered. Dorsal rhizotomy is generally preferred before the age of 6 years because the size of the implanted pump poses an obstacle in young children. Dorsal rhizotomy is proposed when definitive action targeted to certain muscle groups is preferred [1, 2]. For focal spasticity, botulinum toxin injection permits delaying surgery until the child is old enough to undergo selective neurotomy.

Observation of the child in a lying position permits identification of abnormal postures in lower limbs, particularly their asymmetry. This is particularly important for nonambulatory children. They often exhibit left or right windswept posture, bilateral flexion and internal rotation and adduction, batracoid, crossed, or scissoring postures of lower limbs [3]. For the clinical examination of the gait of ambulatory patients there is a classification into five different groups: true equinus, jump gait, apparent equinus, crouch gait, and asymmetric gait. These types of gait reflect pelvic tilt, hip extension or flexion, knee extension or flexion, and ankle dorsiflexion or plantar flexion [4]. Triceps surae is the dominant spastic muscular group for the true equinus gait; the gastrocnemius, hamstrings and psoas for the jump gait; and hamstrings and psoas for the apparent equinus and crouch gait.

It is important to identify which muscular groups harbor a harmful spasticity that disturbs function and should be the target of the treatment and which muscular groups are weak and whose decrease in tone by surgery would be dangerous. Clinical examination should also determine whether or not there are additional irreducible muscular retractions, i.e., contractures that would require adjuvant orthopedic procedures, as they would not be reversed by neurological surgery alone.

Assessment of spasticity is just one element of global function measurement. The gross motor function measure (GMFM) was designed to evaluate motor function capability and changes in children with CP (Fig. 43.2) [5, 6]. There are two versions of the GMFM: the original 88-item measure and the more recent 66-item GMFM. The GMFM is a criterion-referenced measure based on normal gross motor developmental milestones. All items are achievable by a 5-year-old child without any motor disability. With the GMFM-88 it is possible to obtain scores for five separate dimensions: (a) lying and rolling, (b) sitting, (c) crawling and kneeling, (d) standing, (e) walking, running, and jumping. A goal total score is calculated as the mean of the individually selected GMFM dimension scores. An assessment with the GMFM scale every 6 or 12 months gives a curve of evolution and therefore provides an objective basis for therapeutic decisions. Quantifying the patient's functional abilities with the GMFM score is particularly helpful in the longitudinal evaluation of patients who are selected for neurosurgical treatment.

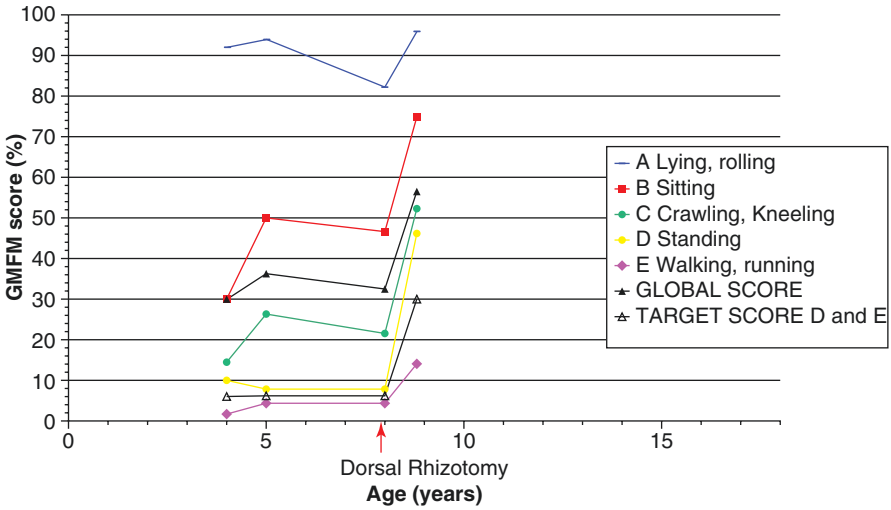

Fig. 43.2 Time course of five dimensions, together with the target and global score, on the Gross Motor Function Measure for a child with spastic diplegia from cerebral palsy. Decision-making for dorsal rhizotomy, slow decrease in Gross Motor Function Measure score. After the dorsal rhizotomy, dramatic improvement in standing and walking, running and global score

43.1 Surgical Techniques

43.1.1 Intrathecal Baclofen Therapy

Intrathecal Baclofen (ITB) therapy consists in an intrathecal catheter connected to an implanted pump, which delivers medication in the cerebrospinal fluid (CSF) surrounding the spinal cord. Baclofen is a γ-aminobutyric acid B agonist, and direct delivery to the intrathecal CSF bypasses the blood–brain barrier (Fig. 43.3) [7].

ITB) can be preceded by a test to screen for adequate response to the medication. In the standard procedure the patient receives baclofen via lumbar puncture or via a temporary lumbar catheter connected to a subcutaneous access reservoir. In the absence of a positive response, indicated by a two-point reduction in the patient's Ashworth score 4 to 8 h following administration, the bolus dose is increased. Once a positive response is observed without unacceptable loss of function, the patient is considered to be a candidate for pump implantation. However, the "bolus method" can be misread as "false-negative responses" in the sense that it may produce a brutal or exaggerated loss of motor power, which might be interpreted as a decrease in functional status. This holds especially true for the patients with the ability to walk. Therefore, the bolus test should be replaced by a continuous infusion test, using an external automatic injection pump connected to a line implanted into a subcutaneous reservoir of the Ommaya-type. The test should last several days so that functional capabilities can be reliably evaluated. Typically the initial starting dose is double the effective screening dose. The dose is then increased daily by 10% to 30%

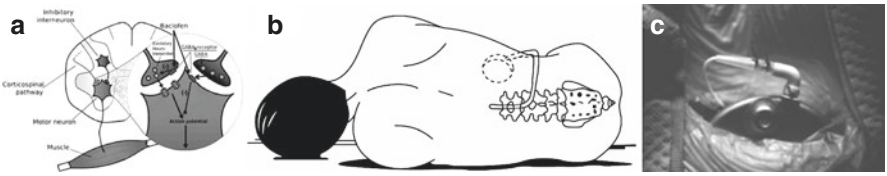

Fig. 43.3 (**a**) Baclofen as a γ-aminobutyric acid (GABA) agonist. Baclofen affects only the B-type receptor in the spinal cord, which is a transmembrane protein. Baclofen produces a profound reduction in monosynaptic and polysynaptic spinal reflexes. (**b**) Positioning of the patient for implantation of the intrathecal catheter. Schematic representation of pump implantation and catheter insertion in the lumbar region. (**c**) Incision site and subcutaneous placement of the pump into the abdominal wall in the subcostal region

until the desired effect is achieved. The most useful criterion for dose adjustment is effective suppression of the hyperactive reflexes, such as tendon jerk, clonus, spasms, cramps, and decrease of muscle tone.

For paraplegic or paraparetic patients with clinically typical hyperspasticity or those with handicapping mixed hypertonia in whom the spastic component is predominant, ITB will be effective on tone regulation. A preliminary bolus test of ITB would not be necessary to prove that such a patient will be a "responder". The patient can undergo implantation directly and doses should be adjusted thereafter. In contrast to that situation, if the indication is not clear, that is, the diagnosis of spasticity is uncertain or involvement of the spastic component in the patient's handicap is not established, a primary test of ITB) should be considered. For patients for whom it is important to evaluate whether a reduction in spasticity will improve function, and to what degree, or on the contrary will weaken functionally useful hypertonia, a preliminary test prior to decision is mandatory. For such an evaluation a continuous infusion test for about one week is much preferable to the bolus method.

Note that whatever the techniques used, lumbar puncture(s) or continuous infusions, CSF depletion or leak may provoke headaches, nausea, and vomiting that confound interpretation until those symptoms disappear. A programmable pump allowing cyclic dose adjustments makes it possible to provide levels that correlate with the daily variability of spastic symptoms.

Adverse effects under continuous-infusion mode are frequent but most often transient. They may include drowsiness, dizziness, mental confusion, lightheadedness, constipation, urinary retention. These side effects are reversed by decreasing the doses. Muscular hypotonia may also occur, leading to loss of muscular power and capacity to stand or walk in ambulatory patients. Adjusting the doses generally reverses hypotonia to the desirable level. Patients with multiple sclerosis or cerebral lesions are more inclined to present those adverse effects, especially fatigue and confusion.

A potential serious risk of ITB is overdose, which could be irreversible because of lack of true baclofen antagonists. Fortunately, **Overdosing** is infrequent. When it occurs it is rarely due to pump malfunctioning. It may rather be the consequence of inappropriate bolus dose, changes in drug concentration, or misprogramming the

pump after reprogramming. Symptoms include weakness with rostral progression, blood pressure changes, respiratory depression and alteration of consciousness: from somnolence to coma. There is no real antagonizing substance (antidote) of baclofen. However, physostigmine administered intravenously at a dose of 2 mg can reverse respiratory depression and lethargy. In the exceptional situation of respiratory distress, assisted ventilation should be performed on emergency.

Baclofen withdrawal syndrome may happen if the pump is not refilled properly or at the scheduled intervals or in a case of pump or catheter malfunction. Symptoms include rebound motor spasticity and spasms, dysesthetic or itching sensations, headaches, drowsiness, confusion or even hallucinations, seizures, tachycardia, labile blood pressure and fever. Treatment is readministration of intrathecal baclofen. In life-threatening situations baclofen should be given by lumbar puncture or external catheter. To avoid a withdrawal syndrome even in a mild form, after intrathecal baclofen has been initiated, oral baclofen should be withdrawn gradually over a period of several weeks.

Catheter problems and CSF leaks are the most common complications. Pump malfunction occurs rarely, the latter approximately at 1% per year. CSF leaks may happen; their appearance is more commonly observed in children than in adults, 12% vs. 3% [8, 9]. Infection of the pump pocket and/or of the CSF may develop, in the order of 3% of the patients. Clinical manifestations of infection may not become obvious before weeks or months after implantation.

ITB is particularly indicated for patients with severe spasticity from a spinal cord origin, especially if painful contractions are present, as in advanced multiple sclerosis or after severe spinal cord injury. ITB can also be indicated for spastic quadriplegia due to brain-stem lesions. ITB has also been included in the neurosurgical armamentarium for cerebral palsy patients.

Several studies have reported the use of intraventricular baclofen (IVB) in refractory spasticity or dystonia [10]. IVB may be also the first option in patients with **generalized dystonia**. The rationale for the use of IVB therapy is that for the treatment of dystonia the site of baclofen activity may be at the cortical level. As a matter of fact, intraventricular infusion results in a baclofen concentration over the cortex greater than that resulting from intrathecal infusion [11]. When treating generalized dystonia, baclofen would act by inhibiting the stimulation of the premotor and supplementary motor cortex.

43.1.2 Dorsal Rhizotomies

Lesioning procedures must be performed so that excessive tone is reduced without suppressing useful muscular tone or impairing any residual motor-sensory functions. In patients who retain some masked voluntary motility, the aim is to re-equilibrate the balance between paretic agonist and spastic antagonist muscles so that treatment results in improvement in (or the reappearance of) voluntary motor function. In patients with poor residual function preoperatively, the aim is limited to halt the evolution of orthopedic deformities and improve comfort.

The surgical approach for dorsal rhizotomy varies significantly from one team to another. The most classic technique—described first by Fasano and coworkers [12] and then by Peacock and Arens [13] and Abbott and colleagues [14]—is as follows: a one-piece laminotomy is performed from L1 to S1 with a high-speed saw, which allows repositioning at the end of the procedure. Bipolar electrical stimulation of the sensory roots is carried out with the assistance of multichannel EMG recordings (in addition to palpation of the leg muscles for evidence of contraction). Roots that when stimulated cause either muscle activity outside their myotome or activity that persists after cessation of the stimulus are deemed abnormal and are separated into their rootlets. The rootlets are in turn stimulated, and the same criteria are used to judge their normality. Abnormally responsive rootlets are candidates to be cut.

To limit the extent of the approach, we and others, especially Park, preferred a limited laminotomy at the end of conus medullaris [15, 16]. For surgery to be effective, approximately 60% of the dorsal rootlets must be cut, the amount depending on the level and function of the roots involved. The roots corresponding to muscles with harmful spasticity versus useful postural tone must be considered when determining the number of rootlets to be cut. In most cases, L4, which predominantly provides innervation to the quadriceps femoris, must be preserved.

To reduce the invasiveness of the approach and to access the roots to be targeted (individually) at their exit from the intradural space to the corresponding dural sheath, a modality, termed *keyhole interlaminar dorsal rhizotomy* (KIDr) is developed (Fig. 43.4) [17]. The lumbosacral spine is approached posteriorly so that the interlaminar spaces selected on the basis of the preoperative chart can be reached. After resecting the ligamentum flavum, the chosen interlaminar space or spaces are enlarged by resecting the lower half of the superior and the upper half of the inferior laminae. Through the fenestrations, the dura is opened in the midline for a height of 2 cm. The L2 and L3 roots can be reached through an L1 to L2 opening, L4 and L5 through L3 to L4, and S1 and S2 through an L4 to L5 or an L5 to S1 opening. The lumbar midline incision and muscle separation are extended according to the number and topography of the interlaminar spaces to be reached, which may be one, two, or three based on clinical presentation and preoperative chart. Both the spinous processes and the interspinous ligament are respected. After resection of the flavum ligament of the selected interlaminar spaces, each space is enlarged by resecting the lower two thirds of the upper lamina and the upper two thirds of the lower lamina.

The microsurgical steps are conducted following the principles of the keyhole interlaminar dorsal rhizotomy. At the exit from the dural sheath, the ventral root is easily identified on its ventral position. The dorsal rootlets (on average, five per root) are also easily identified; they are grouped posteriorly to the ventral root, often separated from the latter by an arachnoid fold. Muscular responses to stimulation with a preferably bipolar electrode to avoid spreading of current are tested first for the ventral root, then for the dorsal root.

After opening the dura on midline at the selected interlaminar spaces, a microscope is installed. The trajectory is oblique at approximately 45 degrees so that the surgeon's view passes underneath the (respective) interspinous ligament. Goal is to

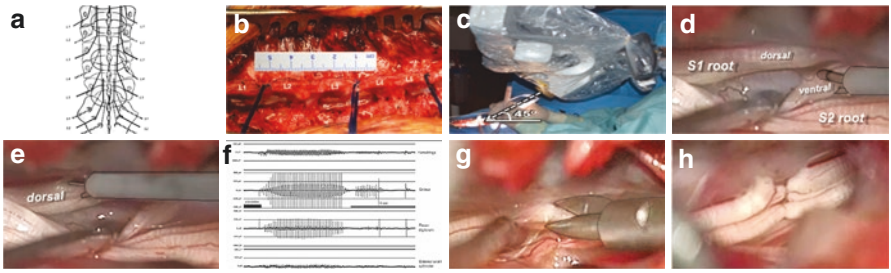

Fig. 43.4 (**a**) Schematic drawing of interlaminar (IL) vertebral levels where selected roots can be targeted for dorsal rhizotomy according to the preoperative surgical planning. *L2, L3* at L1-L2; *L3, L4* at L2-L3; *L4, L5* at L3-L4; *L5, S1* at L4-L5; *S1, S2*. IL spaces to be opened are determined according to the preoperative program for root sectioning (tailored operation). (**b**) Exposure of L1-S1 laminae, with L1-L2, L3-L4, and L5-S1 IL fenestrations as selected at time of surgical planning. At each fenestrated level, the inferior two thirds of the upper lamina and the superior two thirds of the lower lamina are rongeured, and flavum ligamentum is removed to expose dura so that dura and arachnoid are opened on midline. Note at fenestrated level(s) preservation of the spinous processes as well as of the interspinous ligament *(blue tapes)*. (**c**) Surgeon operates with an oblique trajectory, at approximately 45-degree angle, to target, intradurally, through the IL space, the contralateral root, at exit to corresponding dural sheath. Note that trajectory passes underneath the interspinous ligament to access the root, with its ventral and dorsal components. (**d**) Exposure of the *(left)* S1 dorsal and ventral roots at entry into the dural sheath, obliquely seen under the microscope from the contralateral side. Note neighboring S2 root going down to next *(lower)* level. (**e**) The S1 dorsal root is individualized from the S1 ventral root. Stimulation by bipolar electrode of the ventral root. Intraoperative physiologic testing and selected sectioning of dorsal root at 50 Hz, 1 mA. It aims to estimate the level of excitability of the radicular-spinal circuitry by stimulating the corresponding dorsal roots and rootlets. (**f**) The electromyogram shows a sustained response to a 50-Hz train stimulation (of 1 s each train) at threshold (of about 1 mA) and a spread of the response outside the myotome corresponding to the stimulated root. In the illustrative example, which corresponds to stimulation of an S1 dorsal root, note the spreading response outside the myotome corresponding to S1. (**g**) Sectioning with microscissors of the selected dorsal rootlets. (**h**) In this case, three out of the four rootlets, which constitute the dorsal root, were divided

access (intradurally) the contralateral root, with its ventral and dorsal components, at its exit to the corresponding dural sheath.

Each exposed root is electrically stimulated to identify its innervation territory and thereby confirm its topographic level. This phase is *anatomic mapping*. Stimulation (2 Hz, approximately 200 μA) is first performed on the ventral root component, which is easy when the root is accessible at its exit to its dural sheath. To be noted, a motor response by dorsal root stimulation would require a 3 to 5 times higher intensity. Thus the roots corresponding topographically to the muscles harboring “harmful” spasticity are identified before the sectioning decision.

Then the dorsal rootlets undergo *physiologic testing*. Stimulation is provoked with a 50-Hz train with duration of 1 s for each train. Excitability is considered excessive when stimulation elicits an “exaggerated” (sustained or spreading) response. This testing is to confirm or modify the percentage of the dorsal root to be cut, previously specified in the preoperative chart. The number of selected dorsal rootlets to be cut, whose number was specified in the preoperative chart in

proportion to the severity of the spasticity in the corresponding muscular groups, is adjusted accordingly. The amount of dorsal rootlets cut generally ranges between one third and four fifths of a root's constituting rootlets. Then the dural incision is sutured in a watertight fashion, and the dural suture line is covered with fat harvested subcutaneously.

43.2 Decision Making in Children

Most indications are for children with cebral palsy (CP). The choice among the various therapeutic options is difficult at the pediatric age because children are continuously developing and the evolution of spasticity and dystonia, which are frequently associated, has dynamic characteristics. Dorsal rhizotomies improve spasticity but not dystonia, whereas intrathecal baclofen can improve to a certain extent both spasticity and dystonia [1]. As in adults, spasticity in children can be either useful for function or detrimental. Efficient treatments are available, including botulinum toxin injections, intrathecal baclofen, dorsal rhizotomies and neurotomies. These treatments can be used in isolation or in combination with orthopedic surgery. To formulate a treatment plan one must project into the future by extrapolating the extent and severity of musculoskeletal contractures and their harmful consequences, as well as the positive effects of spontaneous psychomotor development.

For diffuse spasticity of the lower limbs, dorsal rhizotomy or ITB administration may be considered. Dorsal rhizotomy is generally preferred in younger as the size of the implanted pump poses an obstacle in young children. Dorsal rhizotomy is proposed when definitive action targeted to certain muscle groups is preferred.

For focal spasticity/dystonia, botulinum toxin injections permit delaying surgery until surgical decision taken.

In children with spastic diplegia, target is to improve quality of walking and decrease amount of assistance (use of canes, crutches, walkers) required for ambulation. In children with spastic quadriplegia aim is to improve ease of caretaking, facilitate function in sitting position, decrease pain and obtain favorable distant effects on upper limbs.

Important, because expectations of both the child and the family can be quite different from what can be achieved, the realistic goals should be clearly explored and written down in the informed patient consent form.

43.3 Conclusion

The goals of surgery for spasticity are well defined. They are to decrease "harmful spasticity," respect "useful spasticity," preserve residual motor/sensory functions, reveal eventually masked capabilities and improve functional ability. Because of its complexity, neurosurgical management of spasticity requires multidisciplinary approach.

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Part VIII
Infections

Chapter 44
Shunt Infection

Jorge Linares, Sara Iglesias, and Bienvenido Ros

44.1 Introduction

Ventriculoperitoneal shunt (VPS) remains the gold standard treatment for multiple forms of hydrocephalus. Although its success has been amply demonstrated, the rate of event-free survival is around 70% in the first year and 40% at 10 years [1]. Among the different causes of shunt failure, in this chapter we will focus on shunt infection requiring long-term hospital admission, removal of the shunt system in the majority of cases, and intravenous antibiotic therapy for a variable period of days or weeks. Hence, the importance of its early detection and the protocolization of its management.

44.2 Definition

Multiple definitions of shunt infection exist. They mostly include a combination of symptoms and signs of shunt dysfunction and infectious semiology, supported by complementary tests that indicate an infectious process, confirmed by the isolation of the causative microorganism. One of the most widely used and broadest definitions is that recommended by the HCRN [2]:

1. Microbiological determination of organisms on culture or Gram stain from cerebrospinal fluid (CSF), wound swab, and/or pseudocyst fluid.

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2. Shunt erosion (wound breakdown with visible shunt hardware).
3. Abdominal pseudocyst (even in the absence of positive cultures)
4. Positive blood cultures in a child with ventriculoatrial shunts.

The Centers for Disease Control and Prevention's National Healthcare Safety Network (CDC/NHSN) definition of health-care-associated ventriculitis or meningitis [3] is more complex. It includes at least 1 of the following criteria:

- Organism cultured from CSF
- At least 2 of the following symptoms with no other recognized cause in patients aged >1 year: fever >38 °C or headache, meningeal signs, or cranial nerve signs, or at least 2 of the following symptoms with no other recognized cause in patients aged ≤1 year: fever >38 °C or hypothermia <36 °C, apnea, bradycardia, or irritability and at least 1 of the following:

  – Increased white cells, elevated protein and decreased glucose in CSF
  – Organisms seen on Gram stain of CSF
  – Organisms cultured from blood
  – Positive nonculture diagnostic laboratory test from CSF, blood, or urine
  – Diagnostic single antibody titer-(immunoglobulin M) or four-fold increase in paired sera (immunoglobulin G) for organism.

The IDSA guidelines [4] present a practical approach for the management of shunt infections and give the evidence of their recommendations. Regarding diagnosis, they suggest several issues to consider:

- Symptoms of infection, CSF pleocytosis and positive culture are indicative of ventriculitis or meningitis.
- An altered CSF biochemistry does not diagnose an infection, just as a normal biochemistry does not rule it out. Likewise, a negative CSF Gram stain does not exclude infection. Although CSF culture is the most important test to establish the diagnosis of meningitis and ventriculitis, it is recommended that cultures be held for at least 10 days to identify slow-growing organisms.
- An elevated CSF lactate or an elevated CSF procalcitonin, or the combination of both, may be useful in the diagnosis of bacterial ventriculitis and meningitis and an elevated serum procalcitonin may be useful in differentiating CSF abnormalities due to surgery or intracranial hemorrhage from those due to bacterial infection.

The fact that there exist different definitions of shunt infection in the literature may due to the variety of clinical situations we can find in practice: from a small erosion on the patient's skin or small abdominal discomfort to bacterial meningitis with a wide spectrum of symptoms, whether or not linked to shunt disfunction. Thus, a high degree of clinical suspicion is necessary and this diagnosis should be considered whenever shunt dysfunction occurs without an obvious explanation.

44.3 Epidemiology

The incidence of shunt infection is variable. Rates between 5% and 41% can be found in different series in the literature, although in recent years the rate has been limited to 4–17%. The incidence of infection by procedure or operative incidence is between 2.8% and 14%. Most authors consider a rate below 10% acceptable, although most series have described a rate lower than 4% [4].

Our center published data on surgical outcome after shunt surgery in 2016, reviewing 166 patients in whom 425 procedures were performed between 2000 and 2015 [5]. This retrospective noncontrolled study showed the following infection rates: shunt infections occurred in 7% of the procedures (30/425) and 15.7% of the patients (26/166) and the percentage of shunt revisions secondary to infection was 11.6%.

A retrospective review of infections for the period between 2000 and 2020, with data yet to be published, showed the following: shunt infection rates per patient and per procedure were 14.64% (41/280) and 6.67% (49/734), respectively.

44.4 Risk Factors

Over the last few years, several case-control studies have reported the main risk factors related to shunt infection. Some factors depend on the patient: prematurity, a history of infectious disease such as sepsis or ventriculitis, complex cardiopulmonary disease, previous CSF fistula … The relationship between the patient's age and the risk of infection is disputed, although most of the literature agrees that the younger the age, the greater the risk of infection. Other factors of a surgical nature include: previous external ventricular drainage, surgery time for shunt implantation, whether the surgery was performed urgently, or the experience of the surgeon. On the other hand, surgical factors such as the use of standardized protocols [6] or the use of antibiotic-impregnated catheters have been found to be protective [7].

Regarding the type of catheters, several publications have confirmed the decrease in rates of shunt infection in those centers that have introduced the use of antibiotic-impregnated catheters. The IDSA guidelines recommend their use with "a strong rating for the quality of the evidence and a moderate grade for the recommendation". However, the most commonly used antibiotics for impregnation of these catheters are rifampicin and clindamycin and several studies have published a relative increase in the frequency of gram-negative infection [8].

One of the most important risk factors is a history of previous shunt revision. The risk of infection is three times higher in those patients with a history of shunt revision compared to those without (HR 3.9, 95% CI, 2.2, 6.5) and up to 13 times higher in those with 2 or more shunt revisions compared to those with no review (HR 13.0, 95% CI, 6.5, 24.9) [9].

In our series, infection was the reason for shunt failure mainly in younger patients soon after the first ventriculoperitoneal implantation or later on in the context of distal dysfunction secondary to a peritoneal pseudocyst [5].

44.5 Pathogenesis

There are four mechanisms by which shunt infection can occur.

- First, the contamination of the VPS during implantation surgery. Here, the infection occurs early in time and is caused by microorganisms that typically colonize the skin of patients, such as gram-positive cocci. However, if the infection is caused by slow-growing bacteria (P. Acnes, S. Epidermidis) that are expressed in a paucisymptomatic manner, the diagnosis may be reached late.
- Second, infection can migrate retrogradely from the distal part of the shunt because of abdominal complications from the shunt, such as pseudocysts or peritonitis, or may be secondary to infectious/inflammatory diseases originated in the abdominal cavity.
- Third, the shunt can be infected through the skin, either by invasive maneuvers such as puncturing the reservoir or by small erosions or ulcerations on the patient's skin that cause exposure of the "hardware".
- The fourth mechanism is hematogenous, characteristically in patients with a ventriculoatrial shunt, which is a foreign body in the bloodstream that exposes them to colonization if bacteremia occurs.

Some authors differentiate between early infection when it occurs before 6 months after implantation surgery and late infection when it occurs beyond that period. The mean time from shunt implantation to infection is 19 days, which is consistent with the general idea that the most common infection mechanism is intraoperative contamination [10]. These early infections are mostly caused by bacteria such as coagulase-negative Staphylococcus species and S. aureus. Late infections are less frequent and a higher proportion of these are caused by gram-negative bacilli, suggesting that this type of infection is caused by a mechanism of retrograde contamination from the distal part of the shunt.

In our series, 35 of 49 (71.42%) infections occurred early (within 6 months of shunt implantation) and 14 of 49 (28.57%) occurred late (more than 6 months after shunt implantation). Regarding the bacterial etiology in our series, coagulase-negative cocci was the most frequent group, causing 20 of the 49 infections (40.81%). Infections caused by S. aureus (6 of 49, 12.24%) and gram-negative bacilli (6 of 49, 12.24%) followed in frequency.

In the pathogenesis of shunt infection, the role of the bacterial biofilm should be mentioned. Bacteria have the ability to adhere to inert material, such as the shunt catheter or valve hardware, thanks to the polysaccharides on the bacterial wall. Bacteria accumulate in a matrix made up of macromolecules such as proteins, DNA,

and other products from bacterial lysis. The result is the formation of a biofilm adhered to the shunt, which is formed by a plactonic layer that is susceptible to the action of antibiotics, and another deep layer, which is inert to their action. For this reason, as we will see below, the complete removal of the shunt is recommended, since antibiotic treatment may be insufficient to eliminate all the bacteria in the biofilm. In addition, the biofilm together with the products of the patient's CSF can cause obstruction and shunt failure [11].

44.6 Clinical Characteristics

The clinical characteristics of shunt infection can be highly variable and depend on its pathogenesis, the virulence of the microorganism, and the type of shunt. For example, some of the bacteria that most frequently produce shunt infection, such as coagulase-negative staphylococci or P. acnes, are indolent and therefore cause minimal inflammation, resulting in minimal ventriculitis without meningeal involvement or shunt dysfunction without inflammation due to the formation of a biofilm on the catheter or shunt hardware [12]. Figure 44.1 shows the symptoms registered in our series of cases. Note that up to a third of patients did not present fever at diagnosis.

The most frequent form of presentation is a patient with new-onset headache, nausea and/or lethargy. This clinical profile generally occurs when the infection settles in the proximal part of the shunt, causing a condition that resembles shunt dysfunction. On the other hand, signs such as erythema or tightness in the

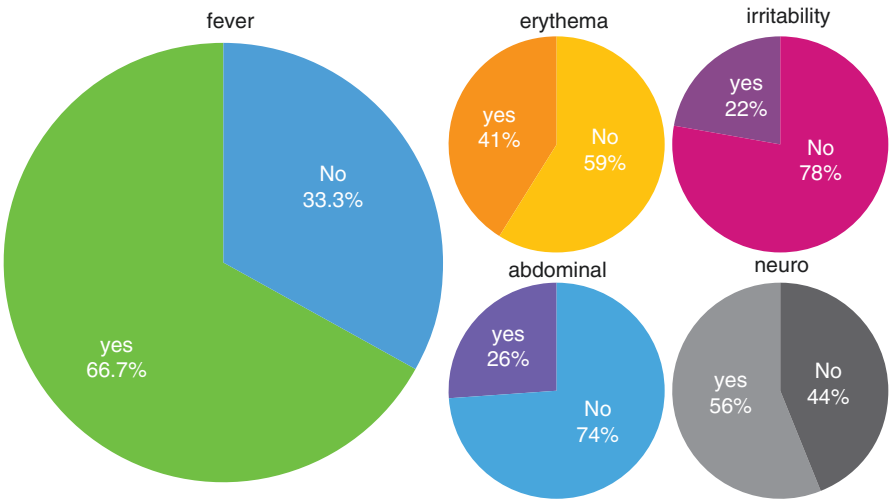

Fig. 44.1 Frequency of symptoms in our series of shunt infections

subcutaneous path of the VPS should suggest its infection. Finally, the symptoms related to distal shunt infection are caused by inflammation of the peritoneum in VPS and of the pleura in a ventriculopleural shunt.

It should be noted that, with low-virulence microorganisms, the symptoms of infection may be nonspecific, such as abdominal pain or tightness. Sometimes the scarring process in the abdomen leads to the formation of an abdominal pseudocyst around the distal catheter in an attempt to contain the infection.

44.7 Diagnosis

The diagnosis of shunt infection can be challenging and requires a high index of suspicion. Faced with a patient with compatible symptoms, a directed anamnesis should be carried out in which information is obtained about the reason for shunting, date of implantation and type of shunt valve. After a physical examination that should include a complete neurological study and inspection of the VPS tract, it is recommended to request blood tests with acute phase reactants such as CRP and more specifically for bacterial infection such as serum procalcitonin. A CT scan should be done as an urgent neuroimaging test to perform the accurate diagnosis of shunt dysfunction. After that, CSF should be obtained by one of the following methods: by puncturing the shunt reservoir, a CSF collection, abdominal collections or an externalized catheter, in order to study the biochemical parameters of the CSF, as well as microbiological studies such as gram staining and CSF culture.

Alterations in CSF biochemical parameters can be subtle, making it difficult to distinguish whether these alterations are due to an infection or some other disease causing the hydrocephalus (tumor, hemorrhage…) or even some other neurosurgical process performed. Although the increase in leukocytes, decrease in glucose and increase in proteins in CSF correlate with the infection, it can nevertheless occur in patients with normal biochemical parameters [13]. Gram stain is commonly used when infection is suspected, although its negative result does not rule out the presence of bacterial infection, especially if the patient has previously received antibiotic treatment.

Given this clinical scenario, we must use more specific infection parameters to guide the diagnosis of the condition, such as CSF lactate. Two meta-analyses have shown that elevated CSF lactate is better than the use of a leukocyte count, glucose or protein in differentiating between bacterial meningitis and aseptic meningitis [14, 15]. Regarding the recommended cut-off number, a CSF lactate greater than 4 mmol/L has a high sensitivity (88%) and very high specificity (98%) in the diagnosis of bacterial meningitis after neurosurgical intervention [16].

CSF culture is the most important diagnostic test in detecting VPS infection, since the result will generally be positive even in those patients without CSF biochemical alterations. Its culture requires several days or weeks of incubation before

determining a negative result, because the presence of slow-growing microorganisms such as P. acnes is not uncommon. If the result is negative and the suspicion of infection remains high, the test should be repeated, especially if the patient is already receiving antibiotic treatment as the sensitivity of the CSF culture decreases from 88% to 70% with the use of any antibiotic therapy. Sensitivity decreases to 59% if antibiotics have been administered more than 24 h before CSF extraction [17].

When a shunt revision surgery is performed and the suspicion of infection is plausible, culture of the catheters and the valve hardware is recommended. However, if a valve system or catheter is removed for some other reason during revision surgery, "routine" culture of these components is not recommended [4].

44.8 Treatment

44.8.1 Surgical Management

When the suspicion of infection is high and the data from the complementary tests support the diagnosis, the patient should be admitted to hospital in order to plan medical and surgery treatment. Different approaches have been published. Several studies have described series in which removal of the infected shunt system is not carried out, in an attempt to avoid the morbidity of repeated surgical interventions and to maintain a CSF shunt. The efficacy described was low (34–36%) and a relatively high mortality rate was found, together with prolonged hospitalization periods and adverse events associated with the instillation of intrathecal antibiotics, sometimes used in this conservative approach [18]. However, an observational study described better results, with up to 92% success in infections caused by microorganisms other than S. aureus, suggesting that the conservative approach may be appropriate for more indolent bacteria like coagulase negative staphylococci or P. acnes [13]. In the only randomized study carried out in children, non-removal of the shunt system was associated with a 70% recurrence rate [19]. In our center, the absence of complete removal of the infected shunt is considered only exceptionally, in patients with a very poor prognosis regardless of the infection or with a very high surgical risk.

The surgical management used in most centers is the complete removal of the shunt system plus the implantation of an external CSF drainage. The presence of external ventricular drainage (EVD) allows the monitoring of CSF biochemical parameters, as well as serial cultures every 24–48 h. In addition, it can be used to administer intrathecal therapy when necessary [20]. After the end of the antibiotic treatment (see below), a new shunt can be implanted, preferably in the contralateral ventricle. The persistence of pleocytosis, hypoglycorrhachia or hyperproteinorrhachia should not delay the placement of the new VPS beyond the recommended periods, as CSF biochemistry can remain altered for a long time.

An intermediate option for surgical management is externalization of the shunt. This may be an option to consider for patients whose infection is limited to the distal portion of the shunt (for example, in those with an abdominal pseudocyst and negative CSF cultures) or in those patients in whom the infection is combined with a situation of shunt overdrainage or slit ventricles, in which insertion of an EVD can be difficult.

On the other hand, patients with old catheters or those attached to the choroid plexus present a technical difficulty for shunt removal and a relatively high risk of bleeding, which may justify the inability to remove the shunt completely. These patients should be closely followed, since the recurrence of infection by the same microorganism supports the indication to carry out a surgical intervention in a programmed way to remove the abandoned part of the previous shunt.

44.8.2 Antibiotic Treatment

After obtaining CSF cultures, antibiotic treatment should be started empirically and intravenously. Current guidelines recommend the use of vancomycin plus a beta-lactam with anti-psudomonal effect such as cefepime, ceftazidime or meropenem. The choice of the beta-lactam antibiotic should be made based on local susceptibility patterns. In case of allergy to beta-lactams, or if meropenem is contraindicated, aztreonam or cirpofloxacin may be an alternative. Table 44.1 shows the recommended doses.

If gram-positive microorganisms are observed during admission, the recommended treatment is vancomycin with or without rifampicin. In the case of gram negative microorganisms, the treatment would be the chosen beta-lactam. Once the germ has been identified in the culture, targeted treatment should be performed. Figure 44.2 shows some examples of targeted antibiotic therapy.

Intraventricular antibiotic therapy is reserved for restricted cases, such as failure of intravenous therapy, difficult-to-eradicate infections caused by multi-resistant bacteria (for example, carbapenem-resistant), or when the indicated antibiotic does not adequately penetrate the CSF. It could also be indicated in patients who cannot immediately undergo removal of the shunt system [21]. Antibiotic dosage depends

Table 44.1 Pediatric doses of the most used antibiotics

Antibiotic	Pediatric dose
Vancomycin	60 mg/kg/day every 6 h
Meropenem	120 mg/kg/day every 8 h
Ceftazidime	200 mg/kg/day every 8 h
Cefepime	150 mg/kg/day every 8 h
Rifampicin	20 mg/kg/day every 24 h
Linezolid	<12 years: 30 mg/kg/day every 8 h >12 years: 20 mg/kg/day every 12 h (maximum 600 mg/dose)

Staphylococcia Methicillin sensitive	Nafcillin or oxacillin = cloxacillin
Staphylococcia Methicillin resistant	Vancomycin
Propionibacterium acnes	Penicillin G / Amoxicillin
Streptococcus pneumoniae	Third-generation cephalosporin
Pseudomonas aeruginosa	Cefepime, ceftazidime, or meropenem
Haemophilus influenzae	Ampicillin / Third-generation cephalosporin
Extended spectrum β-lactamase-producing gram-negative bacilli	Meropenem
Acinetobacter baumannii	Meropenem
Other Enterobacteriaceae	Third-generation cephalosporin
Candida species	Lipid formulation of amphotericin B ± flucytosine

Fig. 44.2 Targeted antibiotic therapy recommendations

on the ventricular size and the drainage debits. In children, the dose should be reduced by 60%. It is recommended to use intrathecal vancomycin for gram positive and intrathecal gentamicin or amikacin for gram negative bacilli. Penicillins and cephalosporins should not be administered by this route, since they have been significantly associated with neurotoxicity, especially seizures [22].

44.8.3 Duration of Antibiotic Therapy

The duration of antibiotic treatment is not completely defined and depends on the cultured microorganism, the clinical impact of the infection and the biochemical parameters of the CSF. According to the recommendations of the IDSA guidelines (Table 44.2), in infections caused by coagulase negative staphylococcus or P acnes without an increase in leukocytes in CSF or minimal increase, normal glucose in CSF and few symptoms, treatment should last 10 days. In the event that the infection caused by these bacteria does cause an increase in leukocytes in CSF, decrease glucose in CSF, or produce considerable neurological or systemic symptoms, treatment should be prolonged between 10 and 14 days. For infections caused by more aggressive germs such as S. aureus or gram negative bacilli, regardless of the CSF

Table 44.2 Recommendations for the duration of antibiotic treatment based on the microorganism causing the infection

Microorganism	Days of antibiotics after VPS removal
Coagulase-negative staphylococcus or P acnes **without** pathological CSF biochemistry and **without** neurological or systemic symptoms	10 days
Coagulase-negative staphylococcus or P acnes **with** pathological CSF biochemistry or **with** neurological or systemic symptoms	10–14 days
S. aureus or gram-negative bacilli	10–14 days (some authors recommend 21 days if gram-negative bacilli)
Repetitive positive cultures	10–14 days from last positive culture

biochemistry, treatment should last between 10 and 14 days, although some experts recommend extending up to 21 days for infections caused by gram negative bacilli.

During antibiotic treatment, a CSF sample should be extracted every 24 or 48 h to examine the evolution of the biochemical parameters and ensure that the cultures are negative. For patients who return to a positive CSF culture, antibiotic treatment should be continued for up to 10–14 days from the last positive culture. Replacing the EVD is highly recommended to improve the evolution of the infection.

44.8.4 New Shunt Reimplantation

The time of reimplantation must be individualized according to the cultured microorganism, the evolution of the CSF biochemical parameters and the clinical severity of the infection. Reimplantation too early can increase the risk of reinfection, while delaying it excessively exposes the patient to the risk of superinfection of the external CSF drainage.

Negative CSF cultures are a fundamental requirement to consider reimplantation of the new shunt. The IDSA guide [4] recommends different waiting periods depending on the isolated microorganism, similar to the duration of antibiotic treatment.

- For an infection caused by coagulase-negative staphylococci or P. acnes, if no associated CSF abnormalities are detected and CSF cultures are negative for 48 h after externalization, a new shunt should be reimplanted as soon as the third day after removal. If there are abnormalities in CSF but negative repeat CSF cultures, a new shunt should be reimplanted after 7 days of antimicrobial therapy. However, if repeat cultures are positive, antimicrobial treatment is prolonged until CSF cultures remain negative for 7–10 consecutive days [23].
- When the infection is caused by *S. aureus* or gram-negative bacillus, the new shunt can be repositioned 10 days after the cultures are negative [24].

The pleocytosis, hypoglycorrhachia, and hyperprotein in the CSF samples obtained for monitoring the biochemical parameters should not delay the placement of the new shunt, since these parameters can remain altered for a long time.

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Chapter 45
Epidural Abscess and Subdural Empyema

A. Tu, J. Hsu, and P. Steinbok

45.1 Introduction

Epidural and subdural infections are life threatening diseases that have plagued humanity for the better half of the last millennium [1–9]. In 1699, de la Peyronie documented the first surgery to treat subdural empyema after head trauma [10]. Prior to the 1900s, intracranial infections were a fatal diagnosis [11–14]. With the advent modern medical imaging, improved surgical technique, and evolving antibiotic therapies, intracranial infections now have significantly better outcomes [11, 12, 14, 15]. Subdural empyema has been deemed "the most imperative of neurosurgical emergencies" emphasizing the importance that expediency of diagnosis has in treating these conditions [16].

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45.2 Epidemiology

45.2.1 Epidural Abscess

Epidural abscess is a purulent collection that develops in the space between the dura mater and the calvarium or skull base. Historically, the most common causes of epidural abscess were extension of otorhinolaryngologic and dental infections; these remain the most common source in developing economy countries [2, 14, 15, 17–21]. In comparison, some literature from developed economy countries report the highest incidence of epidural infection occurring in the post-operative setting; however, other series have found that extension from sinusitis remains the commonest etiology and accounts for 60 to 90% of cases [2, 11, 18, 21, 22]. These infections are commonly associated with cranial osteomyelitis and rarely extend into the subarachnoid space or brain parenchyma. When treated aggressively and in the absence of extension beyond the epidural space, mortality is rare [2, 9, 17, 23–26]. Epidural abscess originating from inadequately treated paranasal sinusitis or otitis media has significantly decreased with early recognition and appropriate medical therapy although latent cases continue to occur. In developed countries, it has been shown that male children with lower socioeconomic backgrounds have higher rates of sinusitis-related intracranial infections compared to children of higher income families [11, 17, 18]. It has been hypothesized that this reflects a disparity in prevention of sinus infection secondary to delayed or inadequate access to care [11]. Furthermore, there is a higher prevalence in males between 20–30 years of age due to higher rate of complicating otorhinolaryngologic infections [18, 27–29]. While It is unclear why this predilection exists, there is a higher self-reported incidence of otorhinolaryngologic infections in females but more complications of infections in males. This disparity is believed to result from delayed presentation to medical attention [30]. Of patients hospitalized with facial sinusitis, there is a 10% incidence of intracranial complications including meningitis, venous sinus thrombosis, and intracranial extension resulting in suppurative collection of the respective epidural, subdural or parenchymal spaces [15, 28, 31].

45.2.2 Subdural Empyema

Unlike epidural abscesses, subdural empyema develops in the potential space between the dura and arachnoid membrane. Despite aggressive contemporary intervention, this malady has significantly higher morbidity [12, 25, 26, 28, 32–40]. Up to half of patients are left with permanent neurological deficits including persistent seizures (12–37.5%) and hemiparesis (15–35%) [31, 37]. Mortality is also significant and occurs in 6–15% of cases [4, 21, 24, 37, 41–47]. These infections can

expand into the subarachnoid space and adjacent brain tissue resulting in rapid dissemination. Historically, otitis media was the most common cause of subdural empyema although this has now been superseded by direct spread from paranasal bacterial sinusitis, accounting for more than 50% of cases [31, 37]. Middle ear, mastoid, and odontogenic infections are the second most common etiology overall, comprising 25% of cases [4, 21, 23, 42, 44, 48]. Bacterial meningitis makes up 1–2% of the causes of this infection and is more frequently seen in neonates or infants [10, 31, 37]. Subdural empyema has also been reported to occur as result of trauma, post craniotomy, and with intracranial pressure monitoring devices; these comprise approximately 20% of cases [21–23, 41–45, 48–60]. Non-sinus infections including epidural abscess, calvarial osteomyelitis, soft tissue infection, and intracranial abscess may also result in transgression into the subdural space [28, 32]. Subdural empyema most commonly manifests in infants and in young adults reflecting the primary etiologic causes [61]. Males are also afflicted three times more frequently than their female counterparts for reasons yet to be determined [30, 37].

45.3 Microbiology

Different bacterial profiles dependant on the source of infection maybe expected and dictate unique antimicrobial regimes (Table 45.2). Common pathogens in subdural empyema cohorts are *streptococcus pneumonia* (16%), group B *streptococcus* (13%), *Haemophilus influenzae* type B (13%), and *Escherichia coli* (10%) [10, 12, 29, 37, 62]. Rare bacteria that have been reported include *Salmonella* and *Tuberculosis* in immunocompromised or patients with medical predispositions [10, 18, 61]. Extension from chronic paranasal sinusitis most often consists of aerobic and anaerobic *Streptococcus*, *Staphylococcus*, and anaerobic bacteria including *Bacteroides* and *Fusobacterium*. Infections arising from the mastoid or middle ear often reveal *Staphylococcus aureus*, aerobic and anaerobic *Streptococcus*, *Pseudomonas aeruginosa*, facultative gram negative organisms and other anaerobes [18]. Traumatic or spontaneous calvarial osteomyelitis causing epidural abscess is typically due to *Staphylococcus*, *Streptococcus* and gram-negative bacteria [32, 61, 62]. In comparison, post-surgical infections generally have a profile in keeping with skin flora bacteria including coagulase negative *Staphylococcus*, *Corynebacterium* and *Propionibacterium acnes* [9, 25, 26, 63, 64]. In cases of subdural infection complicating pediatric meningitis, organisms such as *Haemophilus influenza* type B and group A or B *Streptococcus* are most commonly seen. Cultures may be sterile in up to 25% of patients given that many have antibiotic treatment initiated prior to presentation [28, 57, 65–73]. In addition to surgical intervention, broad spectrum antibiotic coverage should be started as soon as possible and modified according to the culture results. Expeditious intervention is essential for minimizing patient morbidity.

45.4 Clinical Presentation

45.4.1 Epidural Abscess

Epidural and subdural infections typically present with history a history of fever and headache in addition to symptoms related to the primary etiology of their infection, such as maxillary pain from sinusitis and otalgia with facial nerve dysfunction from mastoiditis [18, 28] (Table 45.1). Epidural abscesses typically have a more indolent course. Patients may develop tender swelling owing to sub periosteal abscess in the case of inadequately managed otorhinolaryngologic infection [2, 3, 5, 23, 52]. Sub periosteal abscess developing from the frontal sinus with associated osteomyelitis and swelling of the forehead was recognized by Sir Percival Pott in 1760 and is termed as Pott's Puffy tumor [3, 15, 23, 49, 52, 74, 75]. Untreated epidural abscesses may exert significant mass effect and elevate intracranial pressures with resultant altered level of consciousness. Seizures are not common provided that infection does not transgress the dura. Acute otomastoiditis may also extend through the petrous bone resulting in otalgia associated with otitis media, ipsilateral facial pain, and lateral gaze palsy [15]. This triad was first described in 1904 by Giuseppe Gradinego and is classically referred to as Gradinego's syndrome [76, 77]. While historically associated very significant morbidity and mortality, early recognition

Table 45.1 Comparison of epidural and subdural infection

	Epidural abscess	Subdural empyema
Common	• Rhinitis or otorrhea • Fever • Severe headache in the area of infected sinus, mastoid or wound • Subcutaneous swelling (Pott's puffy tumor)—forehead, nasion, periorbital or temporal region • No neurological deficit	• Rhinitis or otorrhea • Fever • Severe headache in area of infected sinus, mastoid or wound that progresses to generalized severe head ache • Seizures • Hemiparesis • Monoparesis of lower extremity • Hemianopia • Drowsiness • Periorbital or forehead edema • Meningismus
Uncommon	• Hemiparesis • Seizures • Facial pain • Facial paralysis • Abducens palsy • Drowsiness • Coma	• Coma

and modern antimicrobial treatment have significantly reduced the need for aggressive surgical management while dramatically improving outcome.

45.4.2 Subdural Empyema

When infection enters the subdural space, further deficits develop. In addition to cerebritis and meningitis from direct dissemination of bacteria along the surface of the brain, invasion and inflammation of the surface blood vessels may occur. Thrombophlebitis extending into the major venous sinuses results in regional disruption in venous drainage, cerebral edema, and ischemia from venous congestion [5, 10, 23, 24, 28, 33, 78, 79]. The ensuing parenchymal congestion and inflammation significantly decrease seizure threshold and status epilepticus can occur. Disruption of CSF absorption may develop resulting in elevated intracranial pressures and hydrocephalus. Level of consciousness may deteriorate and patients become precipitously obtunded if diagnosis is delayed. Bacterial toxins acting on neural and glial function mediate further neurologic deterioration [10, 12, 37, 61, 80]. Symptoms may also relate to the source of infection such as facial pain and otalgia from inadequately managed infection of paranasal sinus, middle ear or mastoid [27, 29]. In neonates, elevated intracranial pressure may present as irritability, seizure, and bulging fontanelle [10, 37, 80].

45.5 Investigations

Brain imaging in the form of CT to screen suspected disease in patients based on clinical history followed by MRI with gadolinium contrast for better anatomic characterization are the preferred investigations of these authors to accurately diagnose intracranial infection [3, 10, 12, 15, 18, 31, 40, 62]. There are adjunct investigations that may be helpful during the initial workup; however, prioritizing detailed brain imaging over other investigations facilitates expeditious diagnosis and definitive treatment.

In most centres, CT scan is the most readily available and cost-effective imaging modality of choice. Epidural abscesses are usually lentiform or biconvex with lower or intermediate density relative to the surrounding tissues, and may be rim enhancing with contrast administration. CT scan however, can be falsely negative in up to 50% of patients [28, 36, 81–83] (Figs. 45.1, 45.2, and 45.3). MRI, if available, is the preferred definitive imaging modality [10, 14, 28, 31, 37, 62]. Epidural abscesses are hypointense on T1 sequences, hyperintense on T2 sequences, high signal on diffusion weighted imaging and low signal on apparent diffusion coefficient indicating

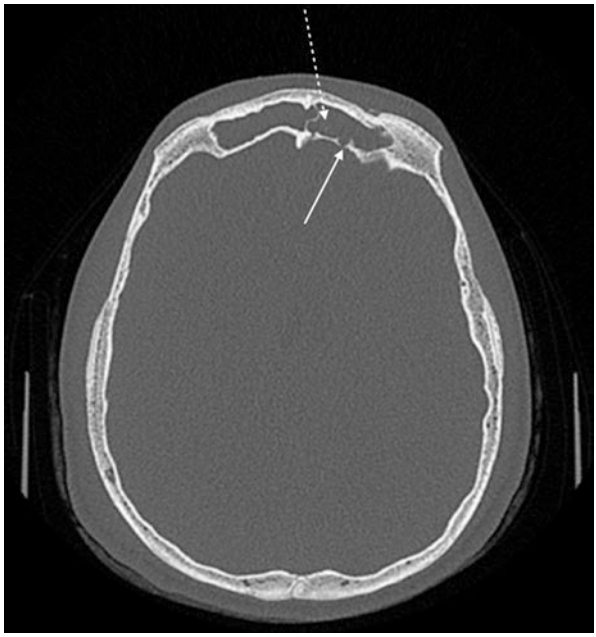

Fig. 45.1 CT scan without contrast of patient with frontal sinusitis leading to intracranial infection. Note complete opacification of the frontal sinuses (dotted arrow) with osseous defect along the posterior aspect of the left frontal sinus suggestive of source of infection and allowing intracranial transgression of infection (solid arrow)

restricted diffusion. MRI with gadolinium contrast may show enhancement with a sensitivity of 93% of infections [10, 18, 37, 62]. MR spectroscopy will demonstrate an elevated lactate peak in keeping with an infective process undergoing anaerobic metabolism (Figs. 45.4, 45.5, 45.6, and 45.7).

In comparison, subdural empyema may be seen on CT as low density crescent shape collection over brain parenchyma or adjacent the falx [10]. Occasionally, collections take on a lentiform shape similar to an epidural abscess owing to adhesions between the arachnoid and dura preventing distribution of purulent material over the convexity of the brain. There may be loculations within the collection. Contrast enhancement is more common and parenchymal changes such as cerebral edema from ischemia or venous congestion may cause mass effect and midline shift (Figs. 45.1, 45.2, and 45.3). On MRI, empyema may appear as isointense to hypointense on T1 sequences and hyperintense on T2 sequences [10]. There is often high signal intensity on diffusion weighted imaging and low signal intensity on apparent diffusion coefficient [10]. Like epidural abscesses, subdural empyema may also demonstrate gadolinium enhancement around the collection and will also have an elevated lactate peak on spectroscopy. Pneumocephalus in the absence of trauma may result from gas forming bacteria such as *Streptococcus pyogenes* or *Bacterioides fragilis* although mixed cultures may also produce similar findings [84–87]. In comparing the MRI to CT, MRI with contrast has been shown to have greater sensitivity for detection of subdural empyema compared to its CT counterpart [10, 32]. In the

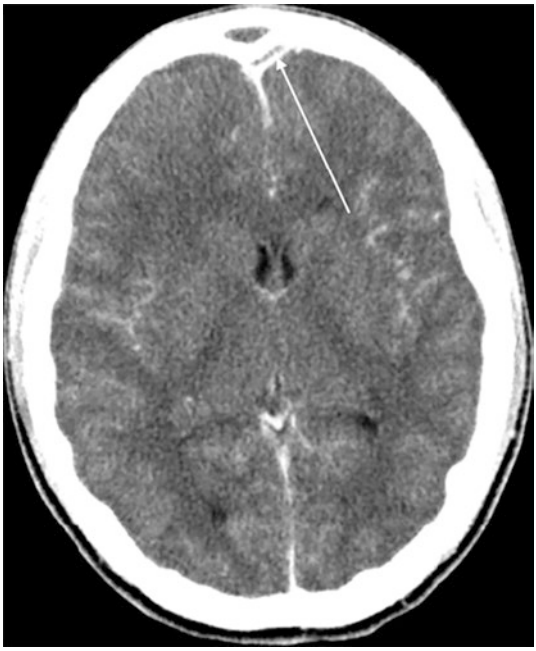

Fig. 45.2 CT scan post contrast imaging in patient with epidural abscess. In this image, there is evidence of a left frontal epidural collection of isointense signal characteristics to the brain parenchyma with associated surrounding enhancement (solid arrow)

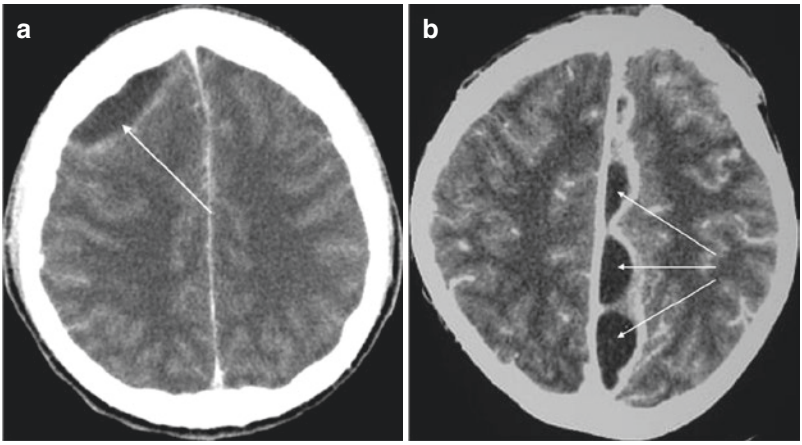

Fig. 45.3 (**a**) CT scan post contrast imaging in patient with subdural empyema. In this image, there is a large right frontal collection that is slightly hypodense and has some contrast enhancement at its periphery, most suggestive of a subdural empyema (solid arrow). In this example, the subdural empyema has taken on a lentiform appearance and without closer inspection, may be mistaken for an epidural abscess. Note the associated displacement of the brain parenchyma. (**b**). CT post contrast imaging in patient with interhemispheric subdural empyema. In this image, we can appreciate the significant hypodense collection in the interhemispheric space (arrows) with avid contrast enhancement at the periphery. The collection is able to extend and fill out the interhemispheric space and is most in keeping with a subdural empyema

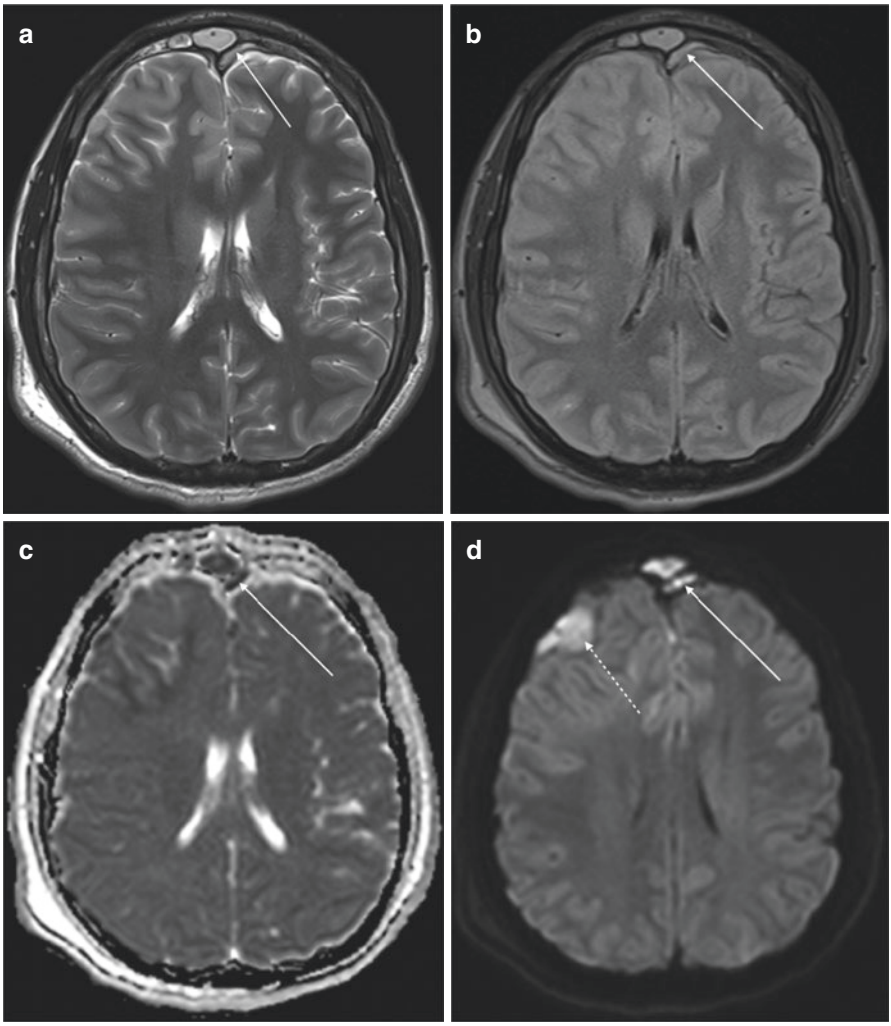

Fig. 45.4 (**a**) Non-contrast MRI in a patient with an epidural abscess secondary to sinusitis. T2, Fluid Attenuated Inversion Recovery (FLAIR), Apparent Diffusion Coefficient (ADC) and Diffusion weight imaging (DWI) images in axial view showing evidence of signal abnormality in the left frontal epidural space beneath the frontal sinus, denoting an epidural abscess (solid arrows). There is also a focus of signal abnormality of the right frontal region on DWI denoting ischemic changes secondary to infection (broken arrow). (**b**) Non contrast MRI in a patient with post craniotomy epidural abscess. T2, Fluid Attenuated Inversion Recovery (FLAIR), and Diffusion weight imaging (DWI) images in axial view showing evidence of signal abnormality posterior to the left cerebellum (solid arrow). The collection does appear to have similar signal characteristics initially to CSF on the T2 image; however on FLAIR we can see that the collection is not CSF in density while on DWI, we can appreciate the collection is restricting, suggestive of purulent, hyper cellular material

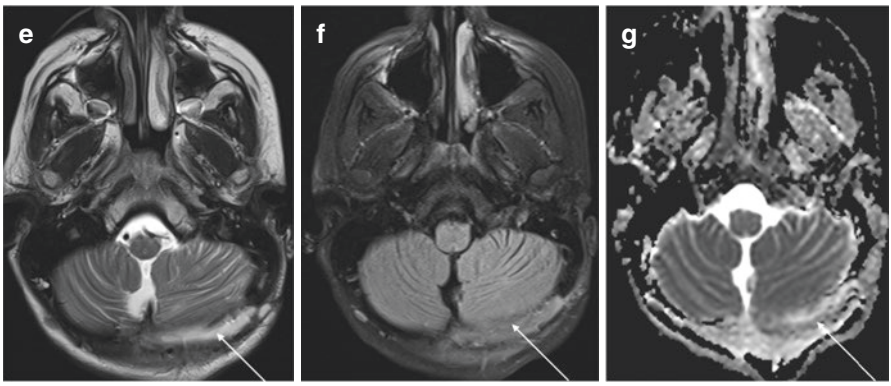

Fig. 45.4 (continued)

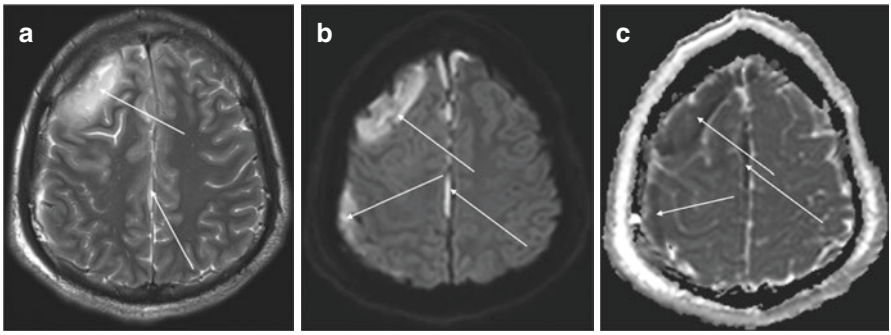

Fig. 45.5 Non-contrast MRI in a patient with a subdural empyema. T2,, Apparent Diffusion Coefficient (ADC) and Diffusion weight imaging (DWI) images in axial view showing evidence of signal abnormality in the right frontal subdural space in keeping with a subdural empyema (solid arrows). There is also evidence of disease in the interhemispheric space

setting of suspected subdural empyema, evaluation of the vascular architecture with dedicated CT or MRI venography is important given the risk of vascular involvement and to identify potential vessel occlusion [88, 89] (Figs. 45.4, 45.5, 45.6, and 45.7).

In addition to imaging, ancillary investigations may assist in work up and diagnosis. With both epidural and subdural infections, serum testing may reveal leukocytosis with left shift, increased erythrocyte sedimentation rate and elevated C-reactive protein [10, 15, 37]. CSF analysis may also show moderate pleocytosis, normal glucose and elevated protein. Serum and CSF culture are neither sensitive nor specific to rule out an intracranial infection and may lead to missed diagnosis if

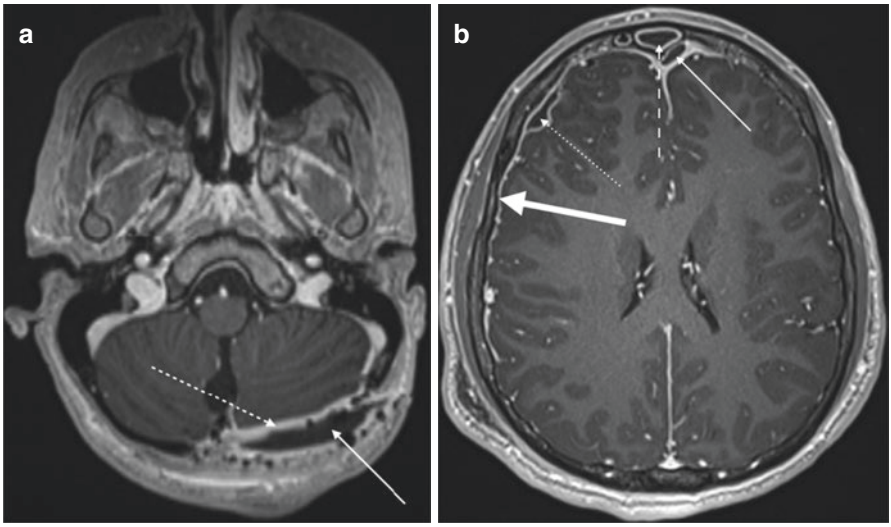

Fig. 45.6 (**a**) Post Contrast MRI in a patient with a post craniotomy epidural abscess. T1 post contrast image in axial view showing hypointense collection (solid arrow) posterior to the cerebellum. The dura underlying the collection is avidly enhancing in response (broken arrow). (**b**) Post contrast MRI in a patient with both epidural and subdural infection. Note in this image of a T1 sequence MRI in axial view post contrast, the patient has evidence of both epidural abscess (solid skinny arrow) as well as a subdural empyema (broken arrow). The frontal sinus is avidly enhancing (dashed arrow) suggestive of a frontal sinusitis and possible nidus for infection. Also note the avid leptomeningeal enhancement on the more afflicted right side (broad solid arrow) in comparison to the left

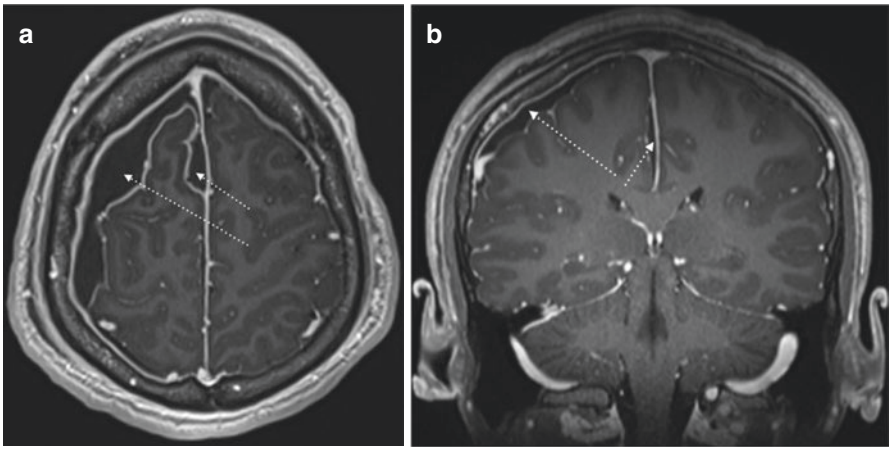

Fig. 45.7 Post contrast MRI of subdural empyema. In these T1 post contrast MRI axial and coronal views, there is evidence of peripheral enhancement of a subdural collection in keeping with subdural empyema (broken arrows). Note also the presence of infection over the convexity in addition to the medial surface of the hemisphere. While convexity disease is manageable with a surgical intervention (i.e. Burrhole or craniotomy) directly over top the disease, interhemispheric disease may require indirect irrigation via placement of a catheter placed via paramedian craniotomy

relied upon to exclusively [10, 29, 37]. The benefit of obtaining CSF is further mitigated by the risk of a lumbar puncture in the setting of elevated intracranial pressure from a suppurative cranial infection with potential for trans compartmental herniation. Carrying out a lumbar puncture should only be for investigation of a potential meningitis. When suspicion exists for a potential intracranial infection, CSF acquisition should be forgone until cranial imaging has been obtained. Infants with an open fontanelle may also be evaluated with intracranial ultrasound to distinguish between subdural empyema as opposed to an effusion that is seen in meningitis. On ultrasound, empyema appears as a crescent shape collection over the convexity or adjacent to the falx with a hyperdense rim [10, 29]. The boundaries will be echogenic. In comparison, subdural effusions lack clearly defined borders and evidence of echogenic material. While not commonly utilized as a primary diagnostic tool, skull x rays have historically been helpful in determine the etiology of intracranial collection [10] Sinusitis may be seen as an opacification of sinuses and fractures as an area of lucency. Osteomyelitis is most often associated with deep soft tissue swelling and cortical irregularities of the involved bone. Foreign retained bodies or extra corporeal debris may also be identified. X ray has largely been supplanted by modern imaging and in the exception of extreme circumstances where better modalities are unavailable, should not be relied upon as doing so may delay obtaining definitive investigations [10].

45.6 Treatment

For both epidural and subdural infections, broad spectrum antibacterial therapy against aerobic and anaerobic cocci and bacilli with CNS penetration is the first choice. Empiric treatment most typically includes vancomycin, metronidazole, and a third-generation cephalosporin. There are no specific validated guidelines on duration of antibiotic therapy; however, most are given for 6–8 weeks of which 2–6 weeks is by IV administration, followed by and oral therapy for the remainder [10, 12, 31, 37, 90, 91]. After a micro-organism is identified and susceptibility testing finalized, treatment should be titrated and targeted (Table 45.2).

45.6.1 Epidural Abscess

Smaller epidural abscesses without neurological deficit or significant mass effect may be treated solely with antibiotic therapy [9, 92]. In many cases however, surgical drainage with debridement of collection and surrounding tissues is necessary [15, 31, 62]. While smaller or liquid collections may be amenable to burr hole drainage, larger collections or those with a well encapsulated component may require an extensive craniotomy for definitive removal of the collection [9, 28, 36, 93]. Care must be taken to preserve dural integrity to prevent intradural extension [18].

Table 45.2 Comparison of microbial source by type of infection and treatment options

Condition	Otorhinological infection	Traumatic or post-surgical	Meningitis	Unknown
Organism	Aerobic and anaerobic streptococcus *Staphylococcus aureus* *Pseudomonas aeruginosa* Other anaerobes	*Staphylococcus aureus* Gram negative	Sterile (most common) *Neonates*: Enterobacteriaceae Group B streptococci Listeria Monocytogenes *Children*: *H. influenza*, *E. coli*, *S. Pneumoniae*, *N. meningitides*	Unknown
First line Antibiotic	Penicillinase resistant synthetic penicillin[a] + 3rd generation cephalosporin[b] + metronidazole	Penicillinase resistant synthetic penicillin[a] + 3rd generation cephalosporin[b]	3rd generation cephalosporin[b] +/− vancomycin	Penicillinase resistant synthetic penicillin[a] + 3rd generation cephalosporin[b] + metronidazole

[a]If beta lactam resistant or allergy, substitute penicillinase resistant synthetic penicillin for vancomycin

[b]3rd generation cephalosporin includes: ceftriaxone, cefotaxime. And ceftazidime if pseudomonas aeruginosa suspected in chronic otitis media

Additional surgery may be required for source control of the primary infection such as that arising from the nasal sinuses, otomastoid cavities, or oral cavity [31].

45.6.2 Subdural Empyema

Given its proximity and tendency to involve adjacent brain parenchyma subdural empyema requires surgical drainage near universally for evacuation and microbial identification [14, 62, 91]. Surgery can be in the form of burr hole drainage, stereotactic drainage for deep parafalcine or tentorial empyema, or formal craniotomy [9, 28, 37, 38, 45, 91, 93–95]. Early in the empyema stage, the collection is more fluid state making burr hole drainage possible. Once the empyema matures it may form loculations or become too thick to aspirate necessitating craniotomy to access [96]. Involvement of the parenchyma may also require debridement of tissues or decompression to alleviate swelling. It has been shown that craniotomy is superior to burr hole with lower morbidity and higher success rate [11, 15, 90, 96, 97]. Burr hole drainage was reported to have mortality of 48% compared to craniotomy with mortality 8% [61]. Management of the bone flap after craniotomy for subdural empyema and epidural abscess is controversial. Some authors have argued for craniectomy and subsequent delayed cranioplasty with autologous bone or

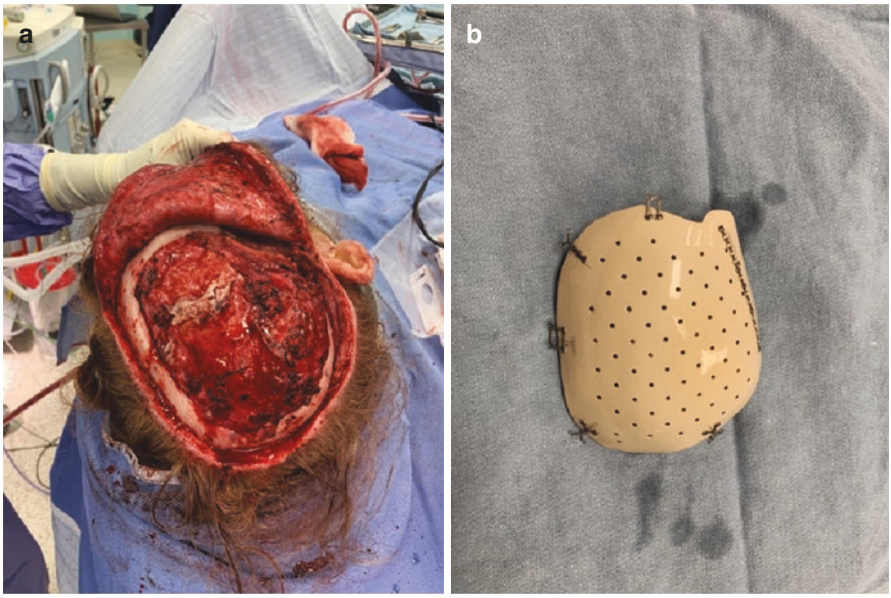

Fig. 45.8 Case: 18-year-old male with subdural empyema from sinusitis with delayed reconstruction utilizing 3d printed allograft. Note significant decompressive craniectomy required for convexity subdural empyema and associated cerebral edema. Large hemispheric defects, especially when a bone flap is to be left out for a prolonged period of time (i.e. For significant cerebral edema or gross contamination) are more likely to require an allograft for reconstruction. In these cases, 3d printed prosthesis may have a role in cranioplasty as they offer a custom fit and in the author's experience, very good cosmetic outcome with low risk of adverse event

artificial graft when the infection has resolved (Fig. 45.8). Other centres have found that craniotomy with immediate replacement of the bone is not associated with increased risk of bone flap infection [11, 15, 24, 28, 98]. Temporary CSF diversion in the form of an external ventricular drain or subdural drain should also be considered when patients present with hydrocephalus [10, 18, 91]. The authors of this chapter routinely utilize antibiotic impregnated catheters and have had good success without introduction of new infection. Postoperative imaging is also recommended for at least 3 weeks after initial surgery to confirm adequate evacuation of purulent material as it has been reported that 1/3 of patients require repeat surgery after subdural empyema. Current literature suggests there is a higher recurrence rate in burr hole treated patients (38%) compared to those undergoing craniotomy (10%) [28, 37, 38, 40, 61, 96, 99, 100]. The authors of this chapter routinely carry out craniotomy for convexity and parafalcine subdural empyema with planned placement of a subdural drain at the end of surgery. Only in cases where the patients are too medically unstable to tolerate a craniotomy or if the collection is deep seated and unreachable via craniotomy is burr hole placement with subdural drain alone performed. Prophylactic antiepileptic's (AED) should be considered for all subdural empyema patients during the acute phase. Some studies have reported

continuing AED for 6–24 months; others suggest continuing AED only if there is history of seizure and until patient is seizure free for 2 years [10, 12, 37]. In rare cases where antibiotics are the sole intervention, patients should be monitored closely through serial imaging to confirm resolution [92]. In patients who have significant raised intracranial pressure from ongoing cerebral edema, corticosteroids can be considered although is controversial [10, 37].

45.7 Prognosis

The prognosis for intracranial infection is heavily dependent on the location of infection, the level of consciousness at diagnosis, and rapidity of treatment. Cranial base and deep infections are generally more severe at presentation and tend to fare worse.

Neuroimaging and antimicrobials have reduced morbidity and mortality from epidural abscesses. Young age, absence of encephalopathy or severe neurological impairment upon presentation, and lack of comorbidities are indicators of good outcome [10]. Cerebral herniation on imaging with delay in diagnosis and treatment are predictors for poor outcome, imparting a worse prognosis [10, 37, 40].

Patients with subdural empyema overall fare worse compared to those with isolated infections of the epidural space. The survival rate of subdural empyema treated early with antibiotics and surgery is more than 90% [10, 12]. If treated within 72 h of symptoms, the risk of disability is 10% [5, 9, 25, 26, 28, 101]. Intervention after 72 h of onset however, increases the risk of major morbidity to 70% [37]. The mortality of subdural empyema is 50% if patients are comatose at presentation in comparison to only 10% if alert at time of diagnosis [5, 33, 35, 44, 61, 102–104]. Patients less than 10 years old or those with lack of focal localizing signs also trend towards worse outcomes. Diffusely spread purulent material seen on imaging or at time of surgery as well as the presence of a sterile culture predicts for a poorer outcome. Long term complications of empyema include persistent seizure and residual hemiparesis in 12–37.5% and 15–35% of patients respectively [15, 31, 37, 61].

45.8 Conclusion

Epidural abscess and subdural empyema are treatable intracranial infections with a tendency to occur in young males subsequent to otorhinolaryngologic infection. Timely diagnosis with cranial imaging followed by urgent surgical intervention and long-term antibiotics is imperative for the best possible outcome.

Key Points

1. Epidural abscess and subdural empyema are more prevalent in males than females (3:1).

2. The most common causes of epidural abscess and subdural empyema include inadequately treated otorhinolaryngologic infections
3. Empiric systemic treatment with penicillinase resistant synthetic penicillin or vancomycin+3rd generation cephalosporin + metronidazole should be considered until specific microorganism(s) is/are identified.
4. Postoperative serial neuroimaging is crucial to monitor for recurrence of infection.

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Chapter 46
Brain Abscess in Children

Suhas Udayakumaran and Chiazor U. Onyia

46.1 Introduction

A cerebral abscess (CA) is a common pediatric neurological problem. Despite this, management protocols have been vague and less objective [1]. There has been a change in the trends for aetiology, age distribution, and microbiological spectrum of brain abscesses in the recent decade. The past decade saw more of the cardiogenic abscess from an untreated primary aetiology [2] and postmeningitic brain abscess probably because of the better survival of preterm and postmeningitic babies.

The management of cerebral abscess has advanced significantly over time. Advanced diagnostics, the introduction of vaccinations, the introduction of newer-generation antibiotics, and early definitive management of primary cardiac and otologic etiologies have been significant contributors to the better present-day outcomes. Nonetheless, the antibiotic protocols and their duration have not changed since antibiotic treatment has been administered for the condition. Moreover, CA associated to uncorrectable cardiac pathologies, immunocompromised states, and trauma, which may challenge times to come.

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46.2 Epidemiology and Predisposing Factors

46.2.1 Incidence

A cerebral abscess (CA) is a life-threatening infection with a general incidence of 0.9 per 100,000 person-years and a 1-year mortality rate of 20% [3, 4].

The peak incidence amongst children is between 4 and 10 years of age [5–8]. Most series include only surgically treated and hence conservatively treated may be grossly underestimated. CAs are rarer in the neonatal age but are associated with a high risk of severe complications and mortality [9].

46.2.2 Aetiopathogenesis

Several conditions are well known to give rise to a cerebral abscess in children [10, 11], and they reach the brain in various ways (Fig. 46.1).

Predisposing conditions are contiguous or systemic infections, immunosuppression, right-to-left shunts (e.g. pulmonary arteriovenous malformations or congenital heart defects), head trauma, and neurosurgical procedures [12]. The aetiology varies according to the age groups. CAs are commonly related to meningitis or sepsis in infants, whereas the local spread of infection predominates in children, primarily ENT infections [13] (Figs. 46.2, 46.3, 46.4, 46.5, and 46.6).

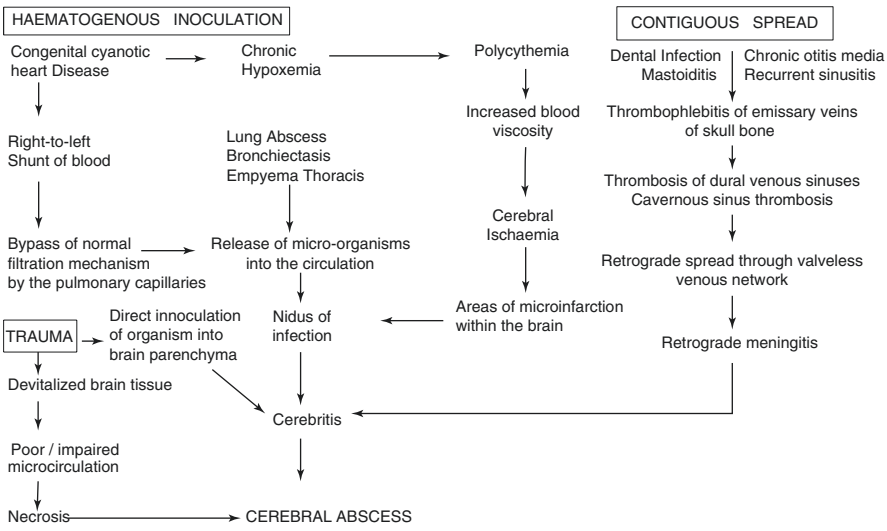

Fig. 46.1 Pathogenesis of brain abcess from various aetiologies

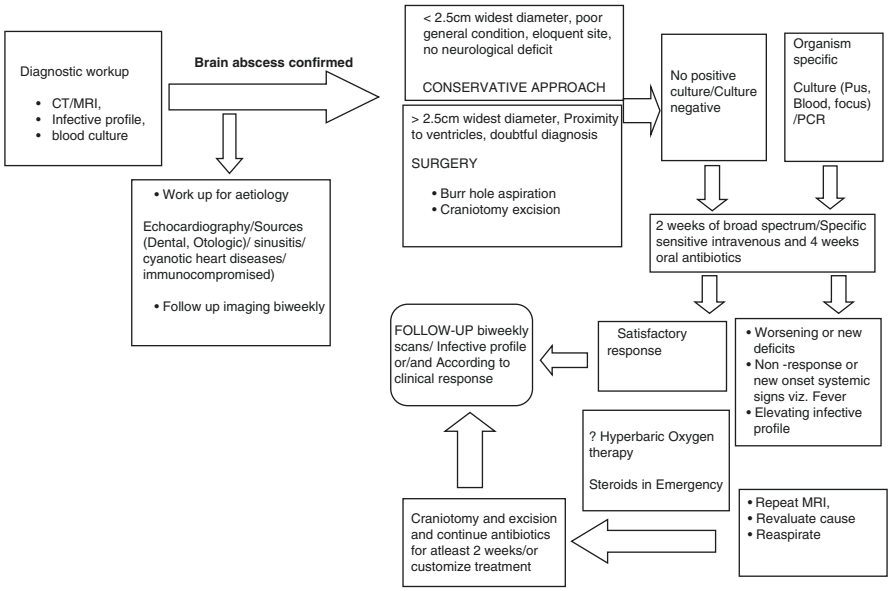

Fig. 46.2 Treatment algorithm for brain abscess

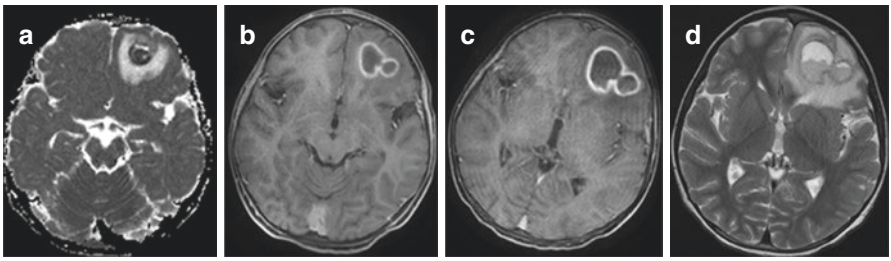

Fig. 46.3 5-year old with cardiogenic abscess (He had Tetralogy of Fallot for which he had undergone a palliative bypass at infancy) presented with seizure (**a**) The cellular pus in the centre of the abscess produces a low ADC value, and DWI shows diffusion restriction with central bright signal (**b**) With the contrast-enhanced axial MRI, he underwent conservative management (**c**), (**d**) The size increased on conservative management when he underwent excision as it was thick-walled and was penetrable for aspiration. The culture was negative, but his molecular diagnostics identified Strep. milleri and Mycobacterium for which underwent treatment

1. Haematogenous spread from a distant focus: Abscess collections from haematogenous sources tend to be frequently multiple and multiloculated. They are typically located deep within the brain substance at the corticomedullary junction in the parieto-occipital regions (due to change in capillary size and calibre at this location leading to stasis of blood flow) [10]. They are usually in the distribution of the middle cerebral artery [10]. Metastatic spread from distant foci

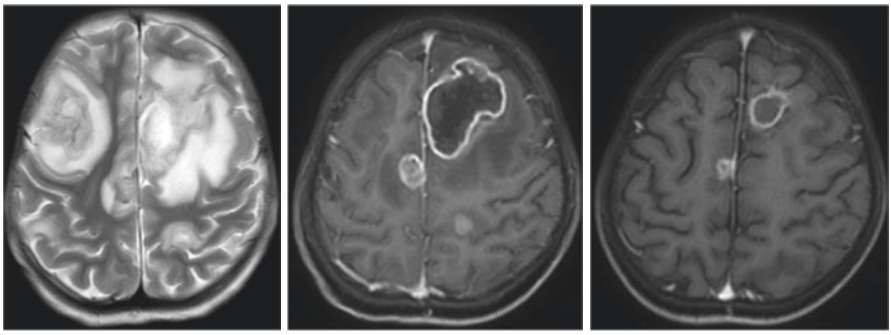

Fig. 46.4 Child on chemotherapy of acute myeloid leukaemia developed seizures, high-grade fever. MRI shows enhancing lesions. Her serum galactomannan was high suggestive of aspergillus abscess. She responded to Intravenous voriconazole (extreme right image)

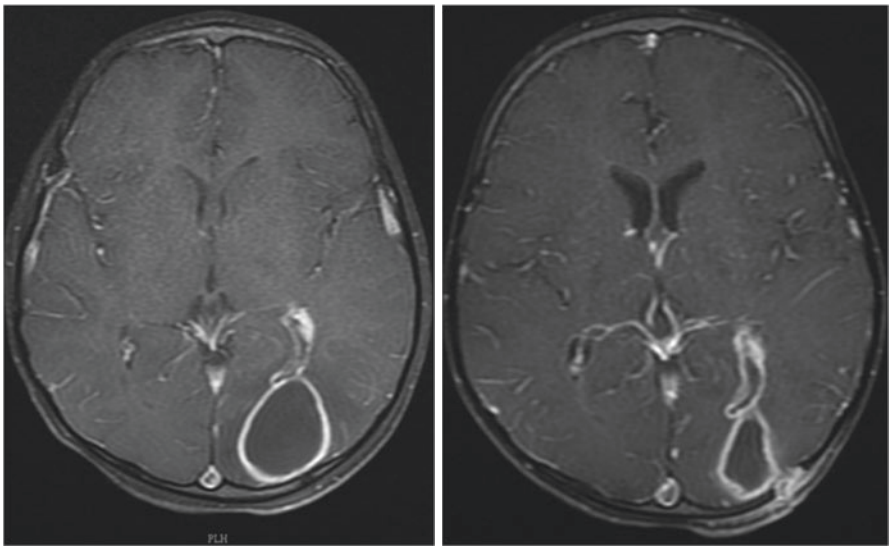

Fig. 46.5 A child with cardiogenic left occipital abscess with ventriculitis. His complaints started high grade developing severe neck pain in the course. He had a Tetralogy of Fallot physiology and had not undergone definitive surgery. In the event of ventriculitis especially with hydrocephalus, ventricular lavage, intraventricular antibiotics and an external ventricular drain may be an option

in children with congenital cardiac or pulmonary right-to-left shunts commonly results in any parenchymal area [1, 14]. Uncorrected congenital heart disease (CHD) remaining uncorrected becomes a nidus for bacteria to settle and a bacteremia source. Tetralogy of Fallot and transposition of the great vessels are the most commonly cited predisposing factors [1, 2, 14].

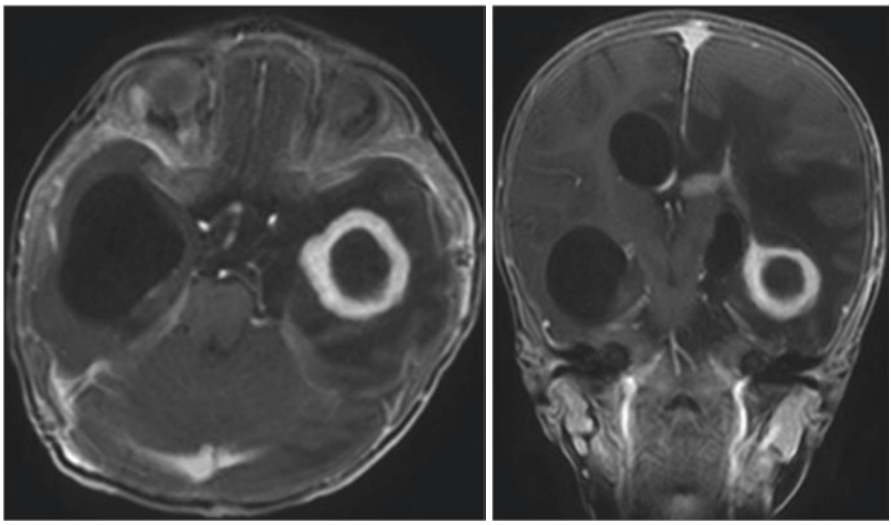

Fig. 46.6 An infant who shunt infection and meningitis developed a left temporal abscess. The temporal abscess is unusually thick-walled as the child had been on antibiotics for long (Antibioma)

2. Directly or through contiguity: Direct spread is through penetrating head trauma or cranial surgery, contamination from a contiguous infective source [10, 15, 16] including chronic osteomyelitis of paranasal sinuses in paranasal sinusitis, otitis media and dental infections [10, 16, 17]. These abscesses are commonly in the frontal lobes (from sinusitis and dental infections), pituitary/sellar region (from sphenoid sinusitis) and the cerebellum or temporal lobes (from otitis) [15]. Unlike CA of haematogenous origin, they typically tend to be single collections and are often close to the infection source [15]. Retained fragments in penetrating head trauma, open depressed skull fracture and basal skull fractures with cerebrospinal fluid leak are examples of a situation for direct contamination [10, 15].

   Conditions of immunocompromise such as retroviral (HIV) illness, post organ transplantation as well as those on immunosuppressive medication (such as chronic use of steroids) are also all well known to lead to abscess formation in children [15].
3. Cryptic source: Despite identifying all these potential sources, 15%-30% of cases were classified as cryptic brain abscess, in various series for which no apparent predisposing factor may be identified [18, 19]. Its clear that the source not being identified, suggests haematogenic spread without the development of septicaemia, especially from cavities in the body with resident microorganisms. This fact is corroborated by metgenomic analysis identifying sinus and dental floras as primary source [20].

46.3 Pathology and its Treatment Implications

46.3.1 Stages of Cerebral Abscess

Regions of brain abscess: There are five distinct regions within a brain abscess collection. From inside outwards, it has a necrotic centre which contains dead tissue and cells which includes dead phagocytes. This central portion is surrounded by a peripheral zone of inflammatory cells as well as fibroblasts which lay down reticulin fibres for collagen formation. A collagen capsule immediately surrounds this and then is an area of neovascularization. The layer of neovascularization layer accounts for 'ring enhancement' on imaging. An area of reactive gliosis with oedema of the surrounding brain, being the last layer of an abscess, may mimic the perilesional oedema of high-grade glioma.

Stages of development:

- Stage of early cerebritis: (From 1st to 3rd day) This stage of the initial genesis of the cerebral abscess is characterized by local inflammatory response surrounding the adventitia of blood vessels, culminating in developing oedema and a central necrotic region.
- Stage of late cerebritis: (From 4th to 9th day) This next stage is the formation of pus which is preceded by an increase in the size of the necrotic centre and oedema till maximum size is attained. It is also during this 2nd stage that fibroblasts lay down reticulin.
- Stage of early capsule formation period: (From 10th day till 13th day) the 3rd stage and is characterized by consolidation of the reticulin to form a meshwork of collagen. It is also in this 3rd stage that isolation of the necrotic centre from the surrounding parenchyma occurs.
- Stage of late capsule formation: (From 14th day and beyond). In this last stage, the 5 distinct regions of a well-formed abscess collection become evident.

The implications of the understanding pathology and stages correlating with imaging are that a well-defined encapsulated lesion is more amenable to surgical treatment, developed only later on in the disease process. Any earlier attempt to surgically excise or aspirate the lesion earlier in the disease process may not yield drainable pus, and the surgical excision of an ill-defined capsule may cause more damage of the oedematous brain around with undesired results. Additionally, the earlier stage may be more sensitive to antibiotic therapy then the capsulated forms.

46.4 Microbiology

Various organisms have been implicated in the formation of brain abscess [21].

1. Pyogenic—*Staphylococcus spp.* was well known as the most common in the pre-antibiotic era [16]. Presently, the most common organism well documented from

most studies is *Streptococcus* [17]. It is also the most typical organism isolated from cardiogenic brain abscesses [16]. Strains include Streptococcus viridans, anaerobic Streptococci and microaerophilic Streptococci. In head trauma with direct inoculation, the commonly implicated organisms are *Staphylococcus aureus, Streptococcus viridans and Streptococcus pneumoniae* [21]. Other bacteria implicated include Gram-negative organisms such as *E. Coli*, *Klebsiella* and *Proteus* [17]. These gram-negative organisms are commonly isolated from hematogenic abscesses and abscesses, which develop following craniotomy [21]. *Enterobacteriaceae, Enterococcus* and anaerobes such as *Bacteroides* have also been implicated as causes, particularly in cases of temporal lobe abscesses from otitis, where the pus may exhibit mixed culture results [16, 21]. In infants, *Proteus spp* and *Citrobacter* have been identified as the most typical cause [16]. Abscesses of dental origin originate from mixed infections by anaerobes such as *Prevotella Melaninogenica* and *Streptococcus Milleri* [21].

2. Fungal—The common ones in this category are *Candida albicans* and *Aspergillus* [16]. Others include *Actinomyces* [16] and *Nocardia* [21]. They commonly occur in immunocompromised children.
3. Mycobacterium—*M. tuberculosis* is rare but well associated with abscess collections in the brainstem, especially in endemic areas where pulmonary tuberculosis is widely common [16, 17].
4. Other rare organisms

   Protozoa—Trophozoites of *Entamoeba Histolytica* have been identified in brain abscess patients with cerebral amoebiasis [21]. They tend to respond well to treatment with metronidazole. *Acanthamoeba* has also been isolated [21].
5. Microbiology of cerebral abscess in immunodeficient

   Transplant recipients and similarly immune-suppressed patients often have brain abscesses caused by fungi, Nocardia, tuberculosis, or parasites. HIV is most commonly associated with toxoplasmosis or tuberculous brain abscess, but the etiological spectrum in these patients also includes bacteria, fungi and other parasites.

   Most abscesses are polymicrobial (60% as reported Stebner et al.) [22] with the utilization of molecular techniques have dramatically increased the number of organisms identified in a specimen making the traditional culture and the concept of causative bacteria-based empirical therapy questionable [20] (Table 46.1).

46.5 Management

46.5.1 Clinical Features

No symptom is pathognomonic of a cerebral abscess [25]. Typically, however, a cerebral abscess is characterized by a triad of fever, presence of neurologic deficits and manifestations of increased intracranial pressure [2, 15, 26, 27] although only a minority (approx. 15%) may present typically [28].

Table 46.1 Microbiology of cerebral abscess according to the predisposing factors and treatment of choice [23, 24]

Pathogenic mechanism and predisposing condition	Common pathogens	Primary treatment choice
Otitis media or mastoiditis, Sinusitis	Aerobic and anaerobic streptococcus species, Bacteroides and prevotella species, Enterobacteriaceae*, *P. aeroginosa* Aerobic and anaerobic streptococcus species, Bacteroides species, *S. aureus*, Enterobacteriaceae*	Cefotaxime + Metronidazole
Penetrating trauma or Postcraniotomy	*S. aureus*, *S. epidermidis*, Clostridium species, Enterobacteriaceae*, aerobic and anaerobic streptococcus species, *P. aeroginosa*	Vancomycin + Meropenem may be added in post neurosurgery abscess if prevalent organism are ESBL
Dental infection	Mixed infection with aerobic and anaerobic streptococcus species, prevotella, fusobacterium, actinomyces, and Bacteroides species	Cefotaxime + metronidazole
Lung abscess, empyema, bronchiectasis	Streptococcus, Bacteroides, prevotella, fusobacterium, and Nocardia species	Cefotaxime + metronidazole
Bacterial endocarditis	*S. aureus*, Streptococcus species	Cefotaxime + Metronidazole
Congenital heart disease	Streptococcus and haemophilus species	Cefotaxime + Metronidazole
Immuno-compromise HIV infection	*Toxoplasma gondii*, nocardia and Mycobacterium species, Cryptococcus neoformans	
Neutropenia	Aerobic Gram-negative bacilli, Aspergillus, candida, and scedosporium species, Mucorales	
Transplantation	Aspergillus and Candida species, Mucorales, scedosporium species, Enterobacteriaceae*, Nocardia species, *T. gondii*, *M. tuberculosis*	

1. Raised intracranial Pressure: The two typical manifestations of increased intracranial pressure include headaches and vomiting [16, 26]. Signs of meningeal irritation may be elicitable in some cases [27]. In several series, the most common presentations were symptoms of increased intracranial pressure, with the classic triad being incomplete in most cases [15, 16, 26, 27].

   In emergent situations of impaired consciousness, this is often due to either herniation of the brain from intense intracranial pressure or rupture of the abscess collection into the ventricles [16].
2. Focal neurological deficit: Focal neurologic deficits seen in children with brain abscess is often dependent on the location of the abscess in the brain, the size, virulence of organisms involved as well as the patient's immune response [15, 16]. Frontal and parietal abscesses tend to present with hemiparesis and (for left-sided lesions) aphasia [10]. Temporal and occipital abscesses tend to manifest with visual field disturbances, while cerebellar symptoms give rise to ataxia and nystagmus and dysmetria [15, 26]. Multiple cranial nerve deficits have also been described [10, 26].
3. Seizures: Supratentorial cortical-based abscesses can typically cause seizures [15]. Seizures are known to occur in half of the cases [16] and are mainly due to irritation of the cerebral cortex secondary to cerebritis or occasionally due to intracerebral thrombophlebitis [15, 16].

   However, most of these symptoms are not peculiar to only cerebral abscess and could arise from other intracranial space-occupying lesions [15, 25]; hence, it is the consistent constellation of presentation, signs and imaging that is definitive of a cerebral abscess.

46.6 Evaluation

46.6.1 Evaluation for Infection

1. **Infective profile**
   Complete blood count, C-reactive protein, Procalcitonin
2. **Blood culture, the culture of any foci material**
3. **Culture of pus in aspirated/excised abscess**
4. **Molecular diagnostics**
5. **Imaging**

C-reactive protein seems a useful marker in diagnosis and monitor response. Hence baseline raised values if present, can be used to monitor response, decide treatment endpoint, need for reaspiration and recurrence [27]. Patients with multiple intracerebral brain abscess aspirations showed significantly higher preoperative CRP values than patients who needed surgery only once [27, 29]. Hence in the event of high CRP or increasing trend during treatment, a closer imaging, as well as

clinical and laboratory exams, may be merited [27, 29]. In CNS infection, procalcitonin is a useful marker for diagnosing systemic bacterial infection. Simultaneously, it may not be useful to diagnose focal bacterial infection like a cerebral abscess, and the diagnostic performance of procalcitonin might be inferior to that of CRP [30].

A blood culture may be positive in 25% of patients, particularly in patients with a hematogenous spread of infection [12]. Lumbar puncture is not recommended because of the risk of brain herniation. An underlying dental, paranasal sinus, ear, or skin foci should be cultured and surgically explored if required.

Brain abscess tissue and material obtained through diagnostic and therapeutic aspiration must be sent for gram stain, bacterial, anaerobic, fungal and tubercular cultures. The anaerobic organisms are susceptible to exposure to the environment and hence should be handled appropriately. Culture and subsequent antibiotic sensitivity analysis of the sources, as mentioned earlier, form a key to definitive diagnosis and therapy.

CA diagnostics can be improved by employing cloning and sequencing of 16S-rDNA amplicons [20], or next-generation sequencing. 16S-rDNA-based metagenomic analysis of intracranial abscesses has revealed in many cases, a more diverse bacterial composition than microbiological culture and Sanger sequencing [22]. An increased diagnostic power provided by complementary NGS analysis would enable a more focused, yet sufficiently broad, antibiotic treatment, thereby benefitting the individual patient while matching the goals of antibiotic stewardship [22].

46.7 Imaging in Cerebral Abscess

- **Diagnosis**: Imaging is a crucial adjunct for decision-making in the management of cerebral abscesses. Although CT may be preferred in emergencies, MRI is a more sensitive and specific diagnostic tool [31] and can provide an early diagnosis before the capsular stage of the infection when compared with brain CT [32].

The diagnosis and the treatment endpoints have been traditionally based on radiology, especially the enhancement. With regard to a cerebral abscess, it is well accepted that enhancement suggests a breach of the blood-brain barrier [33] The dose of contrast may also alter the enhancement pattern [33]. An early stage of cerebritis may also show definite enhancement [33].

Imaging may be a pivotal adjunct to understand the treatment response and to support the endpoint of treatment. Reducing size in conservatively managed CAs or comparison with the post drainage size along with the reduction of the surrounding cerebral oedema whenever present, maybe a very sensitive marker for the response.

- **Treatment response and follow up**: A mandatory protocol during treatment to have interval imaging (at least 2-week gap) or if the treatment response is not adequate and in the event of new symptoms or clinical signs. Using enhance-

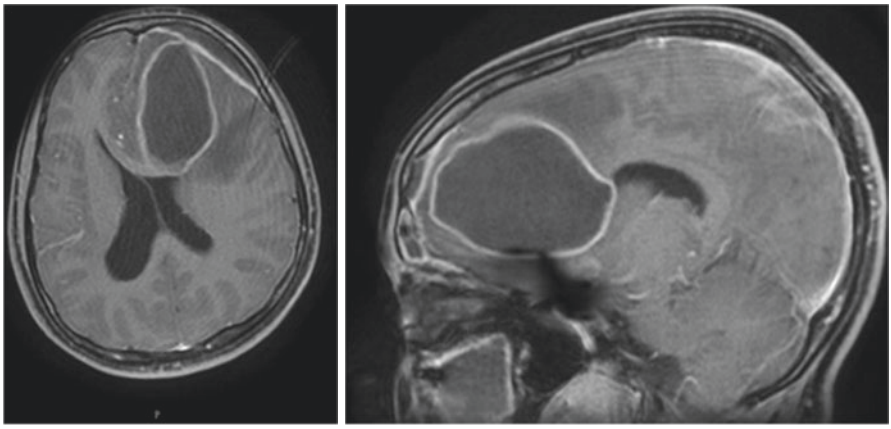

Fig. 46.7 12-year old presenting with left frontal abscess. She had a history of recurrent sinusitis. She underwent endoscopic sinus surgery for treatment of the aetiology subsequent to abscess drainage

ment as a basis for a treatment goal is not well supported [27] as residual enhancement can remain for as long as 8 months. The exact mechanism is unknown, but it probably involves an alteration of the blood-brain barrier, perhaps due to the formation of a different type of small vessel. Thus, prolonged enhancement is a nonspecific response of the brain parenchyma to various insult types [34].

The follow-up imaging should be biweekly (and as per clinical scenario earlier if anything untoward) once recovery is evident until 3 months (This can be tailored with a longer gap if the abscess appears quiescent in consecutive images (Fig. 46.7).

- **Newer imaging modalities**: In the last decade, gadolinium-enhanced MRI with diffusion-weighted images and MR spectroscopy have high sensitivity and specificity, improving diagnostic efficacy and prompter diagnosis [35–38]. Areas with restricted motion exhibit high signal intensity, whereas free water such as the CSF becomes dark (Fig. 46.2a, d). The absolute value of diffusion restriction can be quantified by the apparent diffusion coefficient (ADC) and is independent of the MRI manufacturer and the applied field strength. ADC values correlate to liquids' viscosity and are typically low in abscesses and high in necrotic brain tumours [39–41].

46.8 Treatment

Treatment of brain abscess has been challenging due to the infection's cerebral location with antibiotic diffusion issues related to the blood-brain barrier and the abscess capsule [24, 42]. Additionally, inherent predisposing factors like an untreatable

cardiogenic abscess, immunodeficiency [2] may remain unresolved, leading to inadequate response and recurrence.

46.8.1 Decision-Making Algorithm

Initially, a broad-spectrum antibiotic is chosen, which is later switched to a specific antibiotic based on the culture report or molecular diagnosis (Fig. 46.7). If the culture report is negative for an organism, the broad-spectrum antibiotic is continued. A baseline infective profile, along with the frequent repetition of the same, is a critical element of our decision-making and ultimately guides the duration of antibiotics (Fig. 46.7).

46.8.2 Principles of Medical Management

1. **Indications of nonoperative management: Medical therapy should be considered as a reasonable first option.**

   A nonoperative management strategy for cerebral abscess can be attempted

- For clinically stable patients who are poor candidates for surgery or who have inaccessible lesions [27], and
- Small collections (around 2 cm) are located in well-vascularized cortical areas, which are more likely to respond to antibiotics alone [27].

Cases treated conservatively may require a more prolonged duration of treatment and close clinical and radiographic follow-up.

An indication for the surgical option is discussed in the next section.

2. **Empirical antibiotics:** Medical management is empirical to start with, and specific after an organism report (based on culture or molecular diagnostics) has been received. The basis for selecting the antibiotic is usually the site of the lesion, and the suspected causative organism is presumed based on previous scientific data. In vitro, antibiotic sensitivity results have shown that a cephalosporin and metronidazole regimen, typically used in most neurosurgery units [42–47], is a good presumptive choice of therapy for community-acquired cerebral abscess. Vancomycin may be an empirical addition for a posttraumatic abscess. Otherwise, any higher antibiotics like meropenem or vancomycin were rarely included empirically and should be restricted to, e.g., nosocomial or postneurosurgical brain abscess and other cases with suspected antimicrobial resistance [12, 24] (Fig. 46.5).

3. **Definitive antibiotics**

Uncomplicated Abscess in an Immunocompetent Individual

Initial therapy with intravenous cephalosporins with metronidazole has been a uniform recommendation in most literature. Amongst cephalosporins, especially cefotaxime and ceftriaxone, are recommended [24]. Vancomycin can be added, if methicillin-resistant S. aureus (MRSA) is prevalent in the local setting or the abscess is caused by previous head trauma or neurosurgery (Table 46.2). Ceftazidime or meropenem can be used instead of cefotaxime in patients at risk for Pseudomonas aeruginosa or B. pseudomallei brain abscess.

Other drugs that can be used for antimicrobial therapy, such as fluoroquinolones, rifampicin or clindamycin, are known for their diffusion ability into the brain and abscess pus, and that could support a potential benefit on brain abscess prognosis due to their high degree of bioavailability [48–50].

Depending on geographic location or travel history, tuberculosis and parasites also need to be considered.

Abscess in Immunosuppressed Individuals and Special Conditions

For example, for severely immunosuppressed patients, transplant recipients, voriconazole (fungal brain abscesses) (Fig. 46.3) and trimethoprim-sulfamethoxazole or sulfadiazine (toxoplasmosis and nocardiosis) should be added. If L. monocytogenes is suspected, ampicillin should also be added [24].

In patients with HIV infection, the standard regimen should be combined with pyrimethamine-sulfadiazine in seropositive patients for Toxoplasma gondii. In patients exposed to tuberculosis (e.g. immigrants from endemic countries or socially marginalized individuals) empiric anti-tuberculous therapy should be considered.

Except for those caused by S. aureus, P. aeruginosa, underlying endocarditis or previous neurosurgery most abscesses are polymicrobial, based on DNA based studies [11, 13, 14, 17] hence continuation of cefotaxime and metronidazole should be considered even when culture results suggest a monomicrobial infection.

Consolidation with an Oral Antibiotic

Depending on antibiograms, the suggested oral treatments could consist of cotrimoxazole-trimethoprim, amoxicillin, ciprofloxacin, and/or metronidazole [24].

Duration of Antibiotics

The appropriate duration of antimicrobial therapy for brain abscess remains unclear [51]. A 6- to 8-week course of, parenteral antibiotics has been traditionally recommended provided that the etiological organisms are susceptible, and adequate surgical drainage is achieved [47]. The basis for this traditional regimen is unclear and, to a large extent, may be unfounded.

Unlike in recent times, there were multiple reasons for the persistence of the traditional regimen in the past, for example, when there was a cryptic source for the cerebral abscess. An extended antibiotic regimen was necessary when the

Table 46.2 Antibiotic protocol for empirical and definitive therapy (Adapted from Bodilsen et al.) [24]

Patient profile/organism	Empirical therapy	Alternative
Uncomplicated abscess in an immunocompetent individual	Cefotaxime* + metronidazole Consider adding vancomycin if MRSA is endemic or abscess is caused by previous neurosurgery including implants like Shunt or head trauma	
HIV positive/Immunocompromised	Add pyrimethamine and sulfadiazine to the standard regimen	Pyrimethamine + clindamycin; TMP-SMX; pyrimethamine + azithromycin, clarithromycin, atovaquone or dapsone
Transplant recipients	Add voriconazole and TMP-SMX or sulfadiazine to the standard regimen. Consider adding ampicillin for L. monocytogenes.	Liposomal amphotericin B, itraconazole, posaconazole
Actinomyces spp.	Penicillin G	Clindamyciin
Bacteroides fragilis	Metronidazole	Clindamycin
Enterobacteriaceae	Cefotaxime	Meropenem, fluoroquinolone, TMP-SMX, aztreonam
Fusobacterium spp.	Metronidazole	Clindamycin, meropenem
Listeria monocytogenes	Ampicillin +/− gentamicin	TMP-SMX
Mycobacterium tuberculosis	Isoniazid, rifampin, pyrazinamide, ethambutol	
Nocardia spp.	Trimethoprim-sulfamethoxazole + imipenem Consider adding ceftriaxone in life-threatening or disseminated disease	Meropenem, third-generation cephalosporin, linezolid, moxifloxacin, amikacin, tigecycline, minocycline
Pseudomonas aeruginosa	Ceftazidime or meropenem +/−quinolone	Aztreonam, cefepime, tobramycin/gentamicin
S. aureus Penicillin-sensitive	Penicillin G	Vancomycin
Methicillin- sensitive *S.aureus*	Nafcillin or oxacillin	Vancomycin
Methicillin-resistant *S.aureus*	Vancomycin	TMP-SMX, linezolid, clindamycin, daptomycin
Fungus		
Aspergillus spp	Voriconazole	Liposomal amphotericin B, itraconazole, posaconazole

Candida spp	Liposomal amphotericin B +/− flucytosine	Fluconazole + flucytosine, voriconazole
Scedosporium spp.	Voriconazole	Itraconazole, posaconazole
Cryptococcus neoformans	Liposomal amphotericin B + flucytosine	Fluconazole, voriconazole, posaconazole
Mucorales	Liposomal amphotericin B	Posaconazole
Dematatious fungi	Liposomal amphotericin B + flucytosine +/− itraconazole/ voriconazole/posaconazole	Itraconazole, voriconazole, posaconazole
Toxoplasma gondii	Pyrimethamine + sulfadiazine	Pyrimethamine + clindamycin; TMP-SMX; pyrimethamine + azithromycin, clarithromycin, atovaquone, or dapsone

aetiology could not be identified; thus, the protocol was empirical. For instance, an otologic or a cardiogenic aetiology could not be identified because of the lack of imaging or sensitivity. A high incidence of uncorrected CHD also contributed to the use of a traditional regimen. In the past and developing nations, the treatment for CHD was not as advanced for early diagnosis and correction, leading to a high number of uncorrected CHD cases or patients with advanced sequelae such as pulmonary hypertension and making it impossible to safely correct by current standards.

Shorter durations have been successful and recommended in many reports [27, 52–58] and follows a tendency of shorter (IV) treatment durations for other infectious diseases.

We recommend a short course parenteral therapy for uncomplicated abscess in immunocompetent individual, with close follow up of the infective profile, especially when raised and imaging for objective support to the response [27].

Oral consolidation therapy has been a practice in most treatment recommendations. The duration has been for 2–4 weeks. The endpoint of oral consolidation is again controversial with no clarity.

Response to Treatment

The clinical criteria for a positive response are 1) improving neurological symptoms and signs, and 2) no significant hyperthermia (100 °F or 38 °C). The laboratory criteria for a positive response consist of 1) normal WBC counts, and 2) normal CRP and other inflammatory markers. Follow-up values are collected even after deciding to stop the antibiotics and declare a cure. The MRI protocol at all stages essentially involves T2 and contrast-enhanced sequences, and response to treatment is demonstrated by stable or decreasing radiological signs with no active signs. 1) Decreasing active signs specifically pertain to reduced perilesional oedema (T2 sequence) around the cerebral abscess, reduced nonspecific signs including no new satellite lesion, and decreasing features of effacement, as well as 2) a decreasing lesion size. Note that a comparison of contrast enhancement on pretreatment and posttreatment images was not a criterion for demonstrating a response. Follow-up must show clinical quiescence with decreasing signs on MRI, as described previously. The enhancement size is followed, but a change in the enhancement character is not an essential requirement. All four types of criteria—clinical, laboratory, imaging, and follow-up—are essential and should be satisfied in declaring a cure of the abscess.

Criteria for Stoppage of Antibiotics

Even if the clinical, laboratory and imaging criteria are satisfied, the infective profile may reach baseline values in a delayed manner. Hence, such cases are followed up until they are normalized. We have observed that the infective profile may not always reach the true normal range at 2 weeks but may show a significant decrease to near normal. This has been enough justification for us to stop antibiotics. Any

need for reaspiration in the same period is considered an indication to continue the antibiotic regimen at least 2 weeks beyond the reaspiration. Even if the reaspirated material shows no growth on culture, we prefer to continue the drugs for an additional 2 weeks [27].

Indication for Surgical Approach
Following are the indication for surgical intervention

1. Large-sized abscess with mass effect and low neurological status
2. Ventricular proximity or ventriculitis.
3. Nonresponse or progression under conservative management, which may suggest refractoriness secondary to the underlying predisposing condition (e.g. Cardiac physiology) or nonresponsive organism (suggesting atypical organism, e.g. Fungal, Mycobacterium)
4. Doubtful diagnosis with atypical clinical features

46.8.3 Surgical Options

Depending on the clinical stability of the patient and proximity of the abscess to the cerebral ventricles (short distance to cerebral ventricles increases the risk of rupture of brain abscess), empiric anti-infective therapy can often be withheld if a neurosurgical procedure can be performed at the earliest so that culture samples are informative.

Burr hole aspiration is as effective as excision in managing most purulent collections within the brain but with less morbidity. There have been no controlled prospective studies comparing the various surgical approaches in homogeneous populations of patients with cerebral abscesses, neither in terms of efficacy nor in terms of morbidity. The data comes from studies of retrospective cohorts or descriptive series of cases, which are certainly not suitable for measuring any differences ([27], [59]).

Stereotactic approach to aspiration is an option in the following indication: deep-seated or small abscesses of those located in eloquent areas, multiple hemispheric abscesses, patients who are poor candidates for general anaesthesia. More and more publications advocate using stereotactic aspiration followed by systemic antibiotics as the surgical treatment of choice [60–62]. An additional advantage of stereotactic needle insertion may not be to obtain pus samples but also to administer therapeutic agents and improve therapeutic response and shorten antibiotic course [63].

Neuronavigation can be used as an adjunct to minimize localisation issues and the occasional need for large craniotomies. It also allows a trajectory that avoids critical tracts and eloquent areas to access deep abscesses for stereotactic aspiration.

Aspiration can be performed safely at any stage of brain abscess evolution, and even a biopsy taken from acutely inflamed brain parenchyma can give positive culture results. Even multiloculated abscess can sometimes be treated with aspiration if all loculi can be safely accessed through a small burrhole.

Neuroendoscopic approaches combined with freehand stereotactic aspiration have also been reported, as has the use of flexible or rigid endoscopes to aid microdissection of thick capsules and visually inspect the abscess cavity perform lavage following aspiration [64, 65].

Outcome principally in terms of mortality and long-term outcome is affected above all by the patient's initial conditions rather than the type of surgery [66–69]. When evaluated even if in a select population such as neonates and compared with a different population, the speed with which the operation is made, rather than the type of operation, is the factor that most affects the final condition of these patients [9].

Drainage by craniotomy or craniectomy or excision is used more often in superficial abscesses and those found in the posterior cranial fossa occasionally which can be associated with lesions like dermoid. Furthermore, excision is often used in posttraumatic, postoperative patients and those with a chronic abscess with inadequate response to repetitive aspiration.

46.8.3.1 Monitoring Treatment Response and Endpoint

Treatment response can be monitored postsurgery based on the clinical condition, infective profile, and serial imaging.

1. Infective markers: Infective markers shows a decreasing trend in the presence of satisfactory response
2. Role of serial Imaging: Repeat CT and MRI eventually show a decrease in the size of the abscess, disappearance of surrounding oedema, and decreased enhancement ring. These improvements are usually observed within 1–4 weeks of management, but complete radiographic resolution often extends to several months of follow-up.

46.8.3.2 Role of Steroids

Steroid therapy in these patients is very controversial, given that steroids are known to retard the encapsulation process, increase necrosis, reduce antibiotic penetration into the abscess, and alter CT images [70, 71]. They can also produce a rebound effect when discontinued [70]. Yet steroids can be life-saving therapy for patients with extremely high intracranial pressure [70, 72]. Overall the benefit and disadvantages of routine use in CA is unclear [11, 73, 74] but can be used as a life-saving measure in the presence of extreme cerebral oedema with impending herniation.

46.8.3.3 Other Treatment Considerations

Sources of systemic infections should be sampled for microbiological diagnostics whenever possible and amenable predisposing conditions corrected early during treatment to prevent relapses and recurrences (Figs. 46.4 and 46.6).

46.8.3.4 Timing of Management of Underlying Cardiac Physiology

There is a paucity of current literature on intervention timing to correct cyanotic physiology in children with a cardiogenic abscess. The following criteria are suggested before any definitive intervention: completion of course of antibiotics, including at least 3 weeks of parenteral and 3 weeks of oral antibiotics; improving and stable imaging characteristics; and an insignificant infective profile. Ideally, early corrective management of the cyanotic physiology will remain the critical step in avoiding recurrence and providing satisfactory outcomes [2].

46.8.3.5 Role of Hyperbaric Oxygen Therapy

Specific adjuvant options, such as hyperbaric oxygen therapy (HBOT) are gaining acceptance and may become part of standard treatment protocols for managing [75]. In a study by Bartek et al., the authors concluded that HBOT was associated with fewer treatment failures and reoperations and seemingly improved long-term outcomes. They further observed that HBOT was well tolerated and safe. Prospective studies are warranted to establish the role of HBOT in the treatment of brain abscesses [76].

46.8.3.6 Prognostic Factors

1. Alteration of consciousness at the initial presentation is a poor prognostic factor [18, 69, 77, 78].
2. Intraventricular rupture of the abscess is also a substantial factor in these patients' poor prognosis [47].
3. Underlying conditions: Resolution of the underlying condition is a predictor for recurrence of these lesions.

   A cardiogenic abscess is one of the predictors of inadequate resolution and recurrence [2]. Certain conditions in which the pathophysiological processes can be reversed are associated with an excellent prognosis, with no risk of abscess recurrence due to the condition once the underlying condition is resolved. Patients with cyanotic physiology in whom surgical correction is not possible are at lifelong risk for cerebral abscess, in addition to the poor prognosis of the primary cardiac condition [2]. Similarly, immunodeficiency is an additional cause leading to inadequate response and recurrence.

4. The morbidity rate appeared higher in infants compared with older children, as previously reported [9]. Morbidity is dominated by hydrocephalus, especially in infants, where meningitis is a common predisposing factor [73].
5. Treatment decision, including antibiotic choice, does not seem to have a clear impact on prognosis. The sequelae have been noted to be minimum with aggressively treated brain abscesses [47].
6. Long-term problems common to all cerebral abscesses include the impaired cognitive function and delayed onset of seizures, as well as focal neurologic deficits [47]. Class II evidence is available in adults; brain infection is associated with an increased risk of subsequent epilepsy [79]

46.9 Summary

- An unresolved primary aetiology at presentation is a risk factor for the cerebral abscess's persistence and recurrence.
- Biomarkers of inflammation can be used as a reliable guide for reimaging, surgical intervention during treatment, and overall response whenever elevated at the beginning of treatment.
- A short course of an organism-specific antibiotic can be used successfully in carefully selected and monitored patients. A 2-week antibiotic protocol is undoubtedly more suitable for immunocompetent patients who have a noncardiogenic aetiology.
- A cerebral abscess prognosis is good with minimal neurological sequelae whenever the primary aetiology can be resolved, and diagnosis and treatment are prompt.

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Chapter 47
Encephalitis

Marios Lampros, Georgios Alexiou, and Neofytos Prodromou

47.1 Introduction

Inflammation of cerebral parenchyma (or Encephalitis) is a relatively rare disease associated with a high mortality rate if left untreated. The introduction of antiviral regimens against herpes simplex virus (HSV) such as acyclovir, the increase in the number of immunosuppressed patients, the implementation of widespread vaccination for diseases such as mumps have caused significant alterations in the epidemiological landscape and the management of patients with encephalitis [1, 2]. The risk for encephalitis development is probably higher in the pediatric age group, while different pathogens are observed among different age groups. Currently, new types of auto-immune encephalitis such as Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis have been recognized. In this chapter, we discuss epidemiological, clinical, imaging, and treatment features of pediatric encephalitis and the association of encephalitis with common neurosurgical conditions [3, 4].

47.2 Epidemiology

The epidemiology of encephalitis in the pediatric population is not well described due to a lack of prospective studies in the literature. An incidence ranging from 2–10/100.000 cases has been reported, while the incidence is probably higher in infants. The mean age of children with encephalitis is approximately 6 years. No

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significant sex predilection has been observed [5, 6]. The implementation of vaccination programs against viruses such as measles, rubella, polio, and mumps has eliminated the encephalitis associated with these pathogens, which consisted a significant cause in the past [7]. Despite that, these diseases should be suspected in unvaccinated children with symptoms of encephalitis. Moreover, the spread of Human Immunodeficiency Virus (HIV) and the use of immunosuppressive or chemotherapeutic regimens in patients receiving transplantation or in patients with cancer respectively have caused a significant increase in the number of immunosuppressive patients. These patients are at high risk of encephalitis from herpesviruses (HSV1–2, CMV, EBV, HHV 6–7) [8, 9] Epidemic outbreaks (local or national) of encephalitis are usually associated with infections from arboviruses or enteroviruses [10, 11]. The seasonal distribution of encephalitis is not sufficiently studied. However, some authors suggest the use of oseltamivir as a part of the initial empirical regimen in patients with encephalitis during periods of seasonal (winter months) flu outbreak [12].

47.3 Aetiology

The complete understanding of pediatric encephalitis etiology remains unclear, with viral agents being the responsible pathogen in approximately 60–80% of the cases. Table 47.1 summarizes the main causes of encephalitis in children and their treatment. The cause of encephalitis is not identified in more than one-third of cases of encephalitis despite extensive laboratory testing [5, 6]. Contrary to adult encephalitis where HSV-1 is the leading cause, a wider spectrum of pathogens is involved in children. Despite that, HSV-1 remains a remarkable cause and accounts for 5–15% of pediatric encephalitis cases. The leading pathogens of pediatric encephalitis are Varicella-Zoster Virus (VZV), respiratory viruses and enteroviruses, which account for 20% of encephalitis cases each. Other viruses associated with encephalitis are adenoviruses, Cytomegalovirus (CMV), Human herpesvirus (HHV) 6–7, Epstein–Barr virus (EBV), with immunosuppressed patients being at greater risk for developing encephalitis from these viruses [6]. Arboviruses such as West-Nile Virus (WNV) and Japanese Encephalitis Virus (JEV) are other causes of viral encephalitis and are associated with epidemic outbreaks [13, 14]. Measles, mumps, rubella, and chickenpox should be considered a cause of encephalitis in unvaccinated children.

Bacterial encephalitis accounts for 10–30% of pediatric encephalitis cases and may affect solely the cerebral parenchyma or occur as meningoencephalitis. *Mycobacterium tuberculosis* (*M. tuberculosis*), *Mycoplasma pneumoniae* (*M. pneumoniae*), and *Listeria monocytogenes* (*L. monocytogenes*) are the leading causes of bacterial encephalitis in children. Nonetheless, a wide spectrum of bacteria have been reported as a cause of encephalitis including *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*), *Borrelia burgdorferi* (*B. burgdorferi*), *Bartonella quintana* (*B. quintana*) [6, 15]. An increased incidence

Table 47.1 Summary of the main causes of encephalitis in children and their treatment

Type of encephalitis	Significant causes	Treatment
Viral	VZV	Acyclovir
	HSV-1	Acyclovir[a]
	Enteroviruses	Ribavarin or intravenous immunoglobulins
	Respiratory viruses	Oseltamivir
	EBV	Acyclovir
	CMV	Ganciclovir, Valganciclovir, Foscarnet, Cidofovir
	HSV-2	Acyclovir[a]
	WNV	Supportive
	JVE	Supportive
	HIV	Anti-retroviral
Bacterial	*M. tuberculosis*	Anti-tubercular
	M. pneumoniae	Azithromycin
	L. monocytogenes	Amoxicillin
	S. pneumoniae	Ceftriaxone
	N. meningitidis	Ceftriaxone
	B. burgdorferi	Ceftriaxone
	B. quintana	Doxycycline
Fungal	*C. neoformans*	Amphotericin B or fluconazole
Parasitic	*T. gondii*	Sulfadiazine and pyrimethamine
Auto-immune	ADEM	Corticosteroids, i.v. immunoglobulin
	Anti-NMDAR	Corticosteroids, i.v. immunoglobulin, removal of the ovarian teratoma in women
Rasmussen	Unknown	Corticosteroids, plasmapheresis, iv immunoglobulin, or functional hemispherectomy

Varicella-Zoster Virus (VZV), Herpes simplex virus (HSV), Cytomegalovirus (CMV), Human herpesvirus (HHV) 6–7, Epstein–Barr virus (EBV), West-Nile Virus (WNV), Japanese Encephalitis Virus (JEV), Human Immunodeficiency Virus (HIV), Acute Diffuse Encephalomyelitis (ADEM), Anti-N-methyl-D-aspartate receptor (anti-NMDAR), *Mycobacterium tuberculosis* (*M. tuberculosis*), *Mycoplasma pneumoniae* (*M. pneumoniae*), *Listeria monocytogenes* (*L. Monocytogenes*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*), *Borrelia burgdorferi* (*B. Burgdorferi*), *Bartonella quintana* (*B. quintana*), *Toxoplasma gondii* (*T. gondii*) and *Cryptococcus neoformans* (*C. neoformans*)

[a]Absolute indication to reduce mortality

of encephalitis associated with *Chlamydia pneumoniae* (*C. pneumoniae*) has been reported in recent years [16]. Fungi and parasites are known causes of encephalitis in immunosuppressed patients, but in pediatric series, very few reports of such cases exist. Common pathogens included in this category are *Toxoplasma gondii* (*T. gondii*) and *Cryptococcus neoformans* (*C. neoformans*) [17]. *Naegleria fowleri* encephalitis should be suspected when the patient has a current history of swimming in lakes and is associated with a high mortality rate [18].

Although infective encephalitis is the most common form of encephalitis, many autoimmune causes of encephalitis have also been identified [19]. ADEM is probably the most common form of non-infective encephalitis. It is a demyelinating disease that shares clinical and imaging features with Multiple Sclerosis (MS) and is a type of anti-MOG associated encephalomyelitis. ADEM typically occurs after a viral infection (e.g. VZV, EBV, CMV, Enteroviruses, COVID-19) or very rarely following vaccinations and bacterial infections (e.g. *M. pneumoniae*) [4, 20, 21]. Anti-NMDAR encephalitis is another typical encephalitis that occurs in children and may account for 30–50% of all autoimmune encephalitis cases. Auto-antibodies against the GluN1 subunit of NMDAR are detected and it has been associated with HSV-1 infection. Moreover, it is associated with the existence of ovarian teratoma in approximately 30–50% of the cases in women [19, 22, 23]. Other antibodies that are associated with encephalitis are anti- Gamma Amino Butyric Acid (GABA) Receptors, anti-glutamic acid decarboxylase (GAD) in limbic encephalitis, and voltage-gated potassium channel (VGKC)–protein complex antibodies. Despite that, 60% of autoimmune encephalitis are seronegative and different criteria have been proposed for their diagnosis [5, 19, 24, 25]. Rasmussen encephalitis is another possibly immune-mediated encephalitis associated with chronic seizures in children. This encephalitis in particular is of neurosurgical interest because the definite treatment is functional hemispherectomy [26].

47.4 Clinical Manifestation

Approximately 60% of patients with encephalitis usually have a prodrome period of flu or diarrheal syndrome. The prominent clinical feature of encephalitis is the occurrence of encephalopathy (altered consciousness or behavioral changes) together with fever. Focal deficits, hemiparesis, and seizures may typically be observed in patients with encephalitis [5, 6]. Meningism (headache, neck stiffness, photophobia) is suggestive of meninges involvement and thus of meningoencephalitis usually associated with bacterial infections. Clues that facilitate in the differential diagnosis from other Central Nervous System pathologies such as tumors include the onset of acute symptoms, the presentation of fever, a recent history of viral infection, or recent vaccination (in ADEM). Limbic encephalitis is usually immune-mediated or paraneoplastic and affects structures of the limbic system (e.g. temporal lobe, amygdala, hippocampus), and patients usually occur with loss of short-term memory, seizures, confusion, hallucination, or other psychiatric disturbances. Rasmussen encephalitis is an exceedingly rare type of encephalitis that typically affects one cerebral hemisphere of children and occurs with seizures and loss of functions of the affected hemisphere (e.g. hemiparesis, hemianopia, cognitive impairment) [26]. The onset of hydrocephalus in encephalitis without the involvement of meninges is very uncommon. In the majority of cases, the hydrocephalus concerns patients who have bacterial meningoencephalitis and is treated with an external or ventriculoperitoneal (VP) shunt [27].

47.5 Diagnosis

Encephalitis is generally defined as the onset of encephalopathy of at least one-day duration, as well as exclusion of other pathologies that could explain the patient's clinical picture, with additionally two or more of the following criteria [28, 29]:

- Fever
- CSF pleocytosis (more than 4–5 white cells per mm^3).
- Seizures or neurological deficits that cannot be attributed to other conditions.
- Imaging findings suggestive of encephalitis.
- Electroencephalography (EEG) findings suggestive of encephalitis (slow waves-high amplitude).

Features from the patient's history that may assist in the encephalitis diagnosis is a recent history of flu or gastroenteritis, bacterial infections associated with encephalitis, recent vaccinations, known local epidemic waves of viruses related to encephalitis (e.g. WNV, JEV), and the existence of any known immunodeficiency (e.g. HIV infection). However, as previously discussed, the cause of encephalitis will not be identified in approximately half of the patients.

CSF puncture is the most important initial test that should be performed in any patient with a suspicion of encephalitis. Nevertheless, it is important to exclude any possible signs of raised intracranial pressure (ICP) prior to the procedure due to the risk of brain herniation. Clinical features that raise a concern for elevated ICP is papilledema, seizures, and decreased level of consciousness. In these patients, a Commutated Tomography (CT) scan should be performed to evaluate ICP before the lumbar puncture. CSF findings that suggest encephalitis are pleocytosis (more than 5 cells per mm^3) with most of them being lymphocytes. Glucose and protein levels are usually within the normal range in contrast to cases of bacterial meningitis where glucose levels are low and protein levels are increased [30]. Despite that, low glucose levels and increased protein levels are observed in bacterial, fungal, or protozoal encephalitis (or meningoencephalitis). Polymerase Chain Reaction (PCR) of CSF is performed in all cases with suspicion of encephalitis to detect HSV1–2, VZV, HIV, CMV, HHV 6–7, (Para) Influenza, and Enteroviruses in accordance with the patient's history and the CSF is usually sent for bacterial and fungi cultures. It is important for the clinicians to note that the PCR analysis of CSF may be negative in the first 2 days of the infection. Thus, a single negative result does not exclude an infection. Despite that, the sensitivity of the test is very high after the second day even with the administration of an empirical antiviral regimen [6, 29]. Additionally, blood, throat, and nasopharyngeal samples are collected for culture, biochemical, serology, and PCR analysis for the common pathogens of encephalitis. Serology is commonly utilized to detect an increase in the title of IgM antibodies, or a new increase in the title of IgG antibodies which may facilitate the diagnosis. Stool samples may be collected to detect enteroviruses [5, 6].

Clinically, the differential diagnosis between autoimmune and infectious encephalitis is challenging and cannot be based on the patient's clinical presentation. In

both types of encephalitis, fever and a prodrome period of flu-like symptoms may be observed, but in autoimmune encephalitis, the fever is usually developed later in the progression of the disease. In autoimmune encephalitis, and especially in encephalitis associated with NMDAR, psychiatric symptoms and behavioral alteration are more prominent than in infective encephalitis, while in encephalitis associated with anti-GABA Receptors (GABA-R) seizures are usually the prominent feature. Auto-immune encephalitis is very rare in immunosuppressed individuals [31]. The typical serological workup for auto-immune encephalitis in children includes autoantibodies test for NMDAR, GABA-R, VGKC–protein complex, GAD, MOG (in ADEM), and Leucine-rich glioma inactivated 1 (LGI-1). Despite that, approximately 30–50% of autoimmune encephalitis will be seronegative and their diagnosis is mainly guided by the exclusion of any other known causes of acute encephalitis [19].

47.6 Imaging

Although neuroimaging is typically not diagnostic of encephalitis, it is the most important examination to exclude other intracranial or other CNS pathologies. At the time of admission, a brain CT scan will be performed in the majority of patients to evaluate a possible contradiction for lumbar puncture (increased ICP or herniation) [30]. Additionally, in the initial CT, the presence of a hemorrhagic stroke or space-occupying lesions (e.g. abscesses, neoplasms) can be evaluated. Brain Magnetic Resonance Imaging (MRI) is the neuroimaging examination of choice to evaluate a patient with suspected encephalitis. Generally, encephalitis' lesions display high signal in T-2 weighted images and restricted diffusion in Diffusion-Weighted Images (DWI). In HSV-1 the middle temporal lobes, insular cortexes, inferolateral frontal lobes, and limbic system structures are usually affected bilaterally, while HSV-2 affects diffusely the brain parenchyma. In children, extra limbic lesions are not uncommon. The main differential diagnoses that should be considered are low-grade gliomas, gliomatosis cerebri, and limbic encephalitis (unusual in children). In VZV, the cerebral cortex, the cerebellum, and basal ganglia are usually affected, while areas with hemorrhages may be observed [32].

With the exception of ADEM and probably limbic encephalitis, most types of autoimmune encephalitis have no specific imaging findings, and in many cases the initial brain MRI does not display any pathological feature. In ADEM the prominent feature is the presentation of tumefactive demyelinating lesions with high signal in T2-WI bilaterally in the brain and the spinal cord. These lesions display little to no mass effect even though many of them can be large in size [33]. After Gadolinium (Gd) administration, a ring enhancement of the lesion may be observed in T1-WI. Differential diagnoses for ADEM include MS (dissemination in space and time), Hurst disease, lymphomas, high-grade gliomas (Anaplastic astrocytoma and Glioblastoma). The absence of mass effect and the prominent involvement of the white matter are the key imaging features that assist in the differential diagnosis

from brain neoplasms [34]. NMDAR associated encephalitis usually appears with no lesions in MRI in the initial imaging, and if present the findings are atypical and presented as areas with high signal in T2-WI [35].

47.7 Treatment

At the time of the admission, the pathogen of encephalitis is usually unknown and an empirical regimen is administrated against the pathogens of encephalitis associated with a high mortality rate (HSV 1–2) and against the common pathogens of bacterial meningitis (*N. meningitides*, *S. pneumoniae*, *H. influenza*), especially in cases where the patient presents symptoms of meningism. Infection from HSV-1 and HSV-2 is highly lethal with approximately 80% mortality rate if left untreated, and thus it is of crucial significance to cover the patients with an anti-viral regimen as early as possible [30].

Ideally, a lumbar puncture should be performed immediately after the clinical suspicion of encephalitis, but if the lumbar puncture is delayed more than 6 h a treatment regimen that includes acyclovir should be administrated. The anti-viral regimen of choice for HSV and VZV encephalitis is intravenous (iv) acyclovir. Oseltamivir may be co-administrated in the flu seasons. The UK protocol of pediatric viral encephalitis management suggests the use of iv acyclovir for 2 weeks (or 3 weeks in immunosuppressed), and evaluation of CSF with PCR at the end of treatment. If the virus is still detected in the CSF, acyclovir should be continued for one week. The circle of weekly acyclovir treatment is continued until HSV/VZV is not detected in CSF [30, 36]. If evidence of meningism is present, ceftriaxone is administrated to cover the bacterial causes of meningitis. Moreover, if the patient's history set a suspicion of other causes of encephalitis such as recent pneumonia with *M. pneumoniae*, consumptions of contaminated products (eg. infection from *L. monocytogenes*), a recent tick (eg. Lyme disease) or tuberculosis, the empirical regimen should be modified with the addition of appropriate antibiotics for each pathogen [5, 29]. An anti-fungal and anti-protozoal regimen may be considered in patients with HIV infection if low glucose and high protein levels are present in CSF. A specific protocol for the treatment of auto-immune pediatric encephalitis in children has not been established. In the majority of the cases, corticosteroids are the first-line treatment. Alternative treatments include the use of intravenous immunoglobin and plasma exchange. In women with NMDAR encephalitis associated with a teratoma, removal of the teratoma can lead to a full recovery in approximately 60–70% of the patients [19].

Neurosurgical intervention is usually not required in patients with infectious encephalitis. A call for neurosurgical evaluation is required in cases of hydrocephalus development. In these cases, a VP or external CSF shunt may be required. Risk factors for the onset of hydrocephalus development include cases of mumps encephalitis, bacterial meningoencephalitis, signs and symptoms of meningism, and recurrent seizures (especially status epilepticus). An additional role of the neurosurgeon

in cases of encephalitis used to be to obtain a brain biopsy in cases where the diagnosis cannot be established with the conventional laboratory and imaging methods. However, the introduction of PCR in clinical practice has eliminated the need for a brain biopsy in encephalitis diagnosis [5]. Finally, in the case of Rasmussen encephalitis which does not respond to conservative treatment with corticosteroids, plasmapheresis or iv immunoglobulin, a functional hemispherectomy may be needed to control the seizures and to improve patients' quality of life [26, 35].

47.8 Prognosis

Despite the application of novel treatment protocols and the use of acyclovir, the mortality rate of infectious encephalitis remains high and ranges from 10–30%. The younger age of affected children and infection from HSV1 and HSV-2 are possibly the most significant risk factors for survival. Severe neurological sequelae such as seizures, truncal ataxia, hemiparesis, behavioral disorders, and quadriplegia may be observed in 10–20% of children [6]. In ADEM and encephalitis associated with NMDAR antibodies, the mortality rate is lower (5–15%). Nevertheless, the morbidity remains high, and moderate to severe neurological impairments are observed in approximately 20% of children after the treatment [37–39].

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Chapter 48
Spine Infection in Children

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48.1 Introduction

Pediatric spinal infections are uncommon and include spondylodiscitis, spinal epidural abscess, and intradural (extramedullary and intramedullary) spinal infections.

Anatomic differences between pediatric and adult spinal conformation may explain particular predisposition to spinal infection in pediatric age. The metaphysis of the vertebral body is a highly vascular structure in growing children [1, 2]. Also, the intervertebral disc, which is completely avascular in adults, is conversely extremely vascularized in children: blood vessels ramifications are present throughout the cartilaginous endplates until the age of 8 years, after which they progressively disappear. This might participate in the etiology of most of spinal infections, as a result of spreading of pyogenic and not pyogenic organisms into the vertebral body and the discal space. Fortunately, this high vascularization of the vertebral bodies and the discs in children also favors a relatively good response to antibiotics, compared to adults. For the same reason, infections of the posterior elements of the vertebrae are less common and most challenging to solve with medications, due to their poor blood supply [3].

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Prognosis of spinal infections may vary from benign in most cases of discitis, to potentially disabling consequences (even death) in some cases of epidural or subdural abscess. Delay in diagnosis is the most important factor associated with poor outcome. High level of clinical suspicion, for these rare pathologies, should lead to early diagnosis and prompt management.

48.2 Spondylodiscitis

Inflammation of the intervertebral disc (discitis), of the vertebrae (spondylitis) or a combination of both (spondylodiscitis) is an uncommon entity. Actually, the term "spondylodiscitis" (SD) is usually used to indicate a continuum of primary spinal infections, from discitis to spondylodiscitis and vertebral osteomyelitis with occasional associated soft-tissue abscesses [4]. In fact, an isolated discitis is sporadic: it generally afflicts younger children (<5 years of age) and occurs almost exclusively in the lumbar region. Non-iatrogenic discitis is virtually absent in adults, in which it is possible only as a complication of spinal surgery or other invasive diagnostic procedures [5].

Generally, inflammation involves the disc and the two adjacent vertebral bodies (spondylodiscitis). Vertebral osteomyelitis typically occurs in older children and even if it is more frequent in the lumbar region, it can affect also thoracic and cervical regions [6].

According to etiology, SD are typically divided into pyogenic (the most frequent); unspecific granulomatous; specific (such as tuberculosis); and parasitic [7–9].

48.2.1 Epidemiology

In pre-MRI era, the incidence of SD was estimated to be approximately 1:250,000 of the population [9, 10]. Nowadays, after the popularization/diffusion of the MRI, the diagnosis is more frequent; even if clear epidemiological data are not available, they represent approximately from 3% to 5% of all cases of osteomyelitis [11] and accounted for 3% of all the cases of osteoarticular infections in the pediatric population [12]. SD is more common in immunocompromised children, such as those affected by leukemia, chronic renal disease, sickle cell disease, diabetes mellitus [1].

A characteristic triphasic age distribution has been reported: the first peak of incidence is in children aged only a few weeks or months old, the second one in those between 6 months and the end of the preschool period, and the third peak in school-aged children [1, 9]. Dayer et al., in a multicenter retrospective study on 103 patients, found a higher incidence (79%) in early childhood, between the age of six months and four years, a smaller later peak (20%) in the juvenile and adolescent group, and only exceptional infections (1%) in children under six months [4].

Lumbar spine is the most common site of pediatric SD, seen in 75% of cases [9]. Dayer et al. also noticed that the incidence of spondylodiscitis has increased gradually from the upper to the lower lumbar regions and that the L4-L5 space was the most frequently affected level (26.2%) in their series [4]. In the same study, none of the children presented with pure discitis; in fact, spondylodiscitis was more frequent in toddlers, whereas older children and adolescents mostly presented with suffer vertebral osteomyelitis [4].

48.2.2 Pathogenesis and Etiology

Spondylodiscitis is caused by an infection of the intervertebral discs and/or vertebral endplates: the previous theory of self-limiting inflammatory condition has to be considered obsolete [4]. Usually, pathogens reach the children spine hematogenously, from a previously existing primary site of infection [9]. The spinal infection can first involve the disc and subsequently the adjacent vertebral endplates or originate in the vertebral bone tissue as vertebral osteomyelitis, subsequently involving the disc [9]. Some pathogens might be directly inoculated into the spine during surgery or a diagnostic procedure such as lumbar puncture or positioning of spinal drainage; exceptionally following a trauma [13]. Interestingly, a peculiar cause of SD in infants is the ingestion of batteries or more generally to foreign bodies [14]. Batteries may cause esophageal burns and microperforations, secondary to primary caustic alkali injury, absorption of toxic substances, ulcers and electrical discharge from the cathode to the anode [14]. Pathogens from the upper gastrointestinal tract may reach the prevertebral space leading to SD. Typically this complication occurs between 1 and 6 weeks after ingestion, even if battery has been removed from the esophagus [14].

Three main clinical forms have been described according to the age of the child [15, 16]. The neonatal form affects infants under six months of age and it is the most severe, because part of a systemic disease, with several infective foci, usually as the consequence of *Staphylococcus aureus* septicemia. The infantile form affects children aged between six months (the end of maternally derived immunity) and four years, and this age group represents 60% of cases of childhood spondylodiscitis [4]. The third form affects children aged over four years who are more likely to have vertebral osteomyelitis due to *Staphylococcus aureus*.

Staphylococcus aureus, in fact, is the predominant organism in infants and older children (80% of cases) [9]. Other agents less frequently identified are coagulase-negative *Staphylococcus*, α-hemolytic *Streptococcus*, *Streptococcus pneumoniae*, and Gram-negative bacteria such as *Escherichia coli* and *Salmonella* spp. *Kingella kingae* is the most common causative organism in the age group of 6 months to 4 years [9]. K. kingae is a Gram-negative organism which is difficult to detect. In the last years, the bacterium became more easily to identify through molecular methods, such as real-time polymerase chain reaction (PCR). Therefore, etiology can be determined in many cases that previously were considered of “unknown

origin", due to negative cultures. Moreover, a positive throat swab for K. kingae may ensure the diagnosis also in those cases in which microbiological cultures of the infection site are negative [16].

Subacute and chronic spondylodiscitis can be caused by a wide spectrum of non-pyogenic bacteria such as *Mycobacterium tuberculosis*, *Brucella* spp. and fungi (i.e., *Aspergillus* spp., *Candida* spp. And *Cryptococcus neoformans*) [17]. Fungal organisms like Aspergillus, Candida, and Cryptococcus are more common in immunocompromised children [17]. Brucella can be found in children with exposure to farm animals and consumption of non-pasteurized milk products like cheese [17].

48.2.3 Clinical Aspects

The clinical features are extremely variable and non-specific, and hence, delay in diagnosis is common. A high index of suspicion is necessary to diagnose this condition in an early stage.

In neonates and younger infants the clinical scenario is usually dominated by systemic infection, secondary to sepsi and multiple infectious foci. The vertebrae can be severely damaged and sometimes entirely destroyed, leading to kyphosis, with severe deformity [18].

In toddlers and preschool-aged children, signs and symptoms of disease are frequently mild: low-grade fever, pain (lumbago, abdominal, neck and sciatic pain) and stiffness are the most frequent complaints. Severe neurologic manifestations, such as tetra- or paraplegia are rare, whereas refusing to walk or sitting are frequent symptoms in young children. Cervical lesions may be responsible of torcicollis, neck stiffness, or dysphagia. As reported by Mohanty et al., some clinical signs may indicate lumbar spine involvement in young children: "Gower's sign" (the child uses his hands to get up from squatting position due to proximal muscle weakness.), "quarter sign" (the child experiences pain while bending forwards to pick up a coin), and "log-roll sign" (the child experiences pain in the hip and groin when his legs are extended due to the stretching of the psoas muscle) [1].

Older children and adolescents are more prone to develope vertebral osteomyelitis and the clinical presentation is typically dominated by systemic disease: the patients are febrile and ill-appearing. Sometimes the clinical picture is limited to back pain.

The onset of neurological deficits is usually delayed and may be caused by spreading of the infection into the spinal canal (in the epidural or subdural space) or by pathological collapse of the involved vertebral body, with secondary spinal cord/nerve roots compression [9].

Duration of symptoms and signs before diagnosis may widely vary: as the clinical picture may be non-specific, diagnosis may be delayed, even for months [19]. Patients who develop complications have a significant delay in diagnosis [10, 20]. Extensive septic bone infarcts may also cause cavitation, pathological fractures, instability, epidural empyema and paravertebral abscess.

48.2.4 Neuroimaging

Magnetic Resonance Imaging (MRI) is the gold standard for diagnosing infectious disorders of the spine, especially in the pediatric age group. Computed Tomography (CT) evaluation must be weighed against radioprotection issues and should always be tailored to the minimum possible field of view so as to minimize unnecessary radiation exposure [21]. Plain radiographs of the spine are commonly performed as an initial radiological test. However, they shows limited diagnostic value, in fact, the destruction of end plates, reduction of disc spaces, and spinal deformity may necessitate about 2–3 weeks to develop.

As a consequence of the frequently aspecific clinical presentation of spinal cord compression, MR imaging is usually performed in emergency regime. A significative matter in pediatric MRI is the capability of small patients to cooperate long and well enough to obtain quality imaging studies. Younger or severely ill children typically require sedation, which is administered differently according to individual center protocols. Additionally, it is recommended to perform imaging of brain in the same session, in order to identify possible additional infection sites (such as those typical of tubercular infections) while minimizing the need for further sedation and delaying the diagnosis of cerebral localizations or meningitis [13, 22].

Spinal MRI should include high-resolution sagittal T1-weighted, T2-weighted and short-tau inversion recovery (STIR) images covering the whole spine, to rule out coexisting abnormalities; a coronal STIR acquisition offers the advantage of also scrutinizing the paravertebral regions [23]. Axial sequences on either T1-weighted or T2-weighted imaging are used to study specific regions based on the clinical indications or findings on sagittal images, such as to determine the cross-sectional extent of the spinal cord involvement. High-resolution heavily T2 weighted images (constructive interference in the steady state or driven equilibrium, DRIVE) provide depiction of cord/root/cerebrospinal fluid (CSF) interfaces. DRIVE sequences and 3D T1-weighted images are particularly useful to investigate subtle structural abnormalities in the pediatric population, such as those found in the context of spinal dysraphisms [24]. Postcontrast images are of paramount importance for an adequate identification and characterization of spinal infectious disorders; they should be acquired in the three planes of space with fat-suppression techniques.

In the pyogenic infections, in the very early stages, imaging studies are consistent with discitis. The infected intervertebral disc is typically hyperintense on T2 with loss of the low signal of the normal intranuclear cleft, reduced height and evident contrast-enhancement (Figs. 48.1 and 48.2). In some cases, increased height of the disc space can be observed because of a disc abscess. With advancing disease, the end plates and vertebrae become hyperintense on T2-weighted sequences and may show contrast enhancement. Subsequently, infection may spread into other vertebral bodies via the venous plexus, and posteriorly into the epidural space and/or laterally into the paraspinal space. In this phase, some granulation tissue may be produced and distributed circumferentially around the vertebral body, showing heterogeneous moderate enhancement.

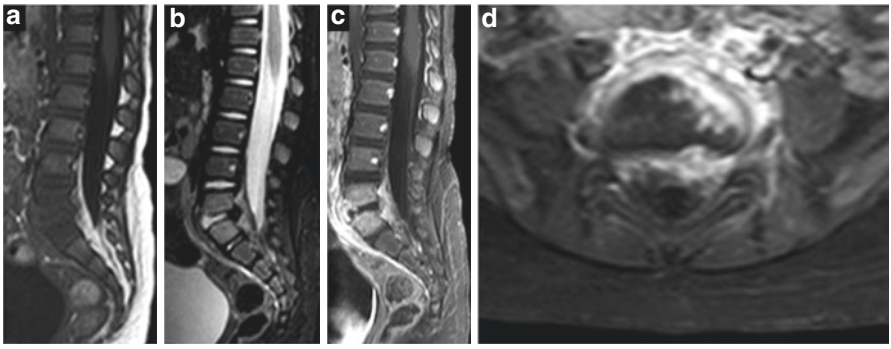

Fig. 48.1 Typical Magnetic Resonance Imaging (MRI) appearance of pyogenic spondylodiscitis. T1-weighted (**a**), Fat suppressed T2-weighted (**b**) and GD-enhanced Fat suppressed T1-weighted (**c**) spine images on the sagittal plane; GD-enhanced Fat-suppressed T1-weighted (**d**) spine images on the axial plane. MRI shows altered signal, typically hyperintense on T2 weighted fat suppressed image, and diffuse contrast enhancing of marrow of L5 and S1 vertebrae; Hyperintensity and narrowing of the abutting intervertebral disc on the anterior portion, with loss of adjacent endplate definition due to cortical osteolysis. GD-T1w with fat suppression images also reveal enhancing prevertebral and epidural infiltrative phlegmon/abscess

In advanced phases, when infection is settled, the affected disc space reduces in size with fusion of the adjacent vertebra to form a "block" vertebra [25].

CT may be an adjunct to MRI to assess bone destruction, presence of pathological fracture, or subluxation. Dynamic flexion-extension X-rays is useful to assess spinal instability. Bone scintigraphy with technetium-99 is highly sensitive to diagnose spinal problems within 1–2 days of disease onset: spots of increased radiotracer accumulation highlight inflammatory changes. Unfortunately, it lacks of specificity and spatial resolution [1]. Positron emission tomography with 18 fluorodeoxyglucose (FDG-PET) may permit to distinguish infections from degenerative and neoplastic changes in the spine [20].

48.2.5 Laboratory Investigations

In most cases laboratory findings are unremarkable, showing only a slight to moderate increase in markers of inflammation [9]. Routine blood investigations namely white blood counts (WBC), erithro sedimentation rate (ESR), blood and urine cultures are basic investigations. Procalcitonin levels and C-reactive protein (CRP), have been described as better reliability compared to WBC, and ESR levels, at least in adults; these markers are also useful in order to monitor the infection trend in the postoperative period [13, 26]. The highest values are usually found in younger patients with severe diseases with multiple infectious foci and sepsis and in older children with severe osteomyelitis involving more than one vertebra [9]. Antigen titers, antibody detection, and polymerase chain reaction (PCR) should be performed in patients where rare and atypical organisms like Brucella or fungal infection are suspected.

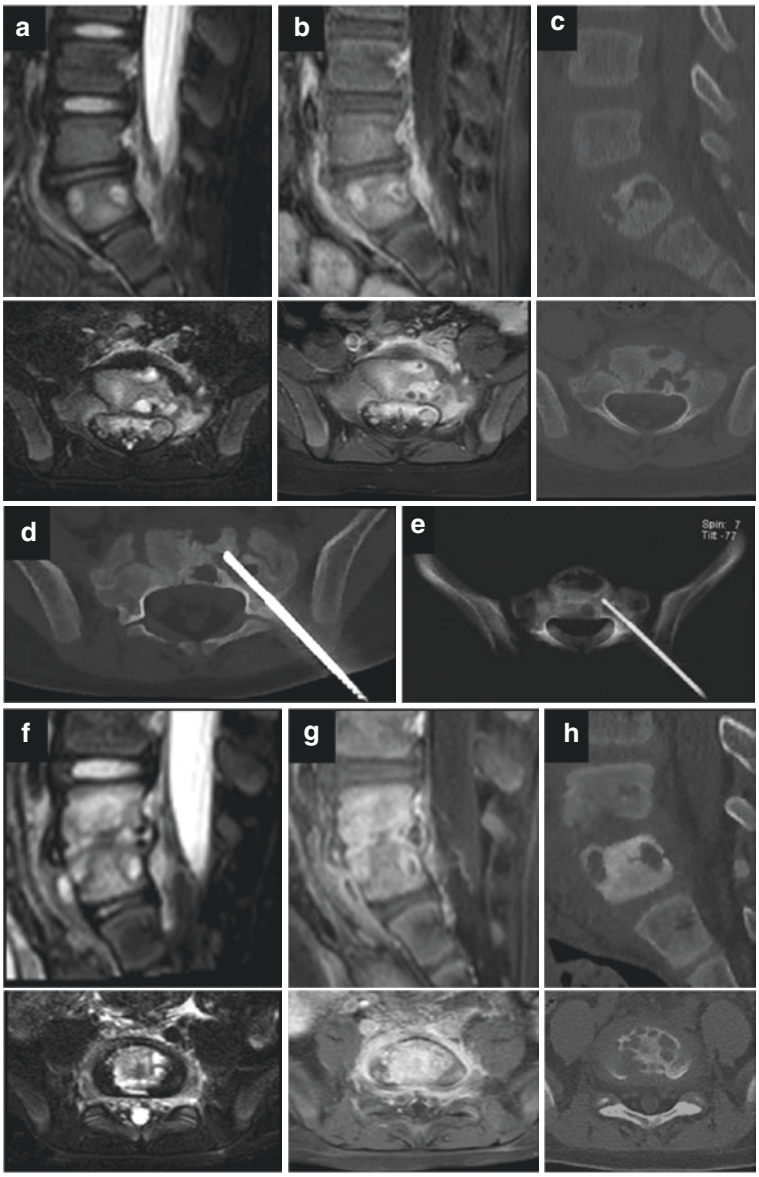

Fig. 48.2 Two year old baby girl, presenting with back pain and refusing to walk. T2-weighted fat suppressed (**a**), GD-enhanced fat suppressed T1-weighted (**b**) and CT scan (**c**) on sagittal plane and on axial plane at S1 level. Images show edema and diffuse contrast enhancing of marrow in S1 vertebra, with coexistent areas of irregular and confluent osteolysis, such as a focus of osteomyelitis; adjacent prevertebral and epidural phlegmon is also appreciable. Axial CT scan (**d**) and MIP Volume Reconstruction (**e**). Percutaneous bone biopsy via left trans-pedicle access reveals inflammatory infiltrate in the osteolytic lesion. T2-weighted fat suppressed (**f**), GD-enhanced fat suppressed T1-weighted (**g**) and CT scan (**h**) in the sagittal plane and in the axial plane passing through the space L5-S1. Images show the evolution in spondylodiscitis of the discosomatic unit L5-S1. Altered signal and enhancement are more extensive, involving the adjacent narrowed intervertebral disc, with irregular definition of the adjacent L5 endplate due to the cortical osteolysis. Prevertebral and epidural phlegmon are also still evident

Blood cultures, usually obtained from two or three samples, are positive in 50% of the cases of unspecified discitis, and are an important guide to antibiotic therapy. Cultures should be obtained before starting antibiotics, otherwise sensitivity drops to 15%. In these cases, the antibiotic therapy should be suspended for 72 h before collecting new blood cultures [22].

Needles aspirations or biopsies of the vertebral body and/or disc space should be considered when no organisms can be identified by less invasive techniques. According with some Authors invasive investigations should be reserved for children who fail to improve with empiric antibiotic therapy, when the presence of atypical microorganisms is suspected, or when the lesion mimics a tumoral lesion [1, 9]. Others consider isolation of the pathogen essential, therefore percutaneous or open biopsies should be recommended in all cases [13].

CT or fluoroscopy-guided needle biopsy has good accuracy (up to 80%) in the identification of the infection pathogen (Fig. 48.2d, e) [6, 25].

Traditional open biopsies have 93.3% sensitivity in some case series, but with increased local morbidity [22].

Samples obtained through these investigations may be tested for pyogenic and non-pyogenic bacteria with culture and if feasible also using polymerase chain reaction (PCR). DNA-based methods are highly sensitive and specific and they can complement standard microbiological methods in patients with negative blood and disc aspirate cultures. Real-time PCR assay is very useful in cases of chronic infective spondylodiscitis, especially in cases, caused by Micobacterium tubercolosis and *Brucella* spp. [17].

48.2.6 Treatment

The goal of treatment is to eradicate the infection, guaranteeing the restitutio ad pristinum, preserving the function and structure of the spine and relieving the pain.

In adults management of spinal infection is based on the guidelines published in 2015 [27]. Recently the ISPN (International Society of Pediatric Neurosurgery) published on its website a guide for spine infection in children [13].

According with these guidelines, management is based on three principles:

1. Identification of the pathogen;
2. Antibiotics or antimycotics as primary treatment in association with painkillers;
3. Surgical debridement +/− instrumentations in cases refractory to medical management, especially in cases of abscess formation and spinal deformation.

In children, conservative treatment is usually sufficient, with most of the patients' symptoms improving satisfactorily and without sequaelae, especially in timely diagnosis.

Spinal immobilization is a fundamental part of the conservative management in children, as supportive treatment of the acute pain, in association with proper medications. In fact, orthosis reduce deformation sequelae and the onset of neurological

deficits secondary to instability. It should be wear since the diagnosis is suspected (even waiting the results of the cultures), particularly in cases of intense pain or risk of spinal instability on neuroimaging [22]. Immobilization should also be ordered for cervical lesions with cervical orthosis or rigid halo brace (in most severe cases), for thoracic or lumbar lesions, with bed rest until pain and spasms disappear, and then with thoracic-lumbo-sacral orthosis (TLSO) or a lumbo-sacral orthosis according with the level of the lesion. Upper thoracic lesions should be immobilized with a TLSO extended to the neck.

Spinal immobilization and restricted activities should be maintained for 10–12 weeks, or until evidence of clinical and laboratory resolution [28].

Even if some cases of spontaneous resolution of isolated discitis in young children are reported [29], antibiotics should be prescribed to all patients.

Obviously, the choice of the antibiotics should be based on the sensitivity tests of the causative agent (if available). As the most commonly isolated organisms are *Staphylococcus aureus* and *Streptococcus* spp., the most recommended empiric antibiotic regimen is a combination of third-generation cephalosporins and oxacillin/clindamycin, based on the weight of the patient and age [22].

When laboratory tests become available, antibiotics can be changed according to the results. In case of PCR on throat swabs positive for *K. kingae*, beta-lactam antibiotics can be prescribed [9].

Intravenous antibiotics should be preferred, because they lead to more rapid resolution of symptoms (usually over 2–4 days) and less recurrences than oral antibiotics [13].

In literature, recommendation on the duration of antibiotic therapy is controversial, ranging from one week to three weeks intravenously, followed by supplementary oral therapy. The criteria for the discontinuation of the antimicrobial treatment include resolution of the symptoms, and normalization of ESR and CRP [26]. A weekly reduction of 50% in CRP represents adequate progression. The total treatment can last from two weeks to six months, according to the patient's response [9].

According with ISPN guidelines intravenous antibiotics can be converted, by day 4, to high-dose (2–3 times normal) oral antibiotics (e.g., linezolid) if the CBC and CRP are trending toward normal. On day 21, the ESR can be checked. If it is <30 mm/h, then one can consider stopping the antibiotics. If the ESR remains above 30 mm/h, MRI can be considered to check the site of infection. Surgical debridement is recommended if inflammation and destruction are noted. The antibiotic treatment should be extended to 6 weeks [13].

48.2.7 Surgery

Surgery is indicated, in the acute phase, for those cases that are refractory to medical management. Appearance of new neurological deficit, such as weakness, numbness, and bowel or bladder incontinence and progressing of infection on neuroimaging, in particular with evidence of abscesses, are red flags for surgery [13]. Progressive

pain may be also suggestive of failure of medical treatment, as well as the lack of response to medications on neuroimaging.

Surgical treatment might consist in focal debridement of the site of infection with or without spinal fixation. The surgical debridement stand-alone is applied as first line in children, but it intensely under debate if spinal instrumentation is required or not in adults, even initially, in acute phase [7, 26, 27].

The aim of surgery, in case of pure debridement, is the toilette of the infected foci, removing the devitalized tissue, concomitantly to decompression of neural elements. Therefore, extensive irrigation with broad spectrum antibiotic, peroxide or saline is recommended. Tissue sample should be sent for aerobic, anaerobic, fungal, acid-fast bacterial cultures in order to have the diagnosis and therefore, target medications [13].

In children, surgical fixation may be indicated also at resolution of infective/inflammatory process, if spinal instability or deformity develop [13, 22, 29].

There is a plethora of surgical approaches, and the choise depends on the charateristic of the patient, the grade of instability, the spinal level and, not least, the surgical experience of the department [13, 27].

In case of discitis, a posterior midline approach is the most commonly used, especially for the lumbar spine. Surgical strategy includes: exposing descending nerve roots and nerve roots exits, incision of the posterior longitudinal ligament and exposing of the affected intervertebral disc. All of the inflammatory disc tissues are debrided down to healthy bleeding bone. Interbody fusion may be achieved by inserting an iliac-bone allograft into the intervertebral disc, if needed. However, some Authors reported the risk of further infections related to the use of heterologous material.

Posterior pedicle screws fixation is the most frequent technique used in deformity correction, especially for thoraco-lumbar location, whereas anterior approach is selected in case of cervical site. A combination of anterior or antero-lateral and posterior instrumentation is prefereed in case of 360 ° instability, but usually it is performed in two surgical steps and in case of first line option treatment failure [22, 30].

The deformity can be corrected by installing pre-bent rods and the material broadly selected is the titanium [31]. In fact, the previous concerns about the risk of microbial colonisation of the osteosyntesis materials are nowadays obsolete; titanium implants have low risk of infection, due to lesser probability of biofilm formation [1, 27, 28]. The porous nature of titanium can allow and facilitate soft tissue attachment and delivery of adequate concentrations of antimicrobial drugs [32].

48.2.8 Outcome

The mortality for spondylodiscitis is very low (less than 5%). Most children have a complete recovery [22]. Radiologically, the affected disc space reduces in size with fusion of the adjacent vertebra to form a “block” vertebra. Sometimes symptoms may become chronic, with decreased mobility and mild back pain. Patients should be followed for at least two years, in order to detect spinal instability and progressive deformity [13].

48.3 Non-pyogenic Spondylodiscitis

A separated argumentation should be done for non-pyogenic spondylodiscitis, which usually have a subacute or chronic course, with gradual onset of symptoms and an indolent clinical course. They can be caused by a wide spectrum of pathogens: *Mycobacterium tuberculosis* (the most common), *Brucella* spp. and fungi (*Aspergillus* spp., *Candida* spp. and *Cryptococcus neoformans*) [17]. Very rarely also bacterial infection may be responsable of a protracted course of illness, such as coagulase-negative staphylococci, viridans group streptococci and propionibacteria spp. [17].

The germ can reach the spine through one of two routes. The first is through haematogenous spread from a distant focus, of which tuberculosis and brucellosis are important examples. The second route of transmission is through contiguous spread from a soft-tissue infection or by direct inoculation of the organism at the time of a surgical intervention, such as with Candida and Aspergillus.

48.3.1 Tuberculosis

Tuberculosis of the spine (Pott's disease) is a significant health burden in developing countries, actually it is also an emerging problem in the developed world. The most frequent site for childhood spinal tuberculosis is the thoracolumbar junction. Tuberculosis in the lumbosacral region is uncommon, and other causes, such as brucellosis, should be considered when this area is primarily involved. Craniocervical involvement may also be seen in children and is accompanied by significant abscess formation [33].

Usually spinal involvement is caused by hemathological spreading from primary foci (pulmonary or genitourinary). One to 6% children with untreated tubercolosis develop skeletal lesion; 13% of osteoarticular tubercolosis involves the spine. In children with spinal tubercolosis a co-existent extra-spinal disease was found in 57% of cases in the series of Eisen et al. [15].

According to the location of the infection, three patterns have been described: anterior, paradiscal, and central [21]. In the anterior type infection begins in the anterior vertebral body and extends under the anterior longitudinal ligament to involve other vertebrae, producing huge prevertebral or paravertebral abscesses; the disc space can be spared. In the paradiscal type, infection begins in the lateral sides of the disc and results in narrowing of the disc space and abscesses originate directly from the disk space. In the central type, infection begins in the middle of the vertebral body, may produce a vertebra plana, and eventually results in acute angle kyphosis. Central infection has a tendency to propagate posteriorly to the spinal canal, causing thecal sac compression.

Differential diagnosis is usually posed with spinal extradural tumors showing large effusive components, such as Ewing or undifferentiated sarcomas. Radiologically, a useful differential sign is the condition of the disk space, which is consistently involved by infectious processes and spared by tumor.

Fundamental for the initial management is to detect if there is an acute miliaris tuberculosis or a chronic one; the diagnosis is performed by chest X-Rays eventually completed with CT scan in case of suspicion and laboratory and skin tests. In the series of Eisen et al., [15] tuberculin test was positive in 18 out of 20, while the Quantiferon-TB Gold test, was positive in nine out of 14 in which it was performed. Other tests are based on Polimerase Chain Reaction and Ziehl-Neelsen staining.

The clinical manifestations are usually reflective of the systemic illness. Focusing on the spinal location, progressive backache is the predominant clinical feature, associated with spine stiffness and spasm of the paravertebral muscles. Cervical involvement may present with torticollis, neck pain and stiffness. Due to difficulty in diagnosis, many cases are detected only when kyphosis or neurological deficits occur. The worst complications are para- or tetraplegia (Pott' paraplegia). Edema of the spinal cord, myelomalacia or direct involvement of the meninges and cord by tubercular infection and inflammation (Fig. 48.3), infective thrombosis, or endarteritis of spinal vessels may lead to severe neurological deficits [9].

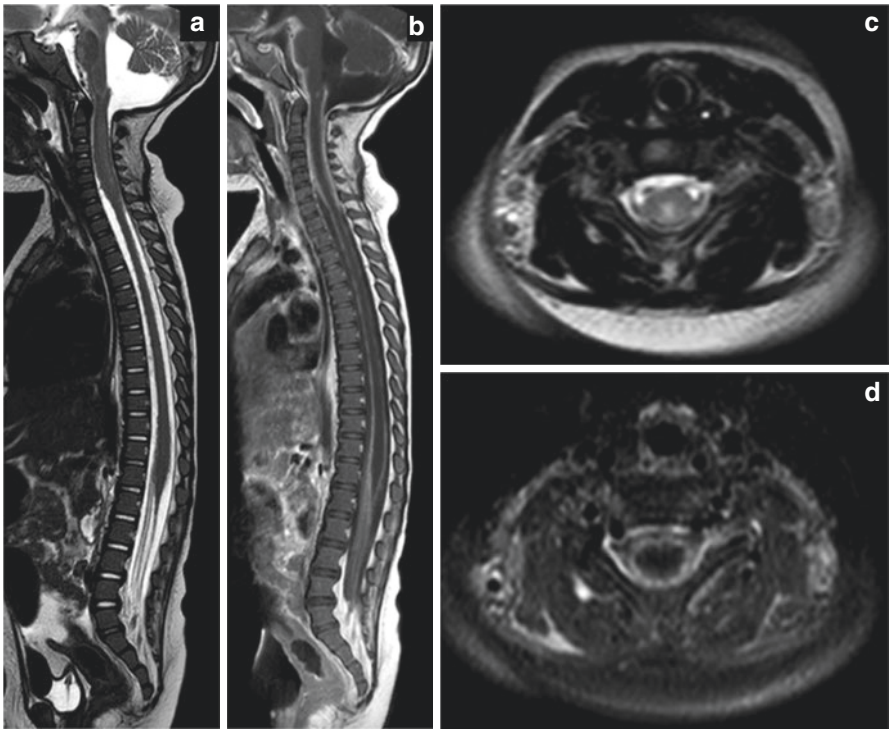

Fig. 48.3 MR appearance of Tuberculous leptomeningitis: T2-weighted (**a**) and GD-enhanced T1-weighted (**b**) spine images on the sagittal plane; T2-weighted (**c**) and GD-enhanced Fat-suppressed T1-weighted (**d**) spine images on the axial plane at cervical level. Diffuse leptomeningeal thickening and enhancement of the surface of the spinal cord and nerve roots, due to inflammatory cells infiltration of the arachnoid is evident. The cervical medulla is more involved, where swelling, intramedullary edema and exudate is observed in the proximal tract of the central canal (*). Images also show thick basal leptomeningitis, with secondary obstructive dilation of the posterior fossa cisterns and fourth ventricle

Computed tomography (CT)-guided needle aspiration and biopsy is the most effective method of establishing the diagnosis in chronic spondylodiscitis.

Treatment is based on administration of antituberculous drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) in various combination, according to *in vitro* sensitivities of the micobacterium. Steroid therapy may be useful in case of spinal cord compression. Surgery has the same indication as for pyogenic infections: it may be appropriate if there is failure of medical therapy, cord compression in patients with neurological deficits, spinal instability, or to enable drainage of paraspinal abscesses [15]. Notably, a faster and prompt diagnosis, compared to other laboratory test, might be obtained using the specific Ziehl-Neelsen staining in the surgical sample, which is a stain specific for alcohol-acid resistant microrganism, namely *Mycobacterium spp.* Children remain at high risk of progressive deformity through disproportional growth of vertebral remnants after the active TB stage, and most spinal deformities may develop with growth [2]. Some advocate prophylactic surgery to prevent kyphosis [34]. The proportion of patients requiring surgery in most sereis exceeds 30% [2, 15].

48.3.2 Other Non-pyogenic Spondylodiscitis

Patients with Brucella spondylodiscitis usually present with back pain accompanied by fever, malaise and weight loss. Diagnosis is very difficult, and delay may lead to the rapid progression of disease [9]. Treatment of Brucella spondylodiscitis consists of bed rest, bracing and medical therapy with antibiotics active against *Brucella* spp. The preferred regimen includes Rifampin 15 mg/kg/day, Cotrimoxazole 15 mg/kg/day and Doxycycline 5 mg/kg/day for a period of 6 months. Surgery is rarely indicated, according to the same principles, previously discussed. Since recurrence is common, close follow-up of the patient after completion of therapy is recommended [9, 20].

In fungal spondylodiscitis, back pain is the most frequent complaint, whilst neurological impairment appears to be relatively infrequent. Kyphosis is also uncommon due to the indolent nature of the infection.

Treatment of fungal spondylodiscitis relies on the prompt institution of appropriate antifungal agents. Treatment is often delayed because of the difficulty in making the diagnosis. When fungal spinal infection is suspected, fungal cultures, fungal antigen detection and PCR are recommended [17]. Most often patients require surgical debridement and systemic antifungal drugs for a minimum of 6 weeks and up to 3 months [17].

48.4 Spinal Epidural Abscess

Spinal epidural abscess (SEA) also less frequently called spinal epidural empyema, is a collection of pus between the bone and the dura mater [35]. Spinal epidural abscess is an infective emergency, warranting both medical and surgical

management [36, 37]. Even if mortality is low, morbidity is high (about 18%) with high invalidating sequelae. Fortunately, incidence is low with a 0.2 to 3 cases every 10,000 hospital admissions [38].

SEA may be a complication of pyogenic or non pyogenic spondylodiscitis, or may be isolated, secondary to hematogenous spread of germs from primary foci (in the urinary tract, skin, lungs, and teeth). Children, in fact, have rich vascularity around the vertebral body predisposing them to hematogenous spread of organisms. Any infection that can cause bacteremia can be the source of infection. A previous infective process can be identified in 44% of the cases [25, 36].

SEA can be caused by either fungal or bacterial microorganisms. *Staphylococcus aureus* (57–80% of cases) is the most frequent pathogen isolated. The proportion of methicillin resistance Staphilococci (MRSA) is not negligible: MRSA account for 15–18% [13]. In fact, the most frequent isolated germs were MRSA followed by *Mycobacterium tuberculosis*, Streptococci (8–17%) and gram-negative bacteria (10–17%) [1, 3, 25, 36].

In children, associated diseases, reported as risk factors, include: diabetes mellitus sickle cell anemia, leukemia, long term systemic use of steroids and other causes of immunodepression [25, 36]: these comorbidities are present in about in one-third of affected children.

Occult spinal dysraphism is another condition predisposing to intraspinal infections, in pediatric population. In children SEA affects predominantly the thoracolumbar levels where epidural space is larger and contains more fat tissue. Similarly, the dorsal epidural space is more commonly affected (Fig. 48.4). SEAs tend to compromise more segments in children compared to adults: extensive almost holocord involvement of the posterior epidural space is not exceptional [25, 36, 37].

Pathogenesis of the neurologic deficits may be multifactorial: direct mechanical compression of the spinal cord may be the main factor, even if vascular damage with secondary thrombosis and hypoxia may also play an important role [39].

48.4.1 Clinical Aspects

Fever, back pain, and neurological deficits are the classical triad associated with SEA. However clinical presentation is various, and the classical triad is rarely the initial form of presentation: it usually indicates a late stage [38]. Back pain is the most common symptom and is present in 71% of the patients, followed by fever (in 66%). SEA can be also diagnosed after whole-body imaging is conducted in search for hidden infections in children with prolonged fever. Gastrointestinal symptoms are present in about 27% of the cases. In younger children irritability is a typical symptom and could be the only manifestation.

Classically, four clinical stages are described [38]. In the first stage the patient presents fever, back pain and tenderness. In the second stage changes in reflexes and signs of meningeal or radicular irritation occur, such as Lasegue's, Kernig's, and Lhermitte's signs, Brudzinski's reflex, and neck stiffness [38, 39]. In the third stage

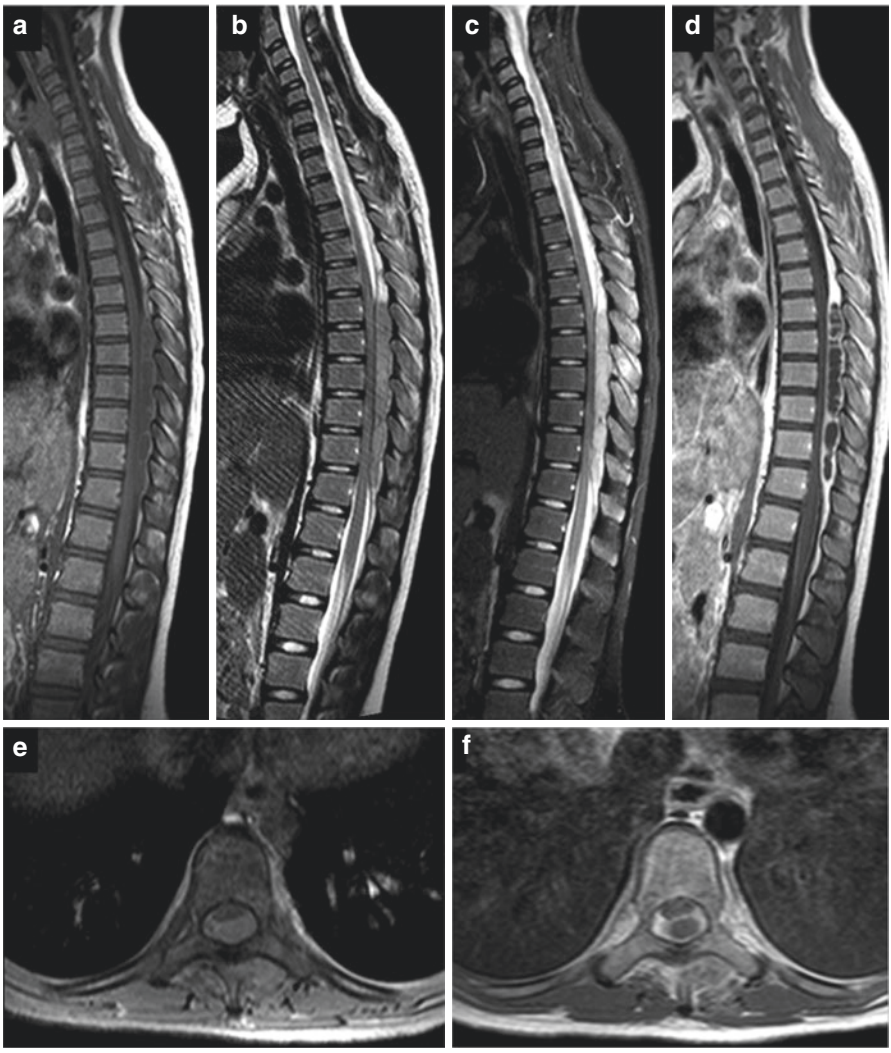

Fig. 48.4 MR appearance of epidural abscess/empyema. T1-weighted (**a**), T2-weighted (**b**), STIR (**c**) and GD-enhanced T1-weighted (**d**) spine images on the sagittal plane; T2-weighted (**e**) and GD-enhanced Fat-suppressed T1-weighted (**f**) spine images on the axial plane. MRI shows extensive dorsal epidural collection at the thoracic spine; the thecal sac is markedly compressed with significant mass effect on thoracic cord: Contrast-enhanced images outline the multiloculated necrotic collection with peripheral enhancement

neurological deficits are evident and include motor and sensory deficits, or bowel and bladder disfunction. In the last stage, symptoms of a complete spinal cord injury arise. The progression between these stages is generally rapid. In a review published in 2019, the time of progression from stage 1 to stage 2 (pain to radicular symptoms) was approximately 3 days. From stage 2 to 3 there were 4, 5 days (pain to

weakness) and from stage 3 to 4 (paraplegia) there were 24 h. The probability of improving after 24–36 h of paraplegia is very low [1, 25].

48.4.2 Diagnosis

Magnetic resonance imaging with Gadolinium has a specificity and sensitivity above 90% and is the diagnostic method of choice [40]. Usually, MRI is performed on emergency basis in patients with symptoms and signs of spinal cord compression. MRI shows a soft tissue mass within the epidural space encroaching on the thecal sac, spinal cord, and/or spinal nerve roots, generally 2 to 4 vertebral bodies in length (Fig. 48.4). The MRI signal depends on the content of the lesion. Spinal epidural abscess can be hypointense, isointense, or slightly hyperintense compared with the spinal cord on T1 images. T2 images are mostly hyperintense, being difficult to differentiate from cerebrospinal fluid (CSF). The lesion enhances homogeneously on postcontrast images and is most often a collection. In cases of frank abscess formation, there is a rim-enhancing abnormality in the epidural space; the non-enhancing center generally corresponds with pus, which shows restriction on DWI with ADC maps. In many patients with epidural abscesses, the spinal cord shows increased T2 signal intensity above, below, and at the level of the abscess. This finding is presumed to represent cord edema secondary to compromised venous drainage, secondary to involvement of the Batson plexus [21].

Many laboratory findings accompanied SEA stages [36, 39]. Erythrocyte sedimentation rates are elevated in 88% of the patients, followed by C-reactive protein in 76%. White blood count can also be elevated (35%).

48.4.3 Management

Emergent surgical drainage of the abscess with decompression of the spinal cord and nerve roots is the treatment of choice of SEA at diagnosis [13, 36]. In fact, a risk of deterioration with non-surgical management is demonstrated, even in patients for whom treatment is begun in the absence of neurologic deficits [25]. Delay in surgery may be cause of severe neurological consequences [36, 37]. Surgery should be followed by several weeks of antibiotics. Laminectomy, which is the removal of the laminae, in order to leave the spinal cord decompressed, and abscess evacuation are the most frequently performed procedure [39]. In children, especially if several levels are involved, laminotomy (surgical procedure in which the laminae are replaced following removal of the abscess) should be preferred to laminectomy to reduce the risk of long-term iatrogenic deformities. Very selected cases can be evacuated by a guided percutaneous needle aspiration. Intravenous empirical antimicrobial treatment must be started immediately once the diagnosis is made. These antibiotics should be of broad spectrum in order to cover staphylococci methicillin resistant, anaerobes and gram negatives. Vancomycin is the preferred antibiotic along with a broad spectrum antibiotic like ceftriaxone or rifampin

or meropenem [1]. Once the pathogen is obtained, antibiotic therapy may be changed according with the antibiogram, and switched to oral formulations (if the sensibility allows it), after at least three weeks of intravenous administration [37].

In conclusion, SEA is an infectious and surgical emergency, because the high risk of neurological sequelae. It is imperative to have a high index of suspicion, otherwise diagnosis can be missed, and treatment delayed. No mortality is reported in children [39], but morbidity is not negligible: a low percentage of patients with plegia improve following surgery [37].

48.5 Intradural Spinal Infection

Intradural spinal infections (subdural extramedullary and intramedullary) are extremely rare. Majority of patients have an underlying spinal dysraphism [41], such as dermal sinus tract, dermoid cyst, and epidermoid cyst. Dermal sinus tract is the most frequent lesion, because of the presence of communication between neural tissue and the external environment, that provides a source of infection. Also spinal lipomas may act as a germ growth pabulum, in case of transient bacteremia or spreading from adjacent rectum [42]. The mean age of intradural infection with spinal dysraphism is 2.9 years, while patients without dysraphism are older. Virtually all children below the age of 1 year have a concomitant spinal dysraphism [1]. Intradural infection, besides spinal dysraphism, may be associated to hematogenous spread of urogenital sepsis, endocarditis, pneumonia, middle ear infection, trauma, spinal cord tumors, and pyogenic meningitis.

Subdural extramedullary infection is the less common form; this is because the relative avascularity of this region. The most common site is the thoracic spine for both extramedullary and intramedullary infections.

Staphylococcus, *Streptococcus*, and *Coliform* bacteria are the most common causative organisms [1, 41, 43], especially in children with spinal dysraphism. In case of dysraphism, also polymicrobial organisms, including aerobic and anaerobic bacteria, are common. *Mycobacterium tuberculosis* is also an important cause, especially in endemic regions.

48.5.1 Clinical Aspects

Children with intradural infection usually presents with non-specific symptoms. In case of extramedullary infection, presence of neurological deficits is the most common presenting symptom followed by fever, meningism, bladder disturbances, and back pain [41]. In case of intramedullary infection, fever is present in only one third of patients. Appearance of neurologic deficits is the most frequent presentation. Two types of presentation of intramedullary abscess are described: few weeks history of fever and neurological deficits resembling transverse myelitis and longer duration

of symptoms such as back pain and progressive neurological deficit without fever, resembling a spinal cord tumor [1].

A febrile child with neurological deficit or back pain, should warrant a close examination of the back to identify any dysraphism [1].

48.5.2 Diagnosis

Like spinal epidural abscess, also intradural infection are usually diagnosed on MRI performed on emergency basis at appearance of neurological deficits and/or back pain, with or without fever (Figs. 48.5 and 48.6).

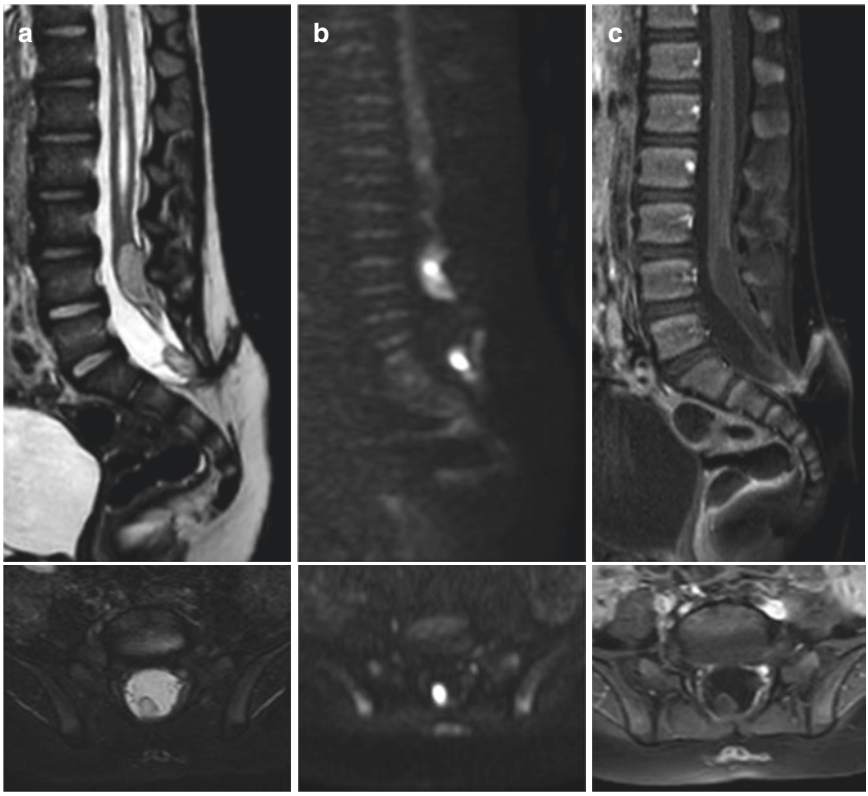

Fig. 48.5 MR appearance of spinal dorsal dermal sinus tract with intradural infection. T2-weighted (**a**), DWI (**b**) and GD-enhanced fat suppressed T1-weighted (**c**) images on the sagittal and axial planes. MRI shows expansion of the medullary conus by hyperintense epidermoid lesion in patient affected by tethered cord. A dermal sinus tract with marginal contrast enhancement, suggestive of inflammatory process, extending from the subcutaneous plane to subdural collection is evident. Note the restricted diffusion and thin hypointense rim with contrast enhancement, suggestive of a capsule. Note the distal central canal dilatation with slight enhancement of the ependyma

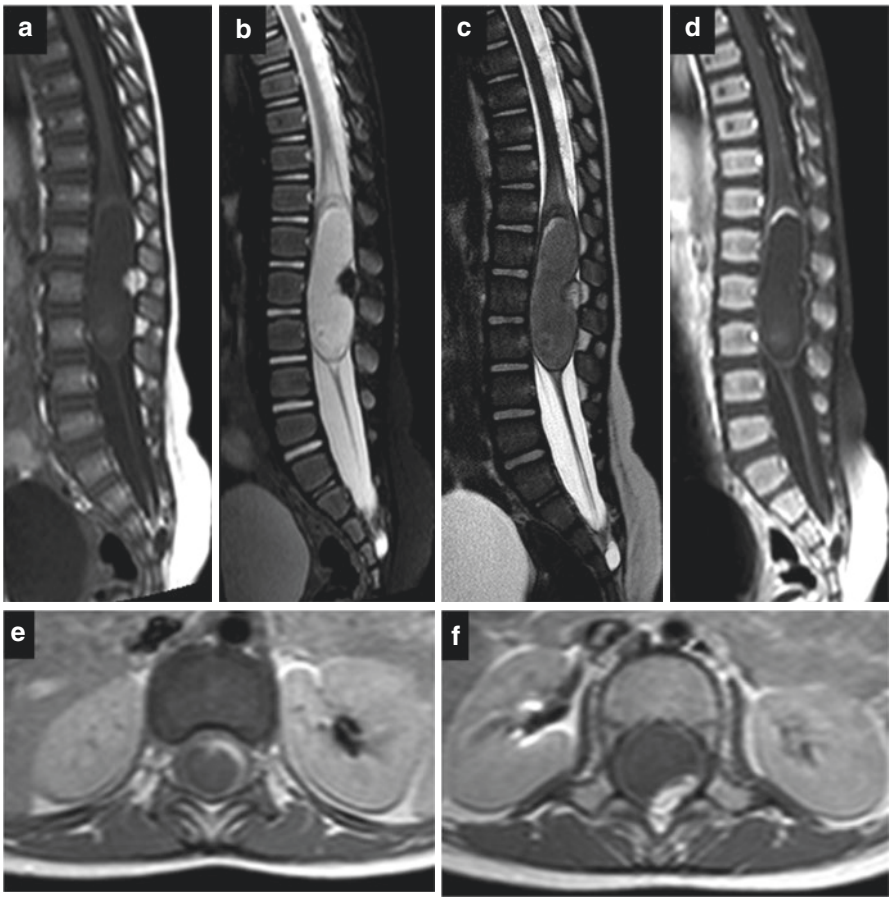

Fig. 48.6 MR appearance of intra-medullary abscess in occult spinal dysraphism. Sagittal T1-weighted (**a**), T2w fat suppressed (**b**), B-FFE (**c**) and GD-enhanced fat suppressed T1-weighted (**d**) images; axial GD-enhanced T1-weighted images at D12 (**e**) and L2 (**f**) levels. MRI shows massive expansion of the medullary conus by fluid collection in patient affected by tethered cord with intradural lipoma. Inhomogeneous signal of the fluid collection with sediment, marginal septa and contrast enhancement at the upper pole is shown. Note the subsequent edema in the adjacent spinal cord

Subdural abscess is seen as a crescentic fluid collection with irregular thick-walled enhancement within the subdural space. The underlying subarachnoid space is narrowed or obliterated. The primary clue on MRI of a subdural rather than epidural abscess is the preservation of the epidural fat on axial and/or sagittal images [44].

In case of intramedullary infection, the infectious process generally begins as a myelitis and, if left untreated, may progress to frank abscess formation (Fig. 48.5). In the early stages of infection, MRI shows a hyperintense lesion on T2-weighted images with poorly defined contrast enhancement. Subsequently, a capsule appears

as a thin T2 hypointense stripe surrounding the lesion. Later MRI shows a fluid collection with restricted diffusion on DWI and apparent diffusion coefficient (ADC) maps and irregular thick-walled rim enhancement [44]. In the context of dermal sinus, DRIVE sequence is useful to assess morphologic features of the closed spinal dysraphism (Figs. 48.5 and 48.6).

Laboratory investigations are not specific. Blood cultures are usually sterile. Lumbar puncture is controversial and is generally avoided due to its inability to differentiate meningitis from a subdural infection, possible neurological injury due to a low-lying cord in spinal dysraphism. Moreover, cerebro-spinal fluid (CSF) may be sterile, if the infection is encapsulated [1]. If a parasitic infection is suspected (like neurocysticercosis and schistosomiasis), detection of antibodies in blood and CSF may be useful [1].

48.5.3 Management

Surgical evacuation, followed by antibiotic therapy, is the treatment of choice, both for subdural extramedullary infection and for intramedullary abscess [1, 13, 41, 43]. Laminectomy or (preferably) laminotomy of the affected level followed by durotomy may be performed to evacuate the subdural collection. In case of intramedullary abscess puncture of the abscess or more extensive myelotomy, possibly guided by intraoperative ultrasound and under neurophysiologic monitoring, are necessary. The abscess cavity is generously irrigated with antibiotic-saline solution. Complete excision of the dermal sinus tract is essential to prevent infections [13]. If a dermoid cyst is present, the cavity of the dermoid, with the infected material inside, should be evacuated; the cyst walls are usually extremely adherent to the surrounding spinal cord tissue, so partial resection may be the most correct choice in the acute setting. Antibiotic therapy follows the same principle discussed for spinal epidural abscess. A standard regimen usually includes 6 weeks of intravenous antibiotics tailored to the organism obtained at surgery [13].

Currently, there are insufficient data to suggest whether a neurologically intact child with an intradural infection can be treated with antibiotics alone. If such a conservative approach is taken, there should remain a low threshold for operative intervention if symptoms develop or if the child remains febrile despite the initiation of antibiotics [13].

Intradural infection, especially intramedullary abscess in children is characterized by high morbidity and mortality. Simon and co-workers reported 20% mortality and 60% residual neurological deficits in children with intramedullary abscess [43]. Periodic clinical evaluation and radiological surveillance with MRI are recommended for at least 1 year, in order to rule out recurrent disease [1].Compliance with Ethical Standards***Funding***: No funding was received for this study.
Conflict of Interest: The authors declare that they have no conflict of interest.
Ethical Approval: All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/

or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard.

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Part IX
Modern Concepts and Practices

Chapter 49
Advances in Pediatric MRI

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49.1 Introduction

Magnetic resonance imaging (MRI) dominates the field of pediatric neuroimaging for many reasons. It is particularly safe because it uses radiofrequency waves and avoids the harmful effects of ionizing radiation. As a result, it can be used for serial monitoring of a disease or with dynamic scans for functional imaging. Also, in some cases it offers alternatives to the administration of contrast agents and avoids their toxicity risks. Beyond safety, the main advantage of MRI lies in the many techniques it provides with different contrasts reflecting multiple aspects of the brain's structure and function. As technology evolves and the main magnetic field of the MRI scanners increases, these techniques are multiplied and become robust, detailed, and specific enabling the clinicians to diagnose, assess and monitor their patients with greater accuracy [1].

Unfortunately, the progress of MRI comes at a price. It has become more and more difficult for radiologists, let alone clinicians, to master the large and complex field of advanced MRI techniques and methods, understand the subtleties distinguishing them, avoid interpretation pitfalls and exploit their full potential. This chapter focuses on modern MRI techniques that are widely applied in the clinical setting. The main principles, basic methodological steps and examples of clinical applications of spectroscopy, perfusion, diffusion and susceptibility are presented. The limited space of a chapter permits only an introduction to these techniques, which we hope can be a reference source for further reading. Our aim is to provide

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a rough sketch rather than a detailed map which can guide without confusing the newcomer in the landscape of the advanced MRI techniques.

49.2 Diffusion

49.2.1 The Diffusion Ellipsoid

Macroscopically, diffusion is the flow of substances from regions of high to low concentration without bulk motion. Microscopically, diffusion (aka Brownian motion) is the random motion of particles propelled by thermal energy. Diffusion weighted imaging (DWI) is an MRI technique sensitive to the diffusion of water molecules in the human tissue [2]. Although the resolution of the diffusion weighted images is at the millimeter scale, comparable with other MRI techniques, their contrast reflects water motion at the micrometer scale providing indirect information about the average cellular microenvironment in any voxel.

Typically, diffusion is encoded using a pair of gradients around a 180° radiofrequency pulse before an EPI pulse sequence [3]. The diffusion-sensitizing gradients produce an exponential signal drop when water is diffusing along the gradient direction. This drop depends on the product of two factors: a) the magnitude of the diffusion process which is quantified by the diffusion coefficient (D) measured in cm^2/s and b) on the b value, a parameter that is determined by the gradient scheme and is measured in s/cm^2. Stronger gradients result in higher b-values, increased sensitivity in slower diffusion, but also lower signal to noise ratio.

Randomness in the diffusion process implies that we cannot calculate the final position of a water molecule diffusing from a starting point. Instead, we can calculate the probability that it will arrive at any position after a certain time, which depends on the diffusion coefficient D. In special cases, when the water molecules diffuse in a homogeneous medium without obstacles (e.g. a cyst, or a ventricle) the diffusion is characterized “free” or “unrestricted”. Then the probability to diffuse at any given distance is the same for all directions and the diffusion is called isotropic. In this case, the diffusion coefficient is a simple scalar, common for all directions and geometrically its directional independence can be visualized with a sphere of radius D (Fig. 49.1). In most other cases, when the water diffuses in a tissue microenvironment, it encounters various obstacles and boundaries (e.g., cell membranes or intracellular organelles). Then the diffusion is restricted and anisotropic and the probability to move in any direction is unknown. A crude model approximating the anisotropic diffusion in tissues is described geometrically by a sphere deformed along three vertical axes, (aka principal axes or axes of symmetry), called diffusion ellipsoid. The size of the diffusion ellipsoid in any direction represents the diffusion coefficient along this direction (Fig. 49.1). Mathematically the shape of the ellipsoid and thus the diffusion coefficient is described by a 3X3 matrix, called tensor. The sizes and the directional vectors of the ellipsoid along its three principal axes are called eigenvalues and eigenvectors of the corresponding tensor respectively.

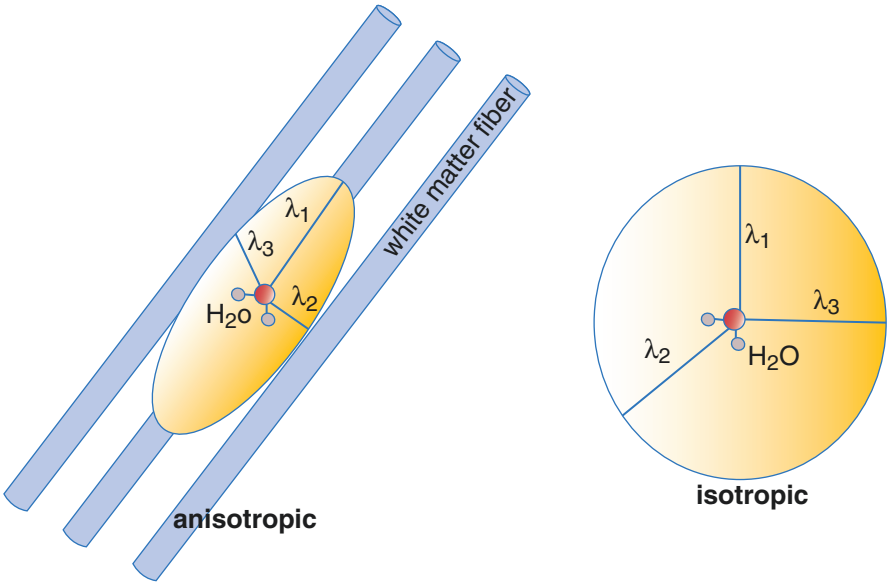

Fig. 49.1 An example of anisotropic diffusion in the white matter (left). In this case the diffusion ellipsoid is elongated along the fiber tracks. In the case of free isotropic diffusion ellipsoid becomes a sphere (right)

A nice example of the tensor model is the water diffusion in the brain's white matter (Fig. 49.1). The existence of large fiber bundles facilitates the diffusion in directions parallel to them and restricts the diffusion in vertical directions. As a result, the diffusion ellipsoids are elongated along the fiber axes which become their major axes with the largest eigenvalues. Conversely, they are squeezed in the vertical directions denoting restricted diffusion.

49.2.2 The Diffusion Metrics

Diffusion tensor imaging (DTI) calculates the diffusion ellipsoid or equivalently the diffusion tensor, using at least one reference/baseline scan without diffusion (b = 0) and six non-collinear diffusion weighted scans [4]. However, although feasible it is impractical to present results of DTI as figures depicting thousands of ellipsoids. Instead maps of specific geometrical metrics of the diffusion ellipsoid are calculated and presented. The most common of them are [5]:

- Mean diffusivity (MD) or apparent diffusion coefficient (ADC). It is related with the average size of the diffusion ellipsoid along its principal axes or equivalently the average diffusion coefficient. It is calculated by averaging the three eigenvalues of the diffusion tensor. It is an inverse measure of cellularity and it is related with the amount of water in extracellular space.

- Axial diffusivity (AD). It is the largest eigenvalue or equivalently the maximum diffusion coefficient along the major axis where the ellipsoid is more elongated. In white matter it represents diffusivity along the axonal tracts. It is less informative from the other metrics and in some cases can be considered a marker of axonal damage [6].
- Radial Diffusivity (RD). It is the average of the two smaller eigenvalues or equivalently the average diffusion across the minor axes where the ellipsoid has the smallest size. In white matter it represents diffusivity vertical to the axonal tracts. It is considered a marker of demyelination or axonal density [6].
- Fractional anisotropy (FA). It is a metric with values between 0 and 1. It is related to the shape of the ellipsoid. In isotropic diffusion where the shape is spherical FA = 0. FA increases with anisotropy and becomes 1 in the extreme cases where diffusion occurs only across one direction. It is an index of microstructural integrity. Usually, FA is depicted in color maps, where intensity represents FA and color the direction of the ellipsoid using a 3D RGB color code (i.e., red: right-left, green: anterior-posterior, blue: inferior-superior).

Diffusion metrics are very sensitive to pathological changes but generally not specific and their interpretation is challenging. They are affected in complex ways by various and sometimes coexisting pathological factors but also by methodological factors during data acquisition and analysis [7, 8].

49.2.3 Tractography

Tractography is an extension of DTI aiming to reconstruct the white matter fibers using the orientation of diffusion along them [9]. A group of tractography techniques characterized as deterministic rely on the hypothesis that in each voxel there is a single predominant fiber orientation parallel to the major axis of the diffusion ellipsoid. Most of the deterministic methods start from a seed point and using integration or interpolation techniques produce 3D-space curves called streamlines, pathways, trajectories or virtual fibers (Fig. 49.2). FACT (fiber assignment by continuous tracking) [10], the Runge-Kutta method [11], and the tensor deflection algorithm [12] are examples of deterministic tractography models.

The crude hypothesis of a single fiber orientation for each voxel fails in many cases and especially in voxels with bending, fanning, crossing or kissing fibers [13]. Others tractography methods called probabilistic assume that many streamlines emanate from each seed point and calculate their distribution [14]. They produce visitation count maps denoting the probability of connection with the seed point.

The simple tensor model of the diffusion ellipsoid is inadequate to describe the complexity of the diffusion process in the brain tissue. Inevitably, tractography based on DTI produces false results which affect clinical decisions especially in presurgical planning [15, 16].

Beyond DTI, more complex models [17] or even model-independent methods [18] have been developed and successfully delineated complex patterns of white matter fibers. However, their translation to the clinical environment remains limited mainly due to their lengthy scan times.

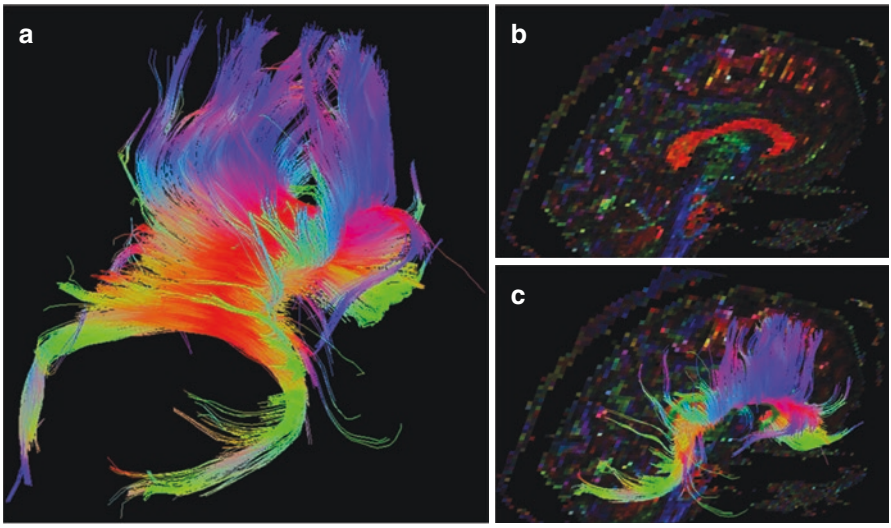

Fig. 49.2 Tractography of the fibers through the corpus callosum (**a**). In the color FA maps the corpus callosum appears red denoting the right-left orientation of the diffusion process (**b**). Modern software can combine in 3D scenes images and tractography data (**c**)

49.3 Perfusion

Perfusion is the blood flow at the microvasculature, which allows exchange of oxygen and other molecules across the semipermeable membrane walls of the microscopic vessels. Imaging of brain perfusion is of diagnostic value for evaluation of tissue hemodynamics and can be performed with many methods [19]. Despite their differences all these methods are monitoring the passage of a tracer through the capillary bed using multiple dynamic scans of the brain tissue. The tracer can be administered intravascularly (exogenous) or preexist in the blood stream (endogeneous). It can be exchanged between the vascular compartment and the brain tissue (diffusible) or it cannot penetrate the blood brain barrier (nondiffusible). Hemodynamic parameters can be derived by associating the changes in the dynamic scans induced by the tracer with a pharmacokinetic model that describes how the tracer passes through or is distributed in the target organ. MRI is widely utilized for brain perfusion assessment because it provides noninvasively and without ionizing radiation many dynamic perfusion weighted imaging (PWI) techniques using either exogenous nondiffusible Gd-based tracers or the native protons in blood water as diffusible endogenous tracers [20, 21].

49.3.1 Dynamic Susceptibility Contrast (DSC)

Gd tracers are highly paramagnetic and they induce local magnetic field gradients affecting the surrounding tissue (Fig. 49.3b). These long-range gradients dephase the water protons rapidly, shortening the T2 or T2* relaxation times of the surrounding tissue, an effect known as susceptibility-induced relaxation [22]. This effect allows the Gd

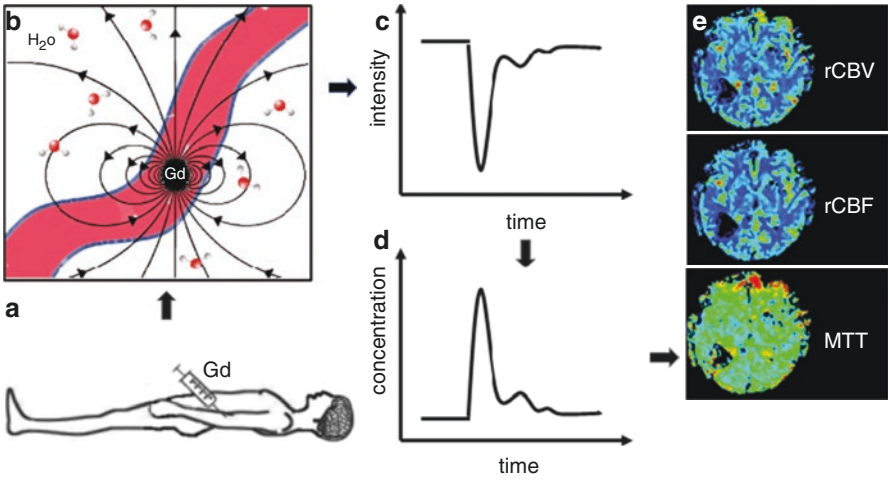

Fig. 49.3 Overview of the DSC perfusion imaging. A Gd-based contrast agent is administered intravenously (**a**). As it passes through the brain's microvasculature it distorts the magnetic field of the brain parenchyma (**b**), producing a signal drop (**c**) in a dynamic T_2* weighted pulse sequence. Inversion of the signal-time curve produces the concentration-time curve (**d**), which is analyzed to produce the perfusion maps (**e**)

tracers, even if they remain inside the vascular space to drop the signal in T2*-weighted images beyond the vessel walls to the adjacent parenchyma (Fig. 49.3c). Typically, DSC method (aka neuro-perfusion) is applied using a bolus administration of Gd-based tracer during a dynamic, ultrafast T2- or T2*-weighted imaging pulse sequence, able to measure with good temporal resolution (≤ 2 s) the signal drops induced by the first pass of the bolus. An inverse relationship between signal and trace concentration [23, 24] is used to calculate concentration-time curve of the tracer (Fig. 49.3d). The hemodynamic parameters that can be extracted by this curve can be classified in two groups:

(a) Descriptive or summary measures related with the shape of the concentration-time curve such as: arrival time (AT) or bolus arrival Time (BAT), Time to Peak (TTP), full-width at half maximum concentration (FWHM) and maximum peak concentration (Peak). These measures are easy to calculate but they are inaccurate, inconsistent and inconclusive, because they are highly dependent on the factors affecting contrast bolus delivery (i.e., injection technique, cardiac output, microvascular structure, extravascular leakage, etc.).

(b) Cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT) (Fig. 49.3e), which are related with physiological parameters of perfusion and are calculated with the tracer kinetic theory [25, 26]. CBV is defined as the total volume of flowing blood in 100 grams of brain tissue (mL blood/100 g). CBF is the volume of blood passing through 100 grams of brain tissue per minute (mL/100 g/min). MTT is the average time the blood spends within a given brain region (min). The simple equation CBV = CBF * MTT known as the central volume theorem, relates these measures [25].

Absolute quantification of the perfusion measures CBF, CBV and MTT is challenging because it requires knowledge of brain tissue density (ρ), trace concentration-time

profiles (aka arterial input functions or AIF) for all arteries feeding the various parts of the brain and the hematocrit of arteries (Ha) and microvasculature (Hc). Usually, as a crude approximation the AIF of the middle cerebral artery of the lesioned hemisphere is used for the whole brain along with the values $\rho = 1.04$ g/mL, Ha = 0.45 and Hc = 0.25. Alternatively, values of the perfusion measures in the pathological region are normalized by dividing them with the corresponding values in the contralateral healthy region. The normalized measures are called relative CBV (rCBV) or relative CBF (rCBF) and sometimes can be confused with the regional CBV (rCBV) or regional CBF (rCBF) which have the same notation, but they refer to absolute measurements.

Care must be given in cases where the blood-brain-barrier is disrupted and the tracer leaks to the extravascular space. This causes shortening of T1 and signal increase which counteracts or mutes the signal drop due to T2* effect, leading to underestimation of perfusion. Several post-processing methods have been developed to account for the impact of leakage in DSC quantification [27]. Alternatively, administration of a small amount of tracer before the main bolus can saturate the leaky tissue and mask the T1-effect [28].

49.3.2 Arterial Spin Labeling (ASL)

There are many ASL techniques, but they all have a preparation and an acquisition phase [29]. In the preparation phase an 180^0 RF-pulse inverts the magnetization of the upstream arterial water protons, below the imaging plane. After the so-called "post-labeling delay", during the acquisition phase, these protons, also known as labelled or tagged protons, enter the imaging plane, diffuse at the capillary level through the blood brain barrier and interact with the tissue water protons. The result is a reduction of signal intensity proportional to the cerebral blood flow. Typically, ASL techniques calculate the signal drop by acquiring and then subtracting two successive sets of images: one with (labeled scan) and the other without the preparation phase (control scan). The method initially proposed for ASL used a continuous inversion pulse at the neck level (continuous ASL or CASL) [30]. Although CASL offers strong perfusion contrast it deposits high amounts of energy in the tissue (SAR). Additionally, the long inversion pulse labels the off-resonance water protons attached to the macromolecules in the imaging region, producing magnetization transfer contrast that is independent to the blood flow resulting to an overestimation of perfusion. Variants of CASL have been developed to overcome these drawbacks but at the expense of feasibility and practicality. Currently the most common ASL methods used in the clinical setting are the pulsed ASL (PASL) and pseudocontinuous ASL (pCASL) [31].

49.3.3 Pulsed ASL (PASL)

PASL methods use a short inversion pulse over a large labeling slab close to the imaging plane. They are divided in symmetrical or asymmetrical based on their approach to handle the magnetization transfer issue. In symmetrical methods like

FAIR [32], the difference between the labeled and the control scan is the presence of a slice-selection gradient. The inversion pulse is applied in both scans and MT effects are eliminated during their subtraction. In asymmetrical methods like EPISTAR [33] or its variants [34], labeling of downstream water protons during the control scan counterbalance the MT effects of upstream labeling during the label scan without affecting perfusion measurements.

49.3.4 Pseudocontinuous ASL (pCASL)

pCASL is the most recent and most widely used variant of ASL due to its ease of implementation and its high labeling efficiency [35]. It uses a train of very short inversion pulses, which continuously invert the flowing blood as it transcends the labeling plane, resembling a continuous pulse. Contrary to PASL that uses thick slabs for inversion, pCASL uses a thin slice (Fig. 49.4) and therefore all the labelled protons have almost the same post-labeling delay, arriving at the imaging region with the same T1 relaxation decay. However, requirements for efficient labeling and good shimming put the labeling plane far from the brain, vertical to large feeding arteries of the neck (i.e., internal carotids and vertebral arteries). As a result, post-labeling delay increases, and spin labelling becomes less efficient.

Although ASL techniques provide perfusion measurements without exogenous contrast agents they present some limitations compared to the Gd-based techniques. They have a small signal to noise ratio because labeling reduces signal only by 1–2%. They require fast acquisitions and thus they use pulse sequences vulnerable to susceptibility artifacts and they produce images of low spatial resolution. Also,

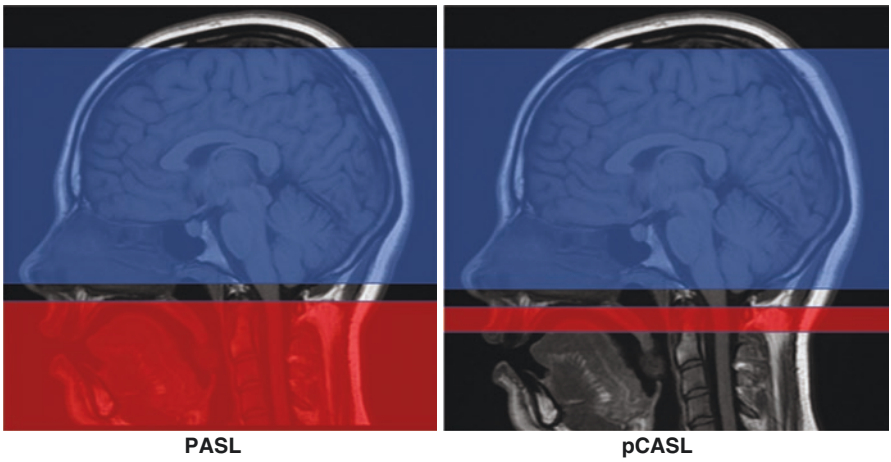

Fig. 49.4 Both PASL and pCASL invert the magnetization of the labelling volume (red) during the preparation phase and after a predetermined delay they acquire images (blue). PASL use a short inversion pulse over a large labeling slab, whereas pCASL use a use a train of very short inversion pulses over a thin slice

motion artefacts can appear after the subtraction of the labeled from the control scan. Finally, correct choice of the post-labeling time is heavily dependent on the blood velocity or equivalently the time it takes for blood to move from the labeling area to the imaging area (aka arterial transit time). In children having faster circulation and smaller transit times the typical post-label delay is 1500 ms, whereas in adults having slower circulation and longer transit times the typical post-label delay is 2000 ms.

49.4 Magnetic Resonance Spectroscopy (MRS)

49.4.1 The Brain Spectrum

There are so many differences between MRS and all the other techniques of MRI that make it a unique and valuable tool in clinical assessment [36, 37]. In theory, MRI detects the signal produced by all the ^{1}H nuclei (i.e., protons) in the human body after they have been excited by radio pulses tuned at their resonant frequency. In practice, MRI images depict predominantly only the ^{1}H protons of the water and lipid molecules because these compounds have the largest concentration and the strongest signal. All other molecules containing ^{1}H have either less concentration and weaker signals or they are MR invisible. A molecule containing ^{1}H is MR invisible when its signal is undetectable because it fades rapidly after excitation (i.e., fast relaxation) due to a strong magnetic interaction with its environment. Contrary to MRI, MRS suppresses the water signal and reveals the weak signal of other small mobile molecules in millimolar quantities, called metabolites because they participate in important metabolic pathways of the human body. Thus, MRS provides a noninvasive biochemical analysis of the human body.

In modern scanners MRI can easily achieve submillimeter resolution but the information in each voxel (i.e., volume element) is only a grayscale value. The faint signal of the metabolites restricts MRS, in the same scanning time, to achieve resolution only at the centimeter scale, but the information in the MRS voxel is a whole spectrum. An MR spectrum depicts many peaks in a 2D XY plot, with Y axis representing the height of peaks in arbitrary units and X axis the resonant frequency (aka chemical shift) in parts per million (ppm) relative to the frequency of tetramethysilane. The metabolite peaks are lying on a baseline originating from background noise and metabolites with low concentration or macromolecules with very wide peaks. A common misconception is that each of these peaks correspond to a different metabolite. The truth is that these peaks are produced by ^{1}H belonging to the same chemical group. For example, all nine ^{1}H in the trimethylamine group ($N(CH_3)_3$) resonate at 3.2 ppm. In the human brain, this peak is called the choline peak (Cho) because it represents phosphocholine, glycerophosphocholine and small amounts of other molecules such as free choline and acetylcholine. All these metabolites are MR visible and share the trimethylamine group in their chemical structure. Often two chemical groups of the same metabolite appear as different peaks. For example, in both creatine and phosphocreatine, the $N(CH_3)$ group appears at

3.03 ppm and the CH_2 group at 3.91 ppm. Both peaks are called creatine peaks (Cr). Finally, the interaction between nuclei of adjacent hydrogens, (aka J-coupling) causes a splitting of a peak into two (doublet) or multiple (multiplet) peaks. This is the reason why the lactate peak (Lac) appears as a doublet and the aminoacids glutamate (Glu) and glutamine (Gln) appear with overlapping multiple peaks (Glx compounds). Table 49.1 summarizes spectral properties of the major peaks in the human brain spectrum and their biochemical role.

Table 49.1 Major MRS peaks of the human brain

Symbol	Chemical shift (ppm)	Contributing metabolites (major in bold)	Role
NAA	2.01	**N-acetylaspartate (NAA)** N-acetylaspartylglutamate (NAAG) N-acetylglutamate N-acetylglucosamine	Marker of neuronal density, function and viability; osmolyte. It decreases in cases of neuron loss, (e.g., glioma, ischemia)
Cho	3.22	**Phosphocholine (PCho)** **Glycerophosphocholine (GPC)** Free choline (Cho) Citidine diphosphate choline Acetylcholine Betaine	Marker of alterations in phospholipid metabolism of cell membranes. It increases in cellular membrane turnover (e.g., tumors) or disruption (e.g., demyelination).
Cr	3.02, 3.94	**Creatine (Cr)** **Phosphocreatine (PCr)**	Marker of aerobic energy metabolism. It is considered constant and used as an internal standard with some exceptions, (e.g., Cr deficiency syndromes, stroke, tumor, trauma, hyperosmolar states)
mI	3.56	**Myo-inositol** Inositol monophosphate Inositol diphosphate Phosphatidyl inositol	Glial marker, osmotic regulator, participates in the phosphoinositide signal transduction pathway. It increases in inflammation, trauma, neurodegeration and it decreases in stroke, tumor, infection and low grade tumors.
Glx	2.2–2.6 3.6–3.8	**Glutamate (Glu)** **Glutamine (Gln)** Gamma-aminobutyric acid Aspartate Glucose	Markers of neuronal Glu repletion and astroglial Gln synthesis. It increases in hypoxic–ischemic injury, hepatic encephalopathies, schizophrenia and epilepsy.
Lip	0.9, 1.3, 2.05, 2.2, 2.8	**Lipids** **Macromolecules**	Markers of apoptosis and necrosis or byproducts of bacterial metabolism. They appear in high-grade tumors, abscesses, acute inflammation and acute stroke.
Lac	1.33	**Lactate**	Marker of hypoxia or mitochondrial dysfunction. It increases in stroke, High-grade tumors, abscesses, mitochondrial disorders, inflammatory Response and macrophage infiltration

Many other metabolites have undetectable contribution in the brain spectrum due to their low concentration and/or their overlapping peaks (e.g., NAAG, aspartate, taurine, scyllo-inositol, betaine, ethanolamine, etc.) [38]. Some of them increase in pathological conditions and become visible [39, 40]. In some cases, peaks from drugs crossing the blood-brain-barrier can be detected and misidentified as brain metabolites [41–43].

49.4.2 Acquisition and Analysis

The production of an MR spectrum involves many successive steps which affect its information content and its correct interpretation. In the following we briefly describe the most important of them in their temporal order:

Shimming It is the process to optimize the homogeneity of the magnetic field in the volume of interest [43]. Magnetic field homogeneity is important for uniform water suppression and produces well-defined, well-separated thin peaks which can be reliably quantified. It might fail near to sources of field disturbance such as metallic objects near or inside the scanner (e.g. teeth bracelets), tissue/air and tissue/bone interfaces (e.g., sinus cavities and ear canals), or lesions inducing inhomogeneities (e.g., hemorrhage, calcification).

Water Suppression If left unsuppressed the water peak will dominate the spectrum because its concentration is 10,000 greater than the concentration of the metabolites. Suppression is typically accomplished with the chemical shift selective (CHESS) method [44], but alternative methods can be used too [45, 46]. Usually, even after a successful water suppression, small residual water resonances remain between 4.4 ppm and 5.0 ppm prohibiting the interpretation of the spectrum in this band. In spectra with poor water suppression the baseline becomes the slope of the water peak changing the relative heights of the peaks.

Fat Suppression It is the process of eliminating contamination of the spectra from signal originating from adipose tissue adjacent to the volume of interest. Signal from subcutaneous and marrow fat can "bleed" into adjacent voxels contaminating their spectra. Usually multiple saturation bands are placed around the volume of interest eliminating not just lipids but any surrounding tissue, a method called outer volume suppression (OVS) (Fig. 49.5) [47].

Localization MRS techniques can be divided in two groups regarding the way they localize the spectral information. The first group comprises single-voxel spectroscopy (SVS) techniques, which acquire only one spectrum from the whole volume of interest (Fig. 49.6). The second group comprises multi-voxel chemical shift imaging (CSI) techniques which acquire multiple spectra after dividing the volume of interest in a two- or more rarely a three-dimensional grid of voxels (Fig. 49.7), CSI

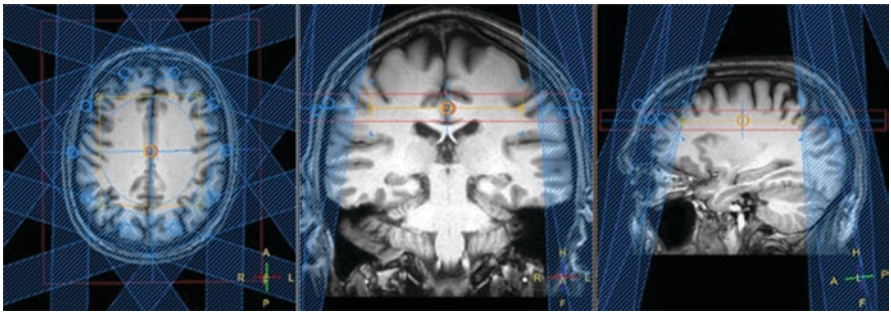

Fig. 49.5 Saturation bands (in blue) suppress signal around the spectroscopy volume (in yellow) preventing contamination of the spectra from adjacent tissue

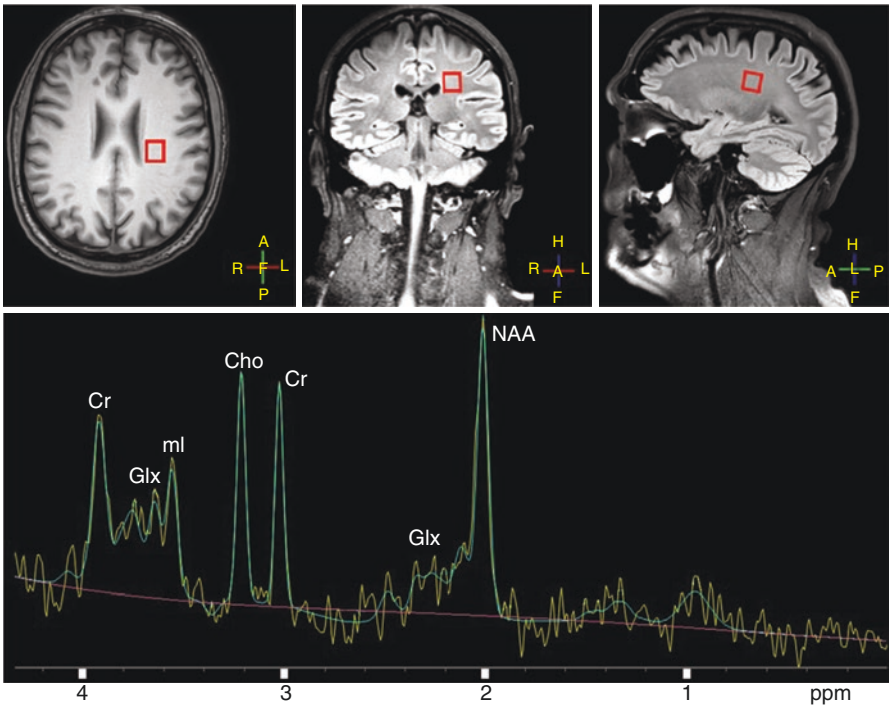

Fig. 49.6 A 3 T short TE = 64 ms, single voxel PRESS spectrum in the white matter (red voxel) of a healthy 52 years old man. The baseline and the fitting curve are overlaid on the spectrum. Typical major peaks are described in Table 49.1

is also known as magnetic resonance spectroscopic imaging (MRSI). The choice between SVS and CSI depends largely on the brain pathology. Usually, SVS is chosen in cases of a medium size homogeneous lesion and the voxel is prescribed entirely within the lesion and not vice versa. CSI is preferred in cases of a large heterogeneous lesion, a widespread disease or multiple small lesions. Compared to

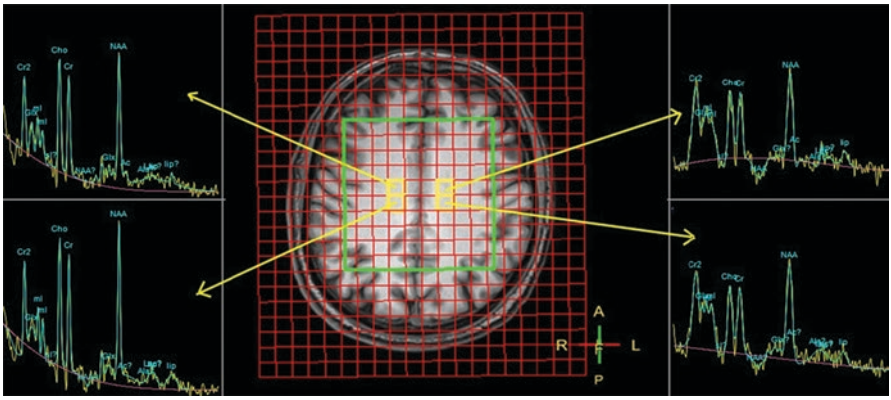

Fig. 49.7 A 3 T short TE = 64 ms, multivoxel PRESS spectrum of a healthy 52 years old man. Four representative spectra of the grid in the volume of interest (green square) are presented

CSI, SVS has limited spatial coverage but it is easier to shim, faster to acquire and has better signal to noise ratio providing better spectra. The most common method to define the volume of interest is the point resolved spectroscopy method (PRESS) [48]. Less popular is the stimulated echo acquisition mode (STEAM) technique, which has lower signal but can achieve better localization accuracy and shorter TEs than PRESS [49, 50].

TE Selection Among the various parameters influencing the morphology of the MRS spectra and the contribution of each metabolite is the echo time (TE). Metabolites with short T2, (i.e., Lip, GLx, mI) do not appear in spectra acquired with long TE (TE $\geq$ 120 ms). These spectra are less crowded, usually have a well-defined baseline and are easier to quantify than spectra with short TE. Spectra acquired with short TE (TE $\leq$ 45) have better signal to noise ratio and richer metabolic information. However, quantification is challenging due to sever overlapping of peaks, which also creates an irregular fluctuating baseline. Differences in the T2 of the metabolites means that MRS quantification is TE dependent and comparisons are meaningful only between spectra acquired with the same TE. The shape of the peaks affected by the J-coupling, depends on the TE. For example, a distinctive feature of the Lac doublet is that it appears inverted at TE = 144 ms and upward in the spectrum at TE = 288 ms.

Quantification It is the mathematical processes calculating the contribution of each metabolite in the spectrum. It is a challenging task, especially for the complicated short TE spectra and many different approaches have been developed, often involving many preprocessing steps [51]. Unfortunately, commercial MR scanners usually provide basic quantification algorithms. Thus, for state-of-the-art analysis, offline processing is required with special packages [52, 53]. Usually, the results are presented as metabolite ratios or in comparison with spectra from healthy regions.

Absolute quantification is more challenging and requires calibration with external or internal standards [54]. In pediatrics, particular care must be given to regional or age dependence of the brain metabolites during the spectrum interpretations [55–57].

49.5 Susceptibility

Magnetic susceptibility (χ) is a physical property describing the ability of a material to be magnetized when inserted in an external magnetic field. Susceptibility is defined as the ratio of the internal magnetization over the external magnetic field. The internal magnetization can either oppose ($\chi < 0$, diamagnetic) or enhance the external field ($\chi > 0$, paramagnetic, superparamagnetic, ferromagnetic). Biological tissue is weakly diamagnetic, but O_2 in the lungs, Gd-contrast agents, and organic free radicals are paramagnetic. Ferritin and hemosiderin are supermaramagnetic.

In MRI, the magnetization of the human body distorts the homogeneity of the external magnetic field producing in extreme cases susceptibility artifacts such as signal void and image distortion. In all other cases the field distortion is subtle, producing spin dephasing and signal drop which can be used as a new "susceptibility" contrast. The T_2* weighted images are predominantly affected by susceptibility effects. For example, they are used in MR venography or in functional MRI to detect differences in hemoglobin's magnetic susceptibility between the oxygenated and deoxygenated states [58, 59].

Based on previous studies [60, 61], in 2004 Haacke et al., introduced susceptibility weighted imaging (SWI) as a new method to enhance the contrast of the susceptibility effect on the T_2* weighted images by combining both magnitude and phase images [62]. Since then, SWI has been established as a powerful tool to narrow the differential diagnosis of many neurologic disorders [63]. More recently, quantitative susceptibility mapping and susceptibility tensor imaging have emerged as more accurate methods of susceptibility estimation [64–67].

49.6 Clinical Applications

Conventional MR sequences (T1, T2, FLAIR) combined with advanced MR techniques offer important information in the diagnostic workup of congenital malformations, inflammatory and infectious disorders, trauma and tumors. Inclusion of these sequences in the imaging protocol allows a global estimation of microstructural, hemodynamic and metabolic alterations induced by different disease processes [68].

Neuroimaging metrics have been widely used for tumor evaluation [69, 70]. Increased ADC indicates tissue cellularity often related with the degree of

malignancy. Tractography assesses the course of the white matter tracts and their integrity in the tumor area. Displacement of the white matter tracts is often observed in benign tumors with some exceptions such as pontine gliomas, while truncation or amputation is mainly observed in malignancies. Perfusion metrics have been associated with tumor vascularization and increased rCBV and rCBF are mostly observed in malignancies. MRS metabolites such as Cho are useful in the differential diagnosis between malignant and benign tumors, while others such as taurine are more specific to the tumor histologic type. In clinical practice, multiparametric assessment narrows the differential diagnosis between tumor types, allows tumor grading and helps preoperative planning [71–73]. Figures 49.8, 49.9, and 49.10 show examples of multiparametric imaging in pediatric brain tumors.

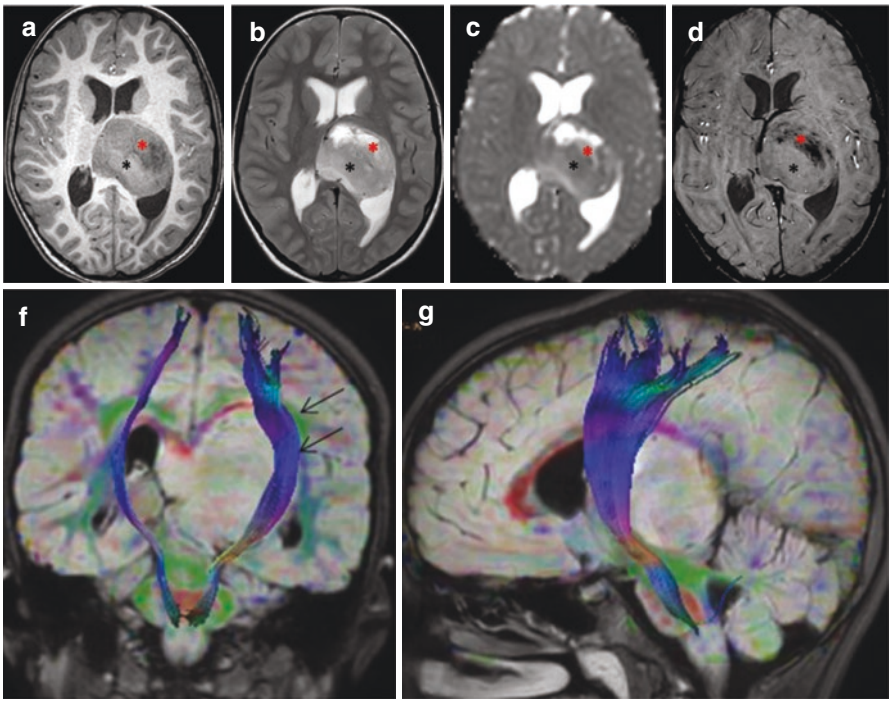

Fig. 49.8 A 10–year old female with left thalamic glioma, Axial scans (**a**) T1, (**b**) T2, (**c**) ADC map, (**d**) SWI, (**e**) ASL rCBF map and (**f, g**) tractography show a heterogeneous mass lesion arising from the left thalamus with: (1) A posterior component (asterisk) with intermediate signal intensity on T1, T2, and SWI, restricted diffusion on ADC and perfusion similar to that of the neighboring gray matter, (2) The anterior component (arrow) of the mass presents intermediate signal on T1, high signal on T2, increased diffusion on ADC, multiple small vessels and hemorrhagic components on SWI and increased perfusion on the rCBV map. Tractography shows displacement of the left corticospinal tract without amputation. The right corticospinal tract is in normal position

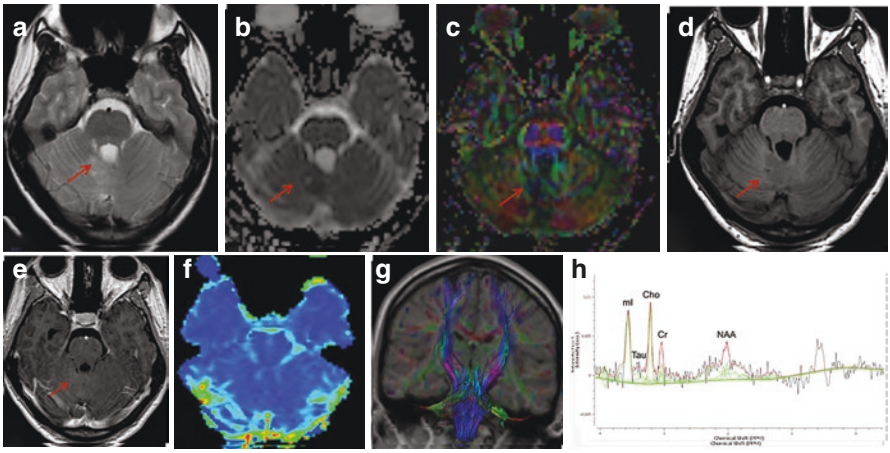

Fig. 49.9 A 15-year old female with meduloblastoma, Axial scans (**a**) T2, (**b**) ADC map, (**c**) FA map, (**d**) plain T1, (**e**) contrast enhanced T1, (**f**) DSC rCBF map, (**g**) tractography and (**h**) MRS showing a mass lesion arising from the right part of the vermis (red arrow) with relatively high signal on T2, restricted diffusion on ADC, asymmetry in the disposition of the white matter tracts on FA, low signal on T1 and punctuate enhancement on contrast enhanced T1, without any perfusion change on rCBF and on MRS increased Cho and Tau and decrease NAA. Major white matter tracts are not displaced or amputated on tractography

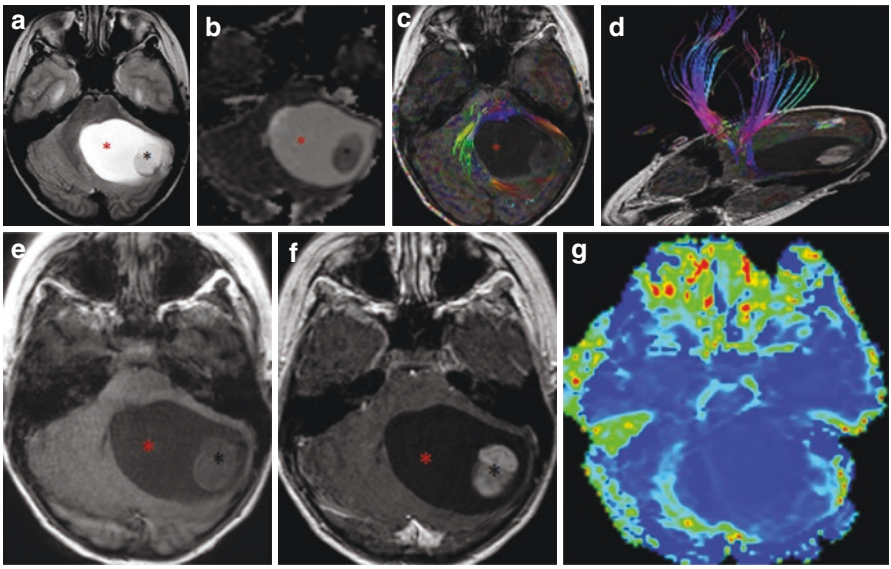

Fig. 49.10 A 9-year old boy with pilocytic astrocytoma, (**a**) T2, (**b**) ADC map, (**c, d**) tractography, (**e**) plain T1 (**f**) contrast enhanced T1 and (**g**) DSC rCBF map show a mass lesion with a cystic (red asterisk) and a mural solid (bleu asterisk) component, with increased ADC and perfusion in the solid component. Tractography shows displacement of white matter tracts surrounding the lesion and normal disposition of the corticospinal tracts

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Chapter 50
Molecular Imaging in Pediatric Brain Tumors

Georgios Alexiou, Chrissa Sioka, and Andreas D. Fotopoulos

50.1 Introduction

Pediatric brain tumors constitute the most common solid malignancy in children and second most common cancer after leukaemia [1]. In children and adolescents, the incidence rate of malignant and non–malignant brain and other central nervous system (CNS) tumors was recently reported to be 6.06 cases per 100,000 [2]. According to the World Health Organization (WHO) grading system, they are classified into four grades (I–IV) and additional molecular parameters to histology are currently used to define several tumor entities [3, 4]. Pilocytic astrocytomas (Grade I) are the most frequent tumor followed by medulloblastomas (Grade IV) and ependymomas (Grade II/III) [1]. These tumors are classified based on their location into supratentorial and infratentorial tumors. Prognosis is largely depended on age of diagnosis, histological type and treatment. The recent advances in molecular classification of these tumors allowed for more targeted treatment strategies to be employed [4]. Nevertheless, still several tumors, such as high risk medulloblastomas, are associated with dismal prognosis.

Magnetic resonance imaging (MRI) constitutes the imaging modality of choice to morphologically characterize brain tumors based on several characteristics such as pattern of contrast uptake, presence of necrosis and peri-lesional oedema. Advanced MRI techniques such as diffusion, perfusion and spectroscopy hold an increasing role in clinical practice. Nevertheless, there might be shortcomings in the diagnosis of radiation-induced changes, from recurrent/progressive disease,

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differentiation of malignant from benign lesions or non-specific changes, such as hyperintensity on T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images [5]. Additionally, a recent study showed that the non-enhancing part of the tumor contains considerable amounts of infiltrative tumor with a high cellularity [6]. Thus, further advances in imaging techniques are needed.

Nuclear medicine techniques such as positron emission tomography (PET) and single-photon emission tomography (SPECT) have also been evaluated in brain tumors [7]. Both techniques utilize radiopharmaceuticals that are categorized as metabolism receptor-binding, able to penetrate blood-brain-barrier, assessing cerebral perfusion and those with antigen-antibody binding. PET compared to SPECT has higher resolution and is the current most sophisticated nuclear medicine imaging modality. Nevertheless, SPECT is associated with lower cost, more wide availability, and gained practical experience [7]. For both modalities' hybrid PET/CT, PET/MRI and SPECT/CT allow for both metabolic and anatomic imaging to be acquired simultaneously. Furthermore, the use of theranostic radiopharmaceuticals in nuclear medicine has been growing rapidly over the past years and show promise for both diagnosis and therapy of pediatric brain tumors.

50.2 SPECT

Various radiotracers have been utilized for brain tumor imaging using SPECT (Table 50.1). The main applications were for the differentiation of tumor recurrence from treatment-induced necrosis, differentiation of low from high-grade tumors, assessment of tumor's proliferation rate and prognosis and stereotactic targeting for brain tumor biopsies [8–10]. Thallium-201 (^{201}Tl) was among the first tracers that were widely employed, mainly for myocardial perfusion imaging. The exact cellular uptake mechanism is still not clearly elucidated; however, the

Table 50.1 Pros and cons of the SPECT tracers used for pediatric brain tumor imaging

SPECT tracers	Advantages	Disadvantages
^{201}Thallium	Absence of tracer uptake in the healthy brain.	Low photon flux Lower spatial resolution Long half-life (73 h)
^{99m}Tc-Sestamibi	High photon flux High spatial resolution Short half-life (6 h)	Uptake by normal choroid plexus, pituitary Influenced by multidrug resistance efflux pumps
^{99m}Tc-Tetrofosmin	High photon flux High spatial resolution Short half-life (6 h) Not influenced by multidrug resistance efflux pumps	Uptake by normal choroid plexus, pituitary
L-3-[^{123}I]iodo-alpha-methyl tyrosine	Amino acid analogue	Uptake in normal brain Limited experience

sodium-potassium ATPase pump is more likely involved, at least in part. Technetium-99 m-labeled compounds were found to be advantageous compared to ^{201}Tl because of the higher photon flux, better spatial resolution, and significant lower half-life. One drawback of technetium-99 m-labeled compounds, compared to ^{201}Tl, is their avid physiological uptake in structures that lack blood-brain barrier such as the choroid plexus. This might hamper the delineation and calculations of lesion to normal tracer uptake of lesions located in the para-ventricular area or near pituitary. Among technetium-99 m-labeled compounds, ^{99m}Tc-hexakis-2-methoxy isobutyl isonitrile (^{99m}Tc-sestamibi or ^{99m}Tc-MIBI) and ^{99m}Tc-tetrofosmin (^{99m}Tc-TF) have been mainly studied in brain tumor imaging (Fig. 50.1). ^{99m}Tc-TF has been proven, both *in vitro* and *in vivo*, advantageous over ^{99m}Tc-MIBI, because it is not affected by the multidrug resistance mechanism that cancer cells have and diminish radiotracer uptake [11, 12]. Studies on pediatric brain tumors using SPECT are scarce and relative old. In pediatric brain stem gliomas there was concordance between the presence of contrast uptake on MRI and ^{201}Tl uptake. No lesion that had ^{201}Tl uptake lacked gadolinium enhancement [13]. In a series of 24 children with various brain tumors, in which MRI was compared to ^{201}Tl SPECT, ^{201}Tl uptake calculated as lesion to normal ration did not correlate with histologic grade, biologic aggressiveness, or tumor type [14]. Technetium-99 m-labeled compounds, have also been utilized for pediatric brain tumor imaging. ^{99m}Tc-MIBI was evaluated in 20 children with CNS malignancies. From the 29 ^{99m}Tc-MIBI studies, 13 were true-positive, 13 were false-negative, and 3 were true-negative compared

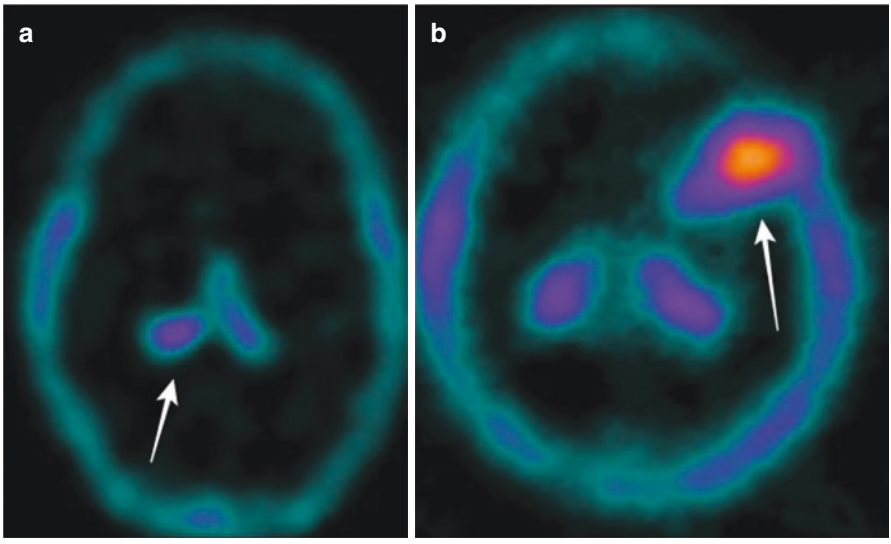

Fig. 50.1 (**a**) Normal distribution of a technetium-labeled compound (^{99m}Tc-Tetrofosmin) for brain SPECT imaging. There is uptake in structures lacking blood brain barrier such as the choroid plexus (arrow). In normal brain there is no tracer uptake, thus a neoplastic lesion can be readily identified. (**b**) A case of a recurrent glioblastoma exhibiting avid tracer uptake (arrow)

to MRI. ^{99m}Tc-MIBI uptake correlated in part with the histologic grade. In one case of recurrent brain stem glioma ^{99m}Tc-MIBI detected the recurrence earlier than MRI [15].

^{99m}Tc-Tetrofosmin was evaluated for detection of recurrent posterior fossa tumors of 11 children. The primary diagnosis was medulloblastoma in six cases, ependymoma in four cases and a grade III glioma in one case. An irregular region of interest (ROI) was drawn around the tumour and the lesion to contralateral normal brain uptake ratio was estimated. The ability of this tracer to detect posterior fossa recurrent tumor was low since only one out of the seven patients with recurrent tumours was detected. ^{99m}Tc-Tetrofosmin uptake was false positive in one patient and was true negative in four patients [16]. L-3-[^{123}I]iodo-alpha-methyl tyrosine has also been evaluated in pilocytic astrocytomas and showed uptake above cortical level in 13/16 cases. The mean uptake in recurrent tumours was higher than in primary or residual tumors. L-3-[^{123}I]iodo-alpha-methyl tyrosine proved superior to 18F-FDG PET in identifying tumor margins [17]. Nevertheless, this tracer has normal uptake from brain parenchyma thus this limits identification of tumors with low tracer uptake.

50.3 PET

50.3.1 Assessment of Tumor Grade

Preoperative assessment of glioma grade is important for proper patients' management, especially for difficult to treat cases, clinical follow-up examinations, and inclusion in clinical research. The 2-deoxy-2[^{18}F]fluoro-Dglucose (^{18}F-FDG) is the most commonly used PET tracer in oncology. Accumulation of FDG is in proportion to glucose metabolism. Thus, there is tracer uptake in the healthy brain. Newer tracers based on amino acid transport and metabolism have provided important information on brain tumor characteristics. A meta-analysis of the main PET tracers used in clinical practice, namely ^{18}F-FDG, ^{11}C-Methionine, and ^{18}F-FET PET, showed that both ^{11}C-Methionine, and ^{18}F-FET PET were superior to ^{18}F-FDG in terms of sensitivity for identifying glioma grade in adults [18]. In a study of 38 pediatric patients, ^{18}F-FDG uptake with a cut-off value of 1.83 was positively correlated with malignancy grading. However, a choroid plexus papilloma and three pilocytic astrocytomas exhibited increased tracer uptake [19]. When ^{18}F-FDG was compared to ^{11}C-methionine PET, the uptake was significantly higher in high-grade than in low-grade tumors for both tracers, however a considerable overlap was found. The patients who died during the follow-up period had significantly higher uptake values of both tracers compared to alive patients [20]. ^{18}F-DOPA PET proved useful for the assessment of pediatric glioma grade and was equal effective as DWI and perfusion ASL [21]. Nevertheless, ^{18}F-DOPA has a high physiologic uptake in striatum, thus lesions located in the vicinity of this structure might be difficult to delineate or detect.

50.3.2 Differentiation of Treatment-Related Changes from Recurrent/Residual Tumor

Amino acid tracers have been shown to be superior to glucose analogue ^{18}F-FDG PET for the discrimination of cancerous from non-cancerous tissue, assessment of tumor extent and potentially treatment response [22]. Gross total excision is the treatment of choice for the majority of tumor types, however treatment related changes or recurrent and residual tumor might be difficult to be diagnosed by MRI alone, given the non-specific postoperative changes in the tumor bed [5]. A hybrid PET/MRI system using 18F-FET was evaluated in the postoperative period after a brain or spinal cord tumor resection. Based on MRI there was residual tumor in 52% of cases. Using follow-up or reoperation as the reference standard the results showed that the specificity for PET/MRI was 100% compared with 75% for MRI. Reactive postoperative alterations and venous infarctions were the main findings in which the role of PET/MRI was crucial [23].

50.3.3 Response to Therapy

^{18}F-FDOPA is an amino acid analog used as a PET tracer and displays relative low uptake in the healthy brain. Thus, a lesion even of low-grade is readily identifiable. ^{18}F-FDOPA uptake correlates with microvessel density and has been evaluated as a marker of response to treatment following bevacizumab therapy. Bevacizumab is a humanized monoclonal IgG antibody against the human vascular endothelial growth factor-A isoform and is currently used for the treatment of high grade tumors. Nevertheless, in a small studied of recurrent pediatric gliomas ^{18}F-FDOPA maximum and mean standardized uptake values and tumor-to-brain ratios failed to predict response 3 months post-treatment [24].

50.3.4 Prognosis

^{11}C-methionine PET has been evaluated for possible prognostic value in a series of children with newly diagnosed DIPG. In 18/22 patients there was tracer uptake greater than that of normal brain tissue. Two out of four patients with a negative PET scan had a histologically proven glioblastoma, whereas two low-grade gliomas exhibited positive scans. No significant correlation was found between ^{11}C-methionine and survival, whereas an increase in uptake was observed following chemotherapy or radiotherapy [25]. One additional drawback of ^{11}C-methionine use is the need for cyclotron on site due to the short half-life (20 min). On the other hand ^{18}F-DOPA uptake correlated with PFS prediction in glioma patients than both DWI and ASL perfusion [21]. Furthermore, ^{18}F-DOPA uptake correlated with

progression-free survival and overall survival in a series of 21 pediatric patients with supratentorial gliomas. MR spectroscopy metrics failed to show a significant correlation with outcome [26].

50.3.5 Other Applications

Selection of the optimal target for performing a stereotactic biopsy is of utmost importance, given that acquisition of a non-diagnostic sample may require additional samples, thus increasing the risk of a devastating hemorrhage or underdiagnosis [27]. In a series of 35 pediatric brain tumor patients that were selected for biopsies a preoperative ^{18}F-FDG and ^{11}C-methionine, PET in comparison to MRI. were performed. There was focal uptake in 22 cases, diffuse in 11 but with focus on an area of maximum uptake and absent in two cases. All biopsy trajectories, that were designed based on PET findings, yielded tumor tissue. In seven biopsies that were MR imaging–guided the samples were nondiagnostic. Additionally, the tumor grade diagnosed by PET-guided trajectory was higher than that established by MR imaging–guided trajectory [28].

The latest WHO classification included a novel entity called diffuse midline glioma (DMG), H3K27M-mutant. This new entity has been associated with dismal prognosis irrespectively of tumor grade. In a study of 22 pediatric patients with DMG a ratio of tumor to normal striatum of 18F-DOPA PET could differentiate H3K27M-mutant from wild-type DMG with 75%sensitivity and 83% specificity. No significant differences were noted for diffusion, arterial spin labelling MR perfusion and spectroscopy [29].

50.4 Theranostics in Pediatric Brain Tumors

Somatostatin receptor expression has been found in pediatric embryonal tumors including medulloblastoma, the most aggressive primary pediatric brain tumor. The development of somatostatin analogs that can be labeled with beta-emitting radionuclides have been tested for therapeutic purposes. Among them, ^{90}Y-DOTA^{0}-Tyr^{3}-octreotide has more than a decade of clinical experience and was tested in children with embryonal and astrocytic brain tumors. There was partial response in a case of anaplastic astrocytoma and no response in a case of pineoblastoma and choroid plexus carcinoma. This radiopharmaceutical showed low toxicity profile with no serious adverse events attributed to its use [30].

The gastrin-releasing peptide receptor (GRPR) has been currently evaluated as a possible therapeutic target in brain tumors. In gliomas, a 100% GRPR immunopositivity was reported, whereas in normal brain tissue, GRPR was found in neurons and not in glial cells [31]. The GRPR-targeting molecular probe ^{68}Ga-NOTA-Aca-BBN (7–14) PET was evaluated in eight children with suspected optic pathway glioma.

In all lesions there was profound tracer uptake with excellent contrast in relation to surrounding healthy brain tissue. All lesions were confirmed GRPR positive [32]. Thus, GRPR may be a possible target for both tumour diagnosis and radionuclide therapy with radiolabelled peptide analogues.

^{89}Zr-bevacizumab is a radioimmunoconjugate comprised of bevacizumab labeled with the radioisotope zirconium (^{89}Zr). This tracer permits the imaging and quantification of VEGFR-expressing tumor cells. Diffuse intrinsic pontine glioma (DIPG) is an almost uniformly fatal tumor in children. Bevacizumab has been shown some positive results in DIPG cases and the main goal is to identify the patients that will response to treatment. In a study of seven DIPG patients that underwent ^{89}Zr-labeled bevacizumab PET imaging, there was focal uptake in 5/7 cases. Scan should be performed 144 h after injection and no adverse effect occurred. 89Zr-bevacizumab PET may be a promising tool for selecting patients for bevacizumab therapy [33].

50.5 Conclusion

SPECT and PET have been utilized for pediatric brain tumor imaging. Although SPECT has not been extensively investigated, PET especially with the amino acid analogue-based tracers provide important information for indications such as tumor grading, differentiation of treatment-related changes from recurrent/residual tumor, response to therapy and prognosis. The use of novel theranostic radiopharmaceuticals that combine the diagnosis and therapy is an emerging field that open new horizons in nuclear medicine.

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Chapter 51
Intraoperative Flow Cytometry in Pediatric Brain Tumors

Georgios Alexiou and George Vartholomatos

Learning Objectives
1. What is flow cytometry.
2. What is the role of intraoperative flow cytometry in pediatric brain tumor surgery.
3. What are the main goals of immunophenotypic analysis of pediatric brain tumors.

51.1 Introduction

Brain tumors are the second most common malignancy in children after leukemia. They are divided into supratentorial and infratentorial tumors. Pilocytic astrocytomas are the most frequent tumors and carry a favourable prognosis. Medulloblastomas are the second most common tumors [1]. Medulloblastomas are high-grade tumors and four distinct subtypes, that correlate strongly with survival, have been identified by molecular analysis [2]. Ependymomas are the third most common tumors.

For more than 30 years flow cytometry has been utilized towards cancer research both in basic and clinical setting. Apart from cancer or other disease diagnosis, flow cytometry may evaluate the therapeutic and side effects of several disease treatments [3]. Flow cytometry is a laser based technique that quantitatively measure several properties of a sample in a liquid form. In sort, cell suspension passes through a laser beam and a signal is produced that is directly related to size, granularity and fluorescent features of the cells. Several applications are available based on the detection of the membrane, cytoplasmic and nuclear antigens [3]. Especially

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in hematology, flow cytometry is an indispensable tool for the diagnosis and classification of hematological disorders from several biological fluids, such as blood, cerebrospinal fluid, pleural effusion and bone marrow [4].

Flow cytometry has not been extensively investigated in solid tumors. When a solid tissue is analyzed first a cell suspension must be made. Several techniques have been developed for sample preparation. Cell cycle analysis was one of the first applications of flow cytometry and most frequent utilized in solid tumor analysis. Cell cycle analysis can provide information on tumor malignancy and prognosis. Recently, intraoperative flow cytometry has been introduced and allowed the identification of tumor grade, tumor margins and diagnosis of central nervous system lymphoma in real time [5].

51.1.1 Flow Cytometry in Pediatric Brain Tumors

Flow cytometry, by analyzing the tumor's DNA content, has been evaluated in several pediatric brain tumors. DNA content analysis involves assessment of ploidy status, the set number of cell chromosomes. Diploid tumors have a DNA index near to 1, whereas aneuploid tumors are those with DNA index more or less than 1. Presence of DNA aneuploidy is related to worse prognosis. Cell cycle analysis evaluate G0/G1, S and G2/M phase fractions. The higher the malignancy the lower the G0/G1 and higher the S and G2/M phase fractions. Pediatric brain tumors show significant flow cytometric and cell kinetic abnormalities, both in common and rare tumor types. In childhood astrocytomas ploidy status proved to be a significant predictor of survival. Among children with diploid tumors, 81% survived, whereas only 33% of patients with aneuploid tumors survived [6]. In medulloblastomas, aneuploid tumors exhibited higher recurrence rates. Aneuploid tumors were more frequent in children aged 3–10 years [7]. In ependymomas, the third most common pediatric brain tumor, there were inconsistent data. This group of tumors is highly variable, and several prognostic factors have failed [8, 9].

51.1.2 Fast Cell Cycle Analysis

Cell cycle analysis was traditionally performed on paraffin-embedded tissues or in fresh tissue samples and required substantially time, thus hampering its intraoperative usage. Two groups of researchers investigated at the same time possible intraoperative use of flow cytometry for assessing grade of malignancy and resection margins of gliomas. Shioyama et al. evaluated 328 separate biopsy specimens obtained during the resection of 81 intracranial gliomas by an approximately 10 min flow cytometry protocol. The ratio of the number of cells with greater than normal DNA content to the total number of cells was defined as malignant index [10]. Alexiou et al. focused on the analysis of cell cycle fractions (G0/G1, S and G2/M) and presence of aneuploidy. The fast analysis protocol was named "Ioannina

Protocol" and was of 6 min duration [11]. Intraoperative flow cytometry permitted the detection of high-grade gliomas and assessment of clear resection margins with high sensitivity and specificity. A 6% of S-phase and 9.7% of G2/M phase fractions were the optimal cutoff values thresholding the discrimination between low and high-grade tumors. Furthermore, during stereotactic brain tumor biopsies, intraoperative flow cytometry permitted the identification of neoplastic cells within minutes, thus diminished duration of operation and the need for several samples. Acquisition of multiple samples increases the risk of a devastating hemorrhage.

Fast cell cycle analysis has also been evaluated in pediatric brain tumor cases. This technique proved useful for the detection of grade of malignancy. Low-grade tumors had significantly higher G0/G1 and lower G2/M phase fractions than high-grade (III and IV) tumors. High-grade tumors had lower than 81% G0/G1 fraction. Tumors with S phase fraction more than 10% or G2/M fraction more than 13% were always high-grade. Grade III tumors also exhibited significant lower G0/G1 fraction than grade IV tumors (Fig. 51.1). Large cell medulloblastomas, that are associated with unfavorable prognosis among medulloblastomas, showed also higher malignancy in cell cycle fractions. Ki-67 index is an immunohistochemical marker of cell proliferation and is present in all non-G0 phases of the cell cycle. Ki-67 index has been found to have prognostic information in several malignancies. A significant positive correlation was found between Ki-67 and S-phase fraction in medulloblastomas and ependymomas [12].

Gross total excision of a brain tumor is of prognostic significance. To date, several techniques have been utilized or are under evaluation for the intraoperative assessment of resection margins. Intraoperative MRI has been shown to increase the extent of resection of pediatric brain tumors. Nevertheless, intraoperative MRI is costly and only available in few institutes. Furthermore, preparation and MRI acquisition requires substantial time, whereas histopahological evaluation of MRI clear resection margins revealed the presence of cancer cells. 5-aminolevulinic acid (5-ALA)-guided surgery has been shown to increase survival in glioblastoma patients. However, a great amount of pediatric tumors are of low-grade, thus low or absence of fluorescence has been reported [13]. Detection of cancer cells by flow cytometry relies on abnormal ploidy status and/or cell cycle fractions. Thus, low-grade tumors can be readily identified especially if aneuploidy exists. Neoplastic from non-neoplastic tissue can be identified by flow cytometry with 100% sensitivity and specificity based on G0/G1 and S-phase fractions with 89% and 2% cut-off values [12] (Fig. 51.2).

51.2 Immunophenotypic Analysis

51.2.1 CD56

CD56, also known as neural cell adhesion molecule (NCAM), except from natural killer cells, has been found to be expressed in brain tumors [14]. In adult gliomas CD56 immunopositivity was found to be inversely correlated with tumor grade. Absence of NCAM staining in gliomas was associated with unfavorable prognosis [14]. CD56 expression in pediatric brain tumors has been investigated and great

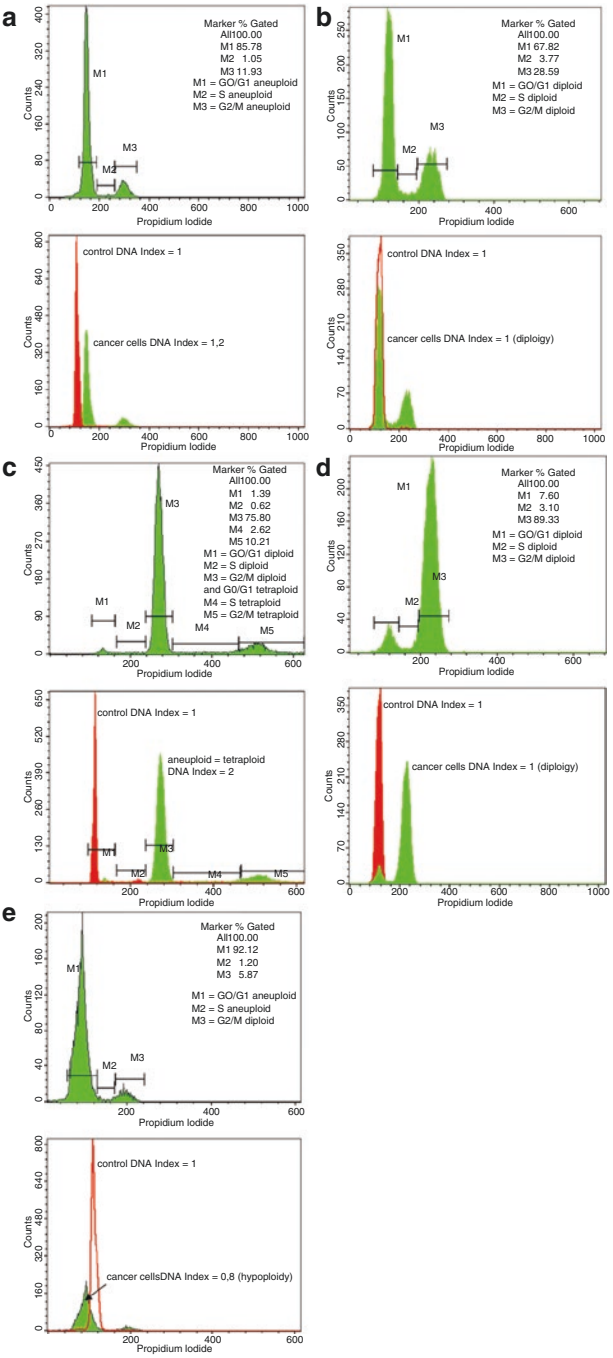

Fig. 51.1 Cell cycle analysis of various tumor types and overlays with control. (**a**) A case of anaplastic ependymoma. (**b**) A medulloblastoma case of large cell/anaplastic histological type. (**c**) A medulloblastoma of classic histological type. (**d**) A case of a grade II meningioma. (**e**) A case of anaplastic ependymoma

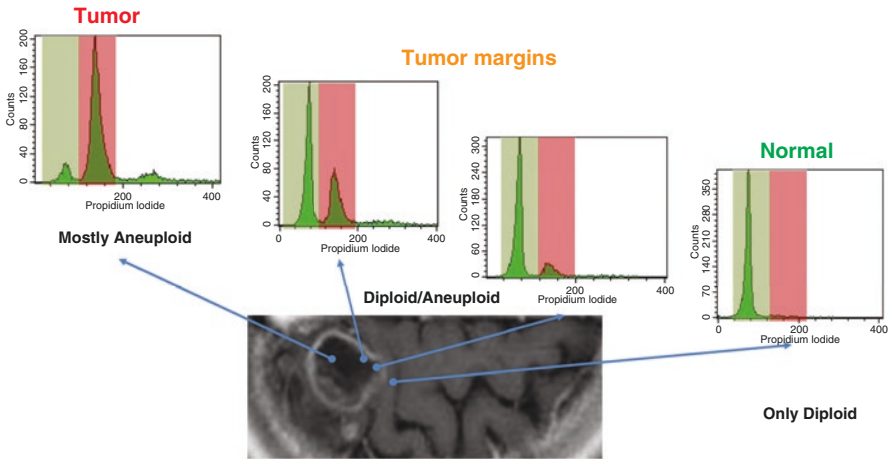

Fig. 51.2 Assessment of tumor margins by flow cytometry

variability in the expression patterns was revealed. High-grade tumors showed significant lower CD56 expression than low-grade tumors and a negative linear correlation with Ki-67 index was found. Furthermore, both low and high-grade tumor groups could be differentiated from normal brain based on CD56 expression [15] (Fig. 51.3).

By using cell cycle analysis with propidium-iodine (PI) staining of CD56+ cells we could accurately differentiate between neoplastic and non-neoplastic tissue, as well as high-grade from low-grade tumors [16]. A cut-off value of 91% in G0/G1 phase fraction and G2/M fraction of 2% could differentiate normal from neoplastic tissue with 100% sensitivity and specificity. Tumors with a S-phase fraction more than 7% were always high-grade. A significant correlation between Ki-67 index and S + G2/M-phase fraction and proliferation index (S + G2/M/G0/G1) was reported, suggesting excellent correlation with tumor's proliferation potentials [16].

51.2.2 CD24

Increased *CD24* gene expression has been reported in pediatric brain tumors being higher in medulloblastomas. This was also verified at protein level. The highest expression levels were detected in SHH-driven tumors. CD24 expression could be an immunomarker in medulloblastomas with possible prognostic and therapeutic role [17]. The CD24 expression was quantified by flow cytometry in histopathological verified tissues obtained from 46 pediatric brain tumor cases and three normal samples obtained during surgery for epilepsy. Quantitative measurement of bound anti-CD24 FITC (ML5) was achieved using the flow cytometry based QIFIKIT® assay (DAKO, Glostrup, Denmark) according to the manufacturer's instructions. There was absence of CD24 expression in normal brain tissue (Fig. 51.4). There

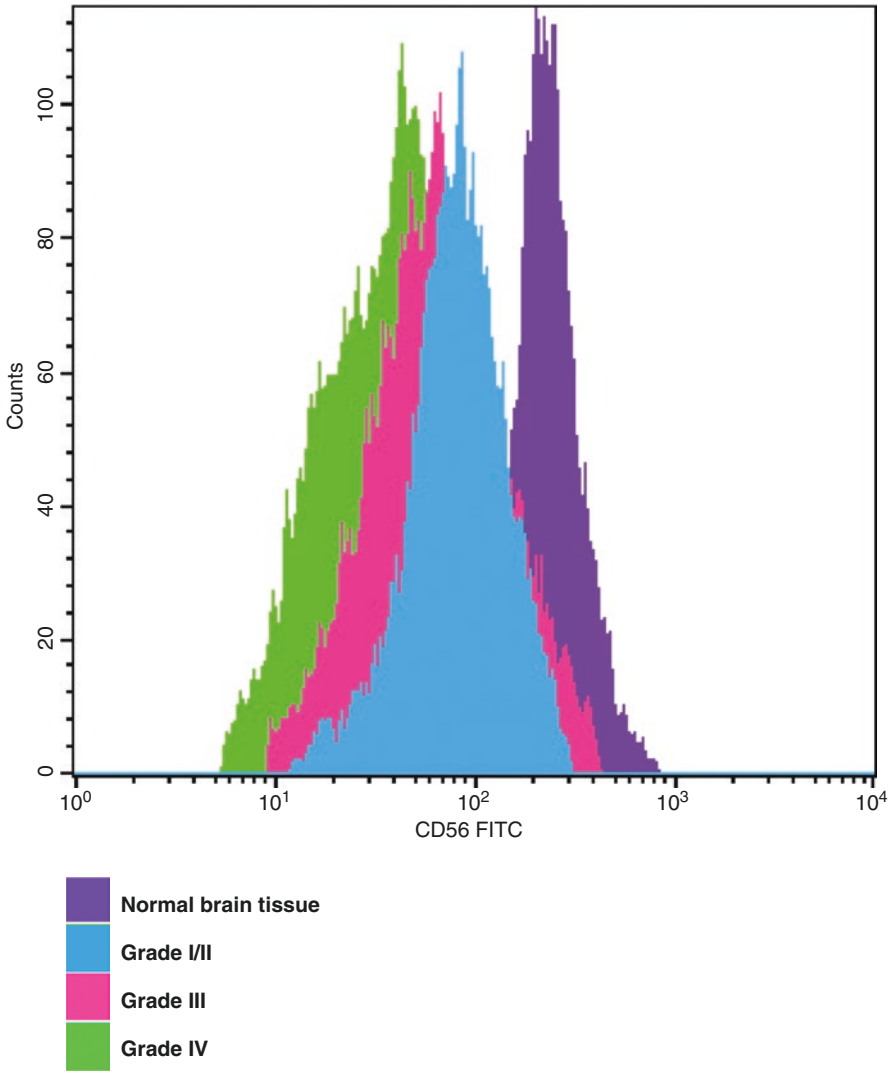

Fig. 51.3 Relationship between histological grade and number of CD56 molecules/cell

was also no expression in low-grade astrocytomas and meningiomas. There was high CD24 expression in 14/17 medulloblastomas and in 8/12 anaplastic ependymomas. Medulloblastomas had significant higher CD24 molecules/cell than ependymomas (median 18.277 vs 4.281 molecules/cell, $p = 0.014$). Interestingly there was high CD24 expression in two cases of myxollopapillary ependymoma (mean 19.100 molecules/cell) and exceedingly high in a case of medulloblastoma with melanocytic differentiation (59.023 molecules/cell). There was also a trend towards a significant correlation between CD24 molecules/cell and Ki-67 index ($p = 0.1$).

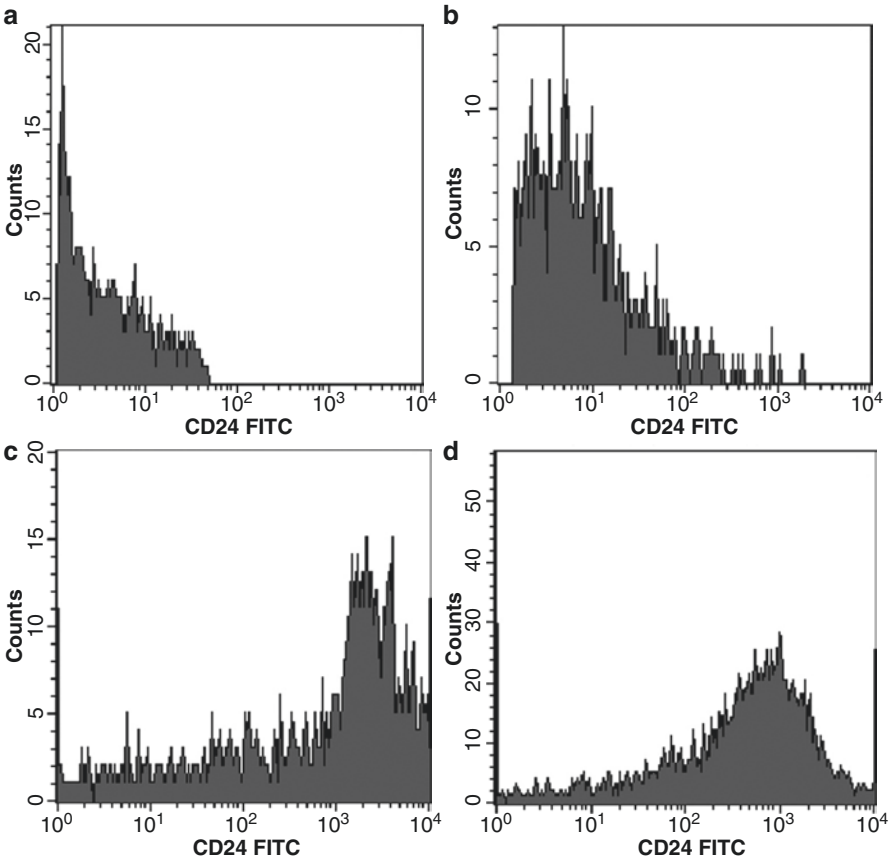

Fig. 51.4 (**a**) Normal brain tissue. There is no CD24 expression. (**b**) A case of diffuse astrocytoma with no CD24 expression. (**c**) A case of medulloblastoma with melanocytic differentiation. High CD24 expression. (**d**) A case of myxopapillary ependymoma with high CD24 expression

The increased CD24 expression in myxopapillary ependymoma might be explained by the fact that this tumor might have solid growth pattern with aggregates of cells with "epithelial morphology", which is associated with CD24 expression [18]. Melanoma cells also exhibit CD24 expression and increased expression has been associated with worse prognosis. This might also explain the exceedingly high CD24 in the medulloblastoma with melanocytic differentiation case. Contrary to immunohistochemistry, flow cytometry can provide objective and quantitative results, even on very small samples. More importantly assessment of CD24 with this technique can be performed within minutes after sample arrival. Thus, this method could be a novel adjunct to the standard histopathological evaluation of tumor samples.

51.3 Central Nervous System Lymphoma

Primary CNS lymphomas (PCNSL) are rare brain lesions accounting for approximately 2.5% of all Central Nervous System (CNS) malignancies [19]. In case of systemic lymphoma, secondary CNS lymphoma can be found. Lymphoma can mimic on imaging other space occupying lesions such as high-grade glioma. Accurate differentiation intraoperatively is of paramount importance since gross total excision should be sought in glioma contrary to lymphoma of which treatment involves systemic chemotherapy [20]. Intraoperative flow cytometry can aid identification of lymphoma based on the expression of CD45 and CD19/CD20 (a B-cell markers) or CD3 (a T-cell marker). Moreover, CD20 expression holds a therapeutic role since treatment with an anti-CD20 monoclonal antibody can be administered [21].

51.4 Conclusion

Intraoperative flow cytometry is a promising novel technique with several applications in brain tumors. On the field of pediatric CNS oncology intraoperative flow cytometry may permit a better gross total excision of brain tumors which certainly have prognostic significance and differentiation of low from high-grade tumors. Immunophenotypic analysis may aid discrimination of grade of malignancy, holds important prognostic information and may identify the histopathology of certain lesions.

Clinical Pears

- Intraoperative flow cytometry permits the discrimination of low from -high grade tumors and assessment of resection margins.
- CD56 expression of brain tumors correlate with grade of malignancy and proliferation indices.
- Medulloblastomas exhibit increased CD24 expression.

Review Questions

1. What are the indications in cell cycle fractions that a brain tumor is malignant?
2. What are the cut-off values of G0/G1 phase fraction and G2/M fraction for the discrimination of normal from neoplastic tissue, based on CD56 expression?

Answers

1. Tumors with an S phase fraction more than 10% or G2/M fraction more than 13% are high-grade.
2. A cut-off value of 91% in G0/G1 phase fraction and G2/M fraction of 2% could differentiate normal from neoplastic tissue.

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Chapter 52
Advances in Radiotherapy for Pediatric Brain Tumours

Pinelopi Gkogkou and Thankamma V. Ajithkumar

52.1 Introduction

Primary central nervous system (CNS) tumours comprise the second largest group of pediatric tumours and radiotherapy is an important element in their multimodality treatment. Gliomas are the commonest primary CNS tumours (53%), with approximately 70% of these tumours being low-grade gliomas (LGGs), followed by 20% meduloblastomas (MB) and 10% ependymal tumours [1]. Radiation therapy (RT) has an important role in the treatment for many childhood tumors, as it can improve life expectancy and cure rates [2, 3]. There are two main aspects of evolution in radiation oncology; radiation therapy technology and molecular therapy. Radiation therapy technologies employ a continuous progress of adaptation of high precision techniques including particle therapy, such as the proton treatment. Proton treatment uses charged particles that can shape the dose around tumor, minimizing the dose to normal tissue [4]. Molecular evolution in pediatric oncology has led to better-stratified disease subgroups. The key approach of modern radiotherapy is to use tailored treatment doses based on disease profile, either by intensifying treatment for those with a predicted worst outcome or deescalating treatment for those with better prognosis. As younger age remains the strongest factor affecting long-term sequelae, merging novel agents with radiotherapy could achieve a better local control and long-term disease remission.

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52.2 Brief Overview of Radiation

The current approach is to withhold radiotherapy over systemic treatment, especially for younger children, and initiate it in those above the age of 8 years old. However, the clear impact of the delay in radiotherapy in terms of clinical outcome is not known due to lack of extended long-term follow up [5].

The importance of radiotherapy quality increases in parallel with the technical complexity and precision of treatment delivery. Patients receive fully fractionated external beam RT that is facilitated by daily image verification that provides accurate, reproducible patient set up to minimize the interaction variability in radiation delivery. Intensity Modulated Radiotherapy with Image Guidance (IMRT/IGRT) rests on accurate tumour identification and targeting, which can improve physical dose distribution, enhancing tumour cell death. IMRT/IGRT has been widely adopted in children and results are encouraging [5]**.** While the number of proton therapy facilities has rapidly increased, both in the public and private sectors, the most important question remains: is proton therapy truly clinically superior to photons? [6, 7].

Whilst we try to answer these questions, we recommend that the best treatment technique should be offered for each child, including referral to another center if required. In pediatric oncology, enrolment into clinical trials is the norm, and radiotherapy for children should be delivered within clinical trials where appropriate, or according to expert consensus guidelines where trial entry is not possible [8, 9].

The current role of pediatric brain radiotherapy based on tumors type and radiotherapy treatment principles differ between tumors. For example, most low-grade gliomas (LGGs) in children are pilocytic astrocytomas, which are well-defined tumours amenable to gross tumour resection (GTR) followed by surveillance. Radiotherapy for LGGs is indicated when there are no further surgical options in children aged between 5 and 8 years. Radiotherapy also has an established role for ependymomas following surgery, even for metastatic disease [10, 11].

52.3 Intensity Modulated Radiation Therapy (IMRT) and Image Guidance Radiation Therapy (IGRT)

There has been a remarkable progress in the treatment of childhood brain cancer through the technical advances which have provided increasingly precise radiation techniques. The fundamental principles of radiotherapy (RT) planning and treatment delivery that can be addressed to CNS tumours are: 1. accurate and reproducible immobilization, 2. high quality imaging to localize tumor and critical normal structures (image guided radiotherapy, (IGRT)), 3. The use of intensity modulated radiotherapy (IMRT), typically with volumetric arc therapy (VMAT), which can facilitate highly conformal and complex dose distributions to brain tumours which are characterized by irregular shapes and to specific anatomic locations, such as the brainstem,

the skull base, the orbit, etc. [12]. The other clinical consideration in CNS tumours treatments is the reduction of the radiotherapy toxicity, especially to serial structures, such as the brainstem and optic pathway [13]. In addition, there is reasonable evidence that IMRT could decrease complications in patients treated for CNS tumors, by reducing the volume of tissue, especially the brain, receiving a high dose of radiotherapy, or avoiding exposure to sensitive structures, such as the hypothalamus and pituitary gland (conformal avoidance). IMRT does not increase the integral dose to the healthy brain, thus could lead to reduced acute and late neurotoxicity, especially with the addition of chemotherapy in some brain tumors [14]. However, concerns have been raised about the long-term side effects of IMRT due to 'low dose bath' to the normal brain, particularly when irradiating benign tumors [15]. This 'low dose bath' could potentially induce a risk for secondary malignant neoplasms [16].

The benefits of IMRT can be augmented with the addition of Image Guided Radiotherapy (IGRT). IGRT devices are built-in treatment machines and are applied to delineate the location of targets during the course of therapy. Improved imaging during the treatment delivery dose encompasses the ability to identify better and define normal tissue (organs at risk (OARs)) to be protected from high radiation doses. In addition, it could facilitate generating and verifying dose constraints for normal tissue [12, 18]. IGRT has helped us understand the treatments limitations of moving targets in certain areas of the body [15].

IMRT-IGRT should be considered as standard-of-care for Cranial Spinal Irradiation (CSI) and could achieve reduced doses to OARs, improved homogeneity of the prescribed dose and avoidance of potential sources of systematic or random errors [15].

52.4 Proton Beam Therapy

Proton beam therapy (PBT) is an optimizing treatment modality reducing the radiation dose to normal tissue. There has been a noticeable reduction in the risk of acute side-effects, as well as the potential for reduction in chronic side effects, leading to an increase to the quality of life [17, 18]. However, PBT should be delivered in highly specialized centers and this makes availability scarce when compared to other techniques [19].

The proton particles in clinical practice are modelled to cover the individual target volumes. The dose distribution of protons is based on their energy loss (linear energy transfer) when interacting with other tissues. Proton beam therapy can stop precipitously in the adsorbed brain tumour and energy beam results in a steep fall-off (Bragg Peak) beyond the target volume. This enables protons to allow for a focused and adjustable dose delivery and avoid the 'low-dose bath' to surrounding tissue, thereby has a potential to decrease the risk of secondary malignancies [19–21]. Additionally, PBT can precisely irradiate selected types of deep-seated tumours such as chordoma and chondrosarcoma, which require a higher than conventional dose to achieve optimal local control [20, 21].

Better conformal coverage of target volumes can be achieved with the introductions of a highly sophisticated technology, the intensity-modulated proton therapy (IMPT). IMPT employs the assistance of computer methods to achieve maximum dose to the tumor, while minimizing the dose to OARs [20].

PBT is used for the treatment of different CNS tumours. Although large prospective studies on children receiving proton therapy are still scarce, the results of proton therapy are promising in terms of equivalence in survival and tumour control and reduction in toxicities compared with historical outcome data on photon therapy. For craniospinal irradiation (CSI), PBT has the advantage of better conformity compared with photon therapy while irradiating irregular and large target volumes. CSI proton is already considered to be the standard-of- care in children as it offers the best and more conformal dose delivery of radiotherapy in comparison with photons [21–23].

There are still many questions to be answered regarding protons, as the advantage of PBT over photon therapy is not currently strongly supported by published evidence. Differences in relative biological effectiveness (RBE) between photons and protons should also be explored to compare these techniques and to enable optimal individualised treatment approaches [22–24].

There are no prospective studies comparing protons with photon in pediatric brain tumours. It is therefore paramount prospectively to accumulate substantive clinical data and elucidate biophysical properties of this relatively new modality. With these caveats in mind, we want to highlight recent technologic advances and several recent reports exploring the clinical utility of Proton beam therapy in pediatric brain tumour patients.

In a retrospective study treating seventy-nine children with intracranial ependymoma, authors compared radiotherapy with IMRT versus PBT. The outcome of the study reported that 3-year Progression Free Survival (DFS) was significantly better after proton therapy (82% versus 60% with IMRT; $p = 0.031$) and recurrence rate was lower with proton treatment (17% versus 55% with IMRT; $P = 0.005$). The results could simple reflect the effect of higher proportion of patients who had GTR in the PBT group [25]. However, in another trial that directly compared PBT with IMRT in children with craniopharyngiomas, the outcomes showed no significant differences for OS, nodular failure-free survival (NFFS) and cystic failure free survival (CFFS) after 3 years. Late toxicities were similar for both groups [26].

In addition, there are retrospective and prospective studies for cohorts of children treated with PBT that showed improved dose conformity in OARs. In a study that included 16 children with craniopharyngiomas treated with proton therapy the results were promising as no treatment-related grade III toxicities manifested during treatment. The most common grade I adverse events during irradiation were skin toxicity events and fatigue [27]. In another study with craniopharyngioma patients the only factor that increased toxicity was the age below 5 years of age. In the same study, the quantified 2-year incidence of grade III late toxicities were of 2.1% with protons [28]. The clinical impact of proton radiotherapy on normal tissue function should be reviewed in multicentric prospective studies.

52.5 Medulloblastoma

Medulloblastoma (MB) is a highly aggressive cerebellar embryonal tumour, representing the most common malignant brain tumour in children and adolescents. It accounts for 20% of all central nervous system tumours. MB has a predisposition of distal metastases or spread through the neuroaxis which is associated with a dismal prognosis [29]. The current standard treatment is a multimodality treatment including surgery [30], radiotherapy and chemotherapy. Postoperative management of patients with medulloblastoma depends on the risk groups: Standard- or high-risk. The risk classification is based on age at diagnosis, presence of metastases, extent of post-surgical residual disease and histological subtype. Based on molecular profiling there are four subgroups of meduloblastomas (Table 52.1), which have different prognosis and therapeutic implications [31]. Modern radiotherapy techniques in MB have involved attempts at both dose de-escalation and target volume reduction. Radiotherapy remains an integral component of the curative treatment and more than 70% of children diagnosed with medulloblastoma are expected to be long-term survivors. RT evolution using adaptive techniques, such as intensity-modulated radiotherapy with imaging (IMRT/IGRT), focus on minimizing long-term treatment related toxicities and improving overall survival (OS). However, it should be noted that neurocognitive and neuroendocrine deficits, as well bone and soft tissue hypoplasia, are considered as the major radiation-induced long-term side effects [32–34].

Table 52.1 Four subgroups of meduloblastomas

Group	Wingless (WNT) group (11%)	Sonic Hedgehog (SHH) group (p53 mutant) (30%)	Group 3 (non-WNT, non-SHH) (15%)	Group 4 (non-WNT/non-SHH, glutamatergic) (35%)
Age	0–12 years	And > 16 years)		All ages, but rare in infants
Gender	Both genders	Both genders	Male infants	Male > female (3:1)
Location	Typically midline tumour	Hemispheres		
Histology/ genetic subtype	Large cell/ anaplastic (very rare),	Large cell/ anaplastic, p53 mutant	Large cell/ anaplastic, their expression of MYC, photoreceptor,	Large cell/ anaplastic, high burden of chromosomal variations
Prognosis and demographic notes	90% of patients survive for more than 5 years	5-year survival 75%, rarely presents with disseminated disease	0% with metastasis at diagnosis, 5-year survival 50%	5-year survival 75–90%

52.5.1 Standard-risk Medulloblastoma

Craniospinal irradiation (CSI) encompassing the entire neuroaxis is a core component of the standard care therapy, with an overall disease survival of 55–70% at 5 years from diagnosis. Previously, all patients with MB were treated with high doses to the craniospinal axis (CSA) (Fig. 52.1a), ranging from 36–40 Gy, followed by focal boost to the posterior fossa (Fig. 52.1b, c), to a final dose ranging from 54–60 Gy [30, 35]. However, this approach led to significant long-term side effects such as neuropsychological, hearing and endocrinological sequelae, especially in very young children [36, 37]. Therefore, there were numerous attempts to reduce treatment volume and CSI dose in patients with standard-risk disease. For example, the SFOP M4 trial attempted to reduce the late toxicity of RT by decreasing the volume of the CSI, excluding the supratentorial part of the brain, as well as reducing the total dose. The results were disappointing, as the majority of the patients experienced supratentorial relapses and the 6-year event-free survival (EFS) was less than 20%. The outcome of the trial supported the ongoing role of CSI [38].

Several trials evaluated whether a reduction in the dose of CSI was feasible, without compromising survival. The CCG A9961 phase III trial included 421 participants with standard-risk medulloblastoma. Patients were treated with a low-dose of CSI (23.4 Gy) with a boost dose to the posterior fossa to a total of 55.8 Gy and chemotherapy using concomitant vincristine and adjuvant lomustine or cyclophoshamide, or vincristine and cisplatin [39]. The trial reported an overall survival of 86% and EFS of 81% at 5 years; a recent update reported 10-year overall survival of 81.3% and EFS of 75.8% [39, 40]. This was the first trial to demonstrate a very promising clinical outcome of a low-dose CSI with the combination of chemotherapy. Although the combination of chemotherapy with low-dose of CSI radiotherapy is effective, the long-term neurocognitive dysfunction

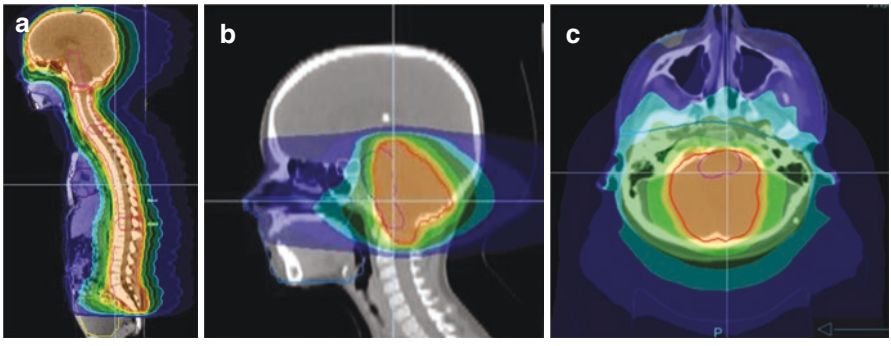

Fig. 52.1 (**a**) Craniospinal axis dose distribution with photons (Tomotherapy) in medulloblastoma patient. (**b, c**). Posterior fossa dose distribution with photons (Tomotherapy) in Medulloblastoma patient

continues to be a significant problem. A recent trial, ACNS 0331, included patients between 3 and 7 years old with standard-risk medulloblastoma. Patients were randomized to either low-dose (18 Gy) or to standard dose (23.4 Gy) CSI and the other randomization was involved-field radiotherapy (radiation to tumour bed) or posterior fossa area boost (radiation to whole posterior fossa). The results demonstrated that a reduced dose of CSI was associated with worse survival. However, involved-field RT is deemed non -inferior to posterior fossa radiotherapy [41]. Based on the above studies, 23.4 Gy CSI followed by a boost dose of 30.6 Gy (tumour bed plus 1.5 cm margin) followed by adjuvant chemotherapy with cisplatin, CCNU and vincristine is the standard of care for standard-risk medulloblastoma,

52.5.2 High-risk Medulloblastoma

The landmark trial SIOP/UKCCSG PNET-3 for high-risk MB patients, showed that two courses of multi-regime chemotherapy (etoposide, carboplatin, cyclophosphamide and vincristine) followed by a dose of 36 Gy to the cranial spinal axis plus a boost to the posterior fossa of 18–20 Gy to a total dose of 54–56 Gy, yielded a 5-year EFS of 34.7% and overall survival of 43.9% [42].

In recent years, numerous approaches were investigated, including the use of high-dose radiotherapy, concomitant chemo-radiotherapy, or high dose chemotherapy alone. Recently, the POG-9031 trial randomized 224 children either to receive three cycles of neoadjuvant chemotherapy (cisplatin and etoposide) followed by radiotherapy (n = 112) or radiotherapy followed by chemotherapy (n = 112). Patients with M0-1 disease received CSI to a dose of 35.2 Gy and those with M2-3 disease received higher dose of 40 Gy. The posterior fossa boost was 18 Gy for patients with M0-1 disease and 14.4 Gy for patients with M2-3 disease. For the M0-1 patients 5-year EFS (66% versus 70%, p = 0.54) and overall survival (73% versus 76%, p = 0.47) were similar in both treatment arms. In this study, the 5-year EFS for patients with M2-3 disease was >60% [43].

A phase I/II study, COG 99701, recruited patients with metastatic medulloblastoma. This trial evaluated the role of carboplatin as a radiosensitizer with the concomitant administration of daily RT to a total dose of 36 Gy CSI with the addition of a boost of 19.8 Gy to the posterior fossa and boosts to sites of metastatic disease. Following radiotherapy, patients received maintenance chemotherapy for 6 months with eithercyclophosphamide and vincristine (regimen A: n = 19) or cyclophosphamide, vincristine and cisplatin (regimen B: n = 22). There was no statistically significant difference in 5-year PFS (71% versus 59%, P = 0.36) and overall survival (82% versus 68%, P = 0.68) between the two regimens. However, the use of carboplatin as a radiosensitizer is thus considered a promising strategy for patients with high-risk medulloblastoma [44]. The current radiotherapy regimen for high-risk meduloblastoma is CSI of 36–39.6 Gy with a posterior cranial fossa boost to a dose of 54–55.9 Gy.

52.5.3 Optimal Radiotherapy Technique for CSI

The clinical target volume for medulobalstoma is the whole arachnoid space, including the whole brain, the cribriform plate, most inferior part of the temporal lobes and the internal auditory canal, and the pituitary fossa. In addition, in the abovementioned volume, we should include the full length of both optic nerves as they pass through the skull base foramina. Attempts to spare any of the above anatomical structure can lead to spread to local meninges surface within the posterior fossa. The spinal target volume should include the entire subarachnoid space, including nerve roots laterally, at the lower limit of the thecal sac [45–47]. The optimal radiotherapy technique in terms of best disease control with the least risk of second malignancies and other late toxicities for CSI is not clear. A recent comparison of different techniques of cranispinal radiotherapy across 15 European centers showed that highly conformal radiotherapy techniques have dosimetric advantages compared with 3D-conformal radiotherapy and proton therapy often leads to the lowest mean dose to OARs [47]. However, for most organs, ranges in mean doses were wide and overlapping between techniques making it difficult to recommend one radiotherapy technique over another. There are also neither any prospective comparative studies of PBT with photon therapy nor long-term data on clinical advantages of proton therapy. In the new era of implementing new radiotherapy techniques, the two main aspects taken into consideration are dose de-escalation for low-risk medulloblastoma and the addition of chemotherapy.

52.5.4 Proton Beam Therapy

PBT offers an advantage by increasing the dose delivered to the tumour, while sparing the organs at risk, minimizing the late sequelae from the treatment. A phase II single arm trial included 59 patients with medulloblastoma treated with proton therapy and showed high survival rates related to proton treatment, such as 5-year PFS of 80% and overall survival of 83% [48]. Two retrospective studies showed that the survival and relapse time was similar between protons and photons in 6-year relapse time (78.8% versus 76.5%), overall survival (82%versus 87.6%) and patterns of failure between proton (n = 45) and photon (n = 43) therapies [22, 48]. Toxicity evaluation in studies that compare proton to photon therapy showed that grade 3 to 4 toxicities were similar in both treatments. Predictive dosimetric studies have shown a potential risk reduction for PBT in medulloblastoma for cardiac toxicities, premature ovarian failure, ototoxicity, neurocognition and secondary malignancies compared to photon-based techniques, though this is yet to be proven clinically. Yock et al. [48] published a phase 2 single arm study of PBT in medulloblastoma which are the first prospectively published data on the use of PBT for medulloblastoma. The outcomes in terms of disease control were similar to published photon data, [49]. Although a clear benefit for proton therapy has yet to be shown, a randomized clinical trial is unrealistic and a robust prospective outcome evaluation is encouraged.

52.6 Ependymoma (Intracranial)

Intracranial ependymoma is a rare primary tumour, more common in children particularly under the age of 5 years. The annual incidence of the ependymomas is 35 patients in UK and 200 in USA, with male predominance. Ependymomas must be treated in the setting of a multidisciplinary team experienced in the management of this disease. Urgent surgical intervention may be needed to manage hydrocephalus and stabilize the patient before primary resection. Children with ependymomas usually undergo maximal safe resection, which improves overall survival, followed by focal tumour bed irradiation, as it increases 10 year survival rates in low and high grade tumours, 80% and 50% respectively [50, 52, 53]. Subtotal resection increases the risk of tumour recurrence and CSF dissemination [50, 52], so a second look operation might be attempted if this feasible. Currently, all children except very young, received postoperative tumour bed radiotherapy (Fig. 52.2 a–d).

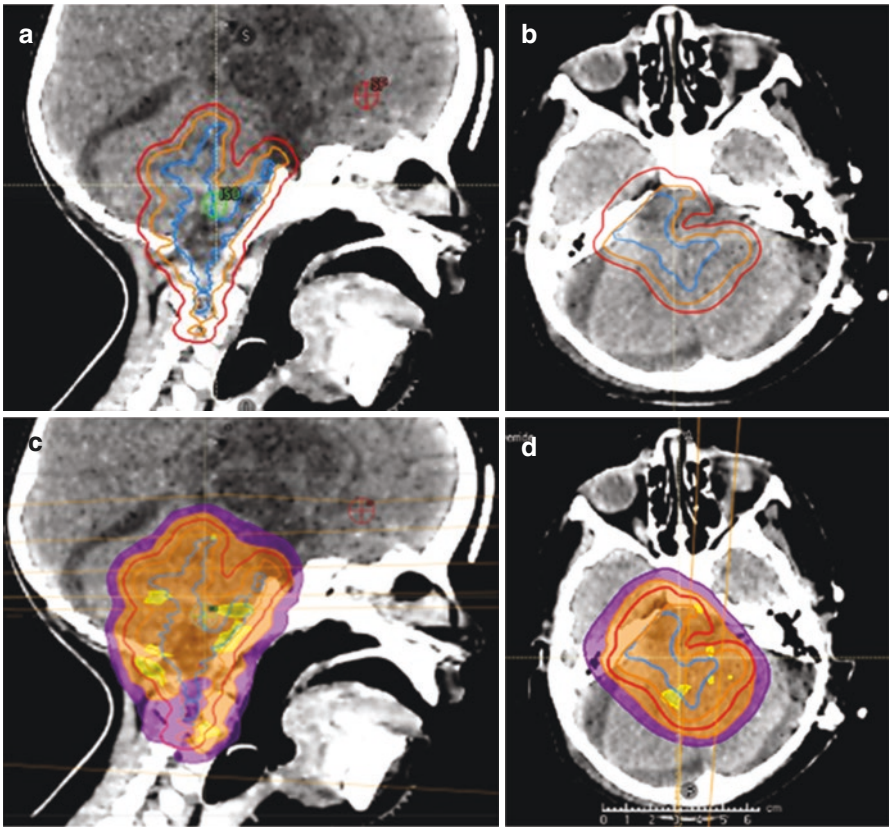

Fig. 52.2 (**a, b**) Posterior fossa isodoses with photons in Ependymoma patient. (**c, d**) Posterior fossa doses distribution with photons in Ependymoma patient

At the time of publication two trials are recruiting; SIOP Ependymoma II and the ACNS 0831 trials The SIOP II is an interventional and an observational study. All participants underwent surgery, central review of imaging and pathology. Patients will be offered the opportunity to undergo second look surgery, if this is feasible. All participants will be divided in 3 stratums. In stratum 1 participated patient aged>12 months and with no measurable residue. All of them will be randomized to evaluate the efficacy of post radiation maintenance chemotherapy (VEC CDDP for 16 weeks). In stratum 2, participants aged older than 12 months with residue measurable inoperable disease. Patients will be randomized frontline phase II chemotherapy study and exploration of the efficacy of a boost of radiotherapy. In stratum III include patients older than 12 months not eligible to receive RT will participate in the observational study.

The ACNS 831 trials is a phase III Randomized Trial of Post-Radiation Chemotherapy in Patients with Newly Diagnosed Ependymoma ages 12 months to 21 years. All of patients underwent initial surgery and then are stratified according to surgery extent, location of the tumour and pathology report into three arms. Arm 1 includes patients with GTR, supratentorial tumours and classic histology. Participants are only offered observation. Arm 2, includes patients with near total resection (NTR), infratentorial tumour and anaplastic histology. Participants will be randomized either to RT followed by observation or to RT followed by chemotherapy. Arm 3, includes patients with subtotal resection regardless location and pathology. Participants are offered induction chemotherapy, second look operation, RT and maintaince chemotherapy or observation.

52.6.1 Newly Diagnosed Non-metastatic Ependymoma

Current standard of practise following complete surgical resection is adjuvant RT, as reduces the relapse rate and increases PFS and overall survivals (OS) [54–57]. The radiotherapy field includes the extent of the tumour bed at the primary site and any residual post-operative enhancing tumour, with a 5 mm margin added to treat subclinical microscopic disease [55, 58]. For patients treated with adjuvant radiotherapy the prescribed dose is 59.4 Gy in 33 fractions. The total dose to the for the serial organs, such as the optic chiasm, brainstem and spinal cord should be limited to 54 Gy or less [55]. Children under 3 years of age, those who underwent multiple surgical procedures or those who have tumours adjacent to the brainstem are considered to be at higher risk of developing brainstem toxicity, and therefore the total dose in these patients should be reduced to 54 Gy. In addition, the AEIOP trial suggested a boost of 8 Gy in two consecutive daily fractions following standard radiotherapy doses of 54–59.4 Gy in patients with inoperable residual disease, may lead to an improved tumour control with acceptable toxicity [55]. The fore mentioned strategy is currently being tested in stratum 2 of the SIOP Ependymoma II Study.

52.6.2 Newly Diagnosed Metastatic Ependymoma

Metastatic disease is unusual at diagnosis and is more frequently encountered when tumour relapses. Different therapeutic approaches are offered and there is a paucity of evidence upon which to guide management decisions. Surgical removal of the primary tumour as well as the metastatic sites of the disease should be offered when it is feasible with the minimum deficits. Adjuvants treatment is based on age of patient. In younger children less than 3 years old, in whom the long-term toxicity of CSI is unacceptable, only chemotherapy can be considered, or a combination of chemotherapy and focal radiotherapy. In older children children CSI to a dose of 36 Gy is standard with a boost to the primary tumour bed of 59.4 Gy and metastatic sites of 49.6 Gy. It is essential to consider the tolerances of adjacent organs at risk, e.g. spinal cord metastases would generally be treated to around 50 Gy (conventionally fractionated). The posterior fossa is best treated with IMRT in order to reduce the dose at the OARs. This achieves the best conformation to the posterior fossa target volume.

52.6.3 Proton Beam Therapy

One of the most common paediatric indications for proton beam therapy is the Ependymoma. Literature on proton therapy has shown that outcomes are comparable with the published photon data in terms of local control rates [25, 28, 59]. PBT could possibly minimize the side effects and long-term toxicity of the radiosensitive adjacent organs at risk, [59, 60]. This could result in a lower integral dose and potentially less late effects from treatment [25, 28].

52.7 Low Grade Gliomas

Low-grade gliomas (LGGs) are the most common central nervous system (CNS) tumours among children, accounting for approximately one-third of pediatric brain tumors [61]. These tumours are classified as Grade I or II by the World Health Organization (WHO) and are consistent with heterogeneous pathologies. Prognosis for these tumours is generally excellent, with a 10-year overall survival (OS) between 85–96% [62]. Some of them are related with genetic syndromes such as NF-1, tuberous sclerosis and Li-Fraumeni syndrome [63]. Most childhood tumours are grade I, such as pilocytic astrocytoma (the most common subtype, which constitutes >15% of central nervous system tumours in 0–19-year-olds), subependymal giant cell astrocytoma and dysembryoplastic neuroepithelial tumour (DNET). Grade II tumours are generally ‘diffuse’ (infiltrative growth into the surrounding parenchyma) and include pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma,

oligodendroglioma, oligoastrocytoma and diffuse astrocytoma. Although in adults they usually transform or evolve into high grade tumours, in children malignant transformation occurs less frequently and it is related to the accumulation of genetic mutations. Molecular testing of gene fusion, mutation and re-arrangements in low grade tumours is of great importance diagnostically. BRAF–KIAA fusions, which lead to constitutive activation of the BRAF protein, are common in cerebellar and optic pathway pilocytic tumors, whereas BRAFV600E mutations are more common in gangliogliomas, pleomorphic xanthoastrocytomas, and cerebral pilocytic astrocytomas [64]. Rearrangements afflicting the genes BRAF and KIAA1549 fusions, lead to constitutive activation of BRAF protein and they are the most frequent somatic driver alterations across all LGGs. The above signaling pathways of LGGs could be potential therapeutic targets or elucidate the mechanism of resistance for targeted drugs.

Due to the lack of evidence on sequencing of treatments, optimal sequencing of non-surgical treatments (chemotherapy and radiotherapy) is not known. The confounding factors for treatment choice are the burden of symptoms, age, site and extent of tumour, and institutional practice.

Management of LGGs typically consists of maximal safe surgical excision which increases survival and disease-free survival rates. A gross total resection is often unachievable for deep-seated, infiltrative tumors, which have worse prognoses than superficial lesions. Patients that have undergone sub-total resection could be followed-up until progression, when the decision for further treatment depends on feasibility of further surgery and non-surgical treatment, which is decided mainly by age and institutional practice. Progression-free survival (PFS) exceeds 85% for complete or near total resection, where a subtotal resection result in less than 50% ten-year PFS [65]. Overall survival rates are >95% at five years from complete resection [65, 66].

When a surgical cure is not possible, complex management of unresectable tumors relies on the use of chemotherapeutic regimes or, if possible, in targeted molecular agents and radiation therapy [67]. The sequence of the adjuvants/radical treatments depends on the age of children and the response to chemotherapy, which used as a bridge to delay radiotherapy.

52.7.1 Systemic Treatment

Chemotherapy can be used for progressive and inoperable disease or as a bridge to delay radiotherapy. There are many regimens that can be used in order to avoid the side effects of radiotherapy with the combination treatment of vincristine and carboplatin [68, 69] or monotherapy with carboplatin, which can be equally efficient as multi-agent chemotherapy [70]. For example, the COG A9952 protocol compares two different combinations of chemotherapy drugs without RT. The first arm consisted of carboplatin and vincristine suffate (CV) and the second arm consisted of thioguanine, procarbazine hydrochloride, lomustine and vincristine sulfate (TPCV). The difference in the 5-year

EFS and the OS between the regimens did not reach significance for either arms [68, 71]. In the HIT LGG 96 trial, the 10-year PFS was 62% following radiotherapy and 44% following chemotherapy, indicating a higher efficacy for radiotherapy [72].

52.7.2 Radiotherapy

Radiotherapy remains the standard of care for patients with incompletely resected tumours [73]. In addition, radiotherapy is highly efficient in symptom control. Specifically, patients with histologically proven diffuse astrocytoma or tumours with thalamus/midbrain location, had a 10-year OS of 76% while patients with pilocytic astrocytoma/ganglioglioma located outside of the thalamus/midbrain had a 10-year OS of 96% ($p = 0.003$) after radiotherapy [73].

The risk of RT is related to patients age, radiation dose and the volume of irradiated brain. The risk-benefit ratio is individualised and may change throughout the course of patients' illness. It is also important to consider that although radiotherapy could lead to significant morbidities, it could also alleviate the risk of disease progression. RT may be safely omitted for many patients in the LGGs subpopulation but should strongly be considered for patients with more aggressive disease, for which early radiotherapy likely holds a vital role [74].

52.7.3 Treatment Response

Treatment response to RT should be interpreted with caution, due to the high ratio of pseudo-progression [75, 76]. However, in a study of 221 children it was shown that, the 10-year cumulative incidence of pseudo-progression was 29% (95% confidence interval 23–35.2) with a median time of pseudo-progression of 6.1 months [77]. In this period of time, children might not have shown any further clinical signs or symptoms. Furthermore, pilocytic astrocytomas have a higher incidence of pseudo-progression (10-yearincidence 42.9%) and development of pseudo-progression was associated with a better 10-year EFS and overall survival. Therefore, any tumour progression following radiotherapy should be interpreted with caution.

52.7.4 Radiotherapy in Leptomeningeal Dissemination

Leptomeningeal dissemination is seen in 4–12% of children with LGGs. Given the rarity of dissemination, the optimal treatment is unclear. Chemotherapy can be an option for disease control or improvement in size, with overall response rates of 25% and 79% of the patients with leptomeningeal dissemination. Upon chemotherapy failure, craniospinal radiotherapy (CSI) is a treatment option [74]. Bian

et al. [78] assessed six children with metastatic pilocytic astrocytoma; four patients underwent CSI, one to the spine only and one to a supratentorial local field. With a median follow-up of 24 months after radiotherapy, five out of six patients were alive, four had stable disease and one showed disease progression. Another study of 12 patients reported a 5-year EFS of 71% and overall survival of 70% with CSI [79]. Therefore, it is possible to achieve long-term disease control following treatment for patients with metastatic leptomeningeal disease.

52.7.5 Proton Beam Therapy

Radiotherapy is optimal treatment for children and TYA patients for LGG yielding a 10-year overall survival rate up to 90%, however, patients are subject to a spectrum of late effects depending on age and the anatomical site of tumour. Greenberger et al. [80] showed that 8-year PFS and OS are consistent with previously published photon data. For the patients in the study with serial neurocognitive testing, no significant declines in Full Scale Intelligence Quotient were seen compared to baseline. Within subgroup analysis there were declines in those treated at an age of less than 7 years and those with significant dose to the left temporal lobe and left hippocampus. Indelicato et al., have recently reported on 174 patients with low grade glioma. At 4.4 years of median follow up, the outcomes in terms of progression free survival and overall survival rates with PBT are 84% and 92%, respectively. The results suggest that disease control is in line with previously published data and PBT has not been associated with no marginal recurrences. In terms toxicity although longer follow up will be required in order to quantify potential improvement in long-term function for these patients, it can be reported that patients irradiated with PBT presented with low rates of hormone deficiency, 1% rate of visual deterioration and a 2% of hearing loss [81, 86].

52.8 Intracranial Germ Cell Tumours

Intracranial germ cells tumours (iGCTs) are a group of brain tumours of neuroepithelial origin. Common anatomical sites of presentation are located around the third ventricle, such as pineal, suprasellar regions and the basal ganglia. They are more common in Asian populations with lower rates seen in European Caucasian populations. Fundamental characteristics of these tumours are the location, histopathology and biological behaviour and age of presentation, with two peaks, in infants and adolescence (13–19 years).

The diagnostic investigations include estimation of serum and CSF tumour markers, MRI of the brain and spine, lumbar puncture and surgical biopsy when tumour markers are negative. Complete staging at diagnosis is crucial in

establishing the optimal treatment. IGCTs are divided, for therapeutic and prognostic purposes, into germinomas (about 70% of all icGCTs) and non-germinomatous germ cell tumours (NGGCTs) [82].

52.8.1 Germinomas

Surgery is restricted to cases of hydrocephalus or acute visual deterioration or in view of obtaining tissue biopsy to confirm the diagnosis. The combined modality treatment with chemotherapy and radiotherapy yields a high cure rate of above 90%.

52.8.1.1 Localized Germinoma

LG is a radiosensitive tumour and historically patients received 30–36 Gy of craniospinal irradiation followed by radiotherapy boost to tumour bed of 14–15 Gy with excellent survival rates [84]. In the SIOP CNS GCT 96 prospectively study patients received either CSI or 2 courses of platinum based chemotherapy, followed by reduced field radiotherapy. The outcome showed that OS and EFS were similar in both groups, however, there was a significant difference in progression-free survival (PFS) (0.97–0.02 versus 0.88–0.04; P = 0.04), favouring CSI [83]. The above study showed that, 6 of the 7 recurrences in the chemotherapy-focal radiotherapy group were either ventricular or combined with primary site recurrence. This outcome led to the current practice: radiotherapy of the whole ventricular volume being the standard of care for the localized germinoma. The pattern of relapse suggests inclusion of ventricles in the radiation field [83, 85]. In terms of radiotherapy, an important question is whether radiotherapy dose could be reduced in patients who achieve a complete response after chemotherapy without compromising the chances of a cure. Two trials are trying to address this question.

In the European SIOP CNS II study, patients with localised germinoma are treated with 2 courses of chemotherapy (two cycles of carboplatin and etoposide alternating with two cycles of ifosfamide and etoposide) followed by WVI (24 Gy in 15 fractions). If complete response (CR) has achieved then there is no RT boost offered, if there is partial response noted then focal RT boost is added (16 Gy in 10 fractions). The option of operation followed by RT if is stable disease. An early report shows that the 4-year EFS for patients who received WVI after achieving a CR (98%) was similar to those who received WVI and a tumour boost after achieving a PR (95%). This study suggest that WVI (24 Gy) can be considered as the standard of care for patients with localised germinoma who achieve a CR after chemotherapy. In the recent ACNS1123 study, germinoma patients achieved a complete response after i) chemotherapy (four cycles of carboplatin and etoposide) receive WVI (18 Gy) and ii) a radiation boost to the primary tumour (12 Gy). Patients with

>0.5 cm (suprasellar) or > 1 cm (pineal) but 1.5 cm residual, not undergoing second-look surgery, are being treated with WVI (24 Gy) followed by a focal boost (12 Gy). The results of these studies will probably shed light on whether response-based radiotherapy is appropriate for localised germinomas. It is important to mention that although European and North American approaches in the management of icGCT tumour are based on the sequential use of chemotherapy and radiotherapy, the Japanese approach is based on concurrent chemoradiotherapy. However, there is no comparative analysis of these diverse philosophies in terms of efficacy and toxicities.

52.8.2 Non-germinomatous Tumours

The optimal treatment for the non-germinomatous tumours should include trimodality treatment; gross total resection, focal radiotherapy and chemotherapy, since this has been show to provide superior safety, diagnostic efficacy and decreased morbidity and mortality at treating hydrocephalus and obtaining biopsies of tumours compared with open surgery or external ventricular drainage [90, 91].

The latest studies showed that the addition of chemotherapy increased survival 60–70% for patients with NGGCTs. However, the addition of radiotherapy in addition to complete surgical resection when possible can effectively control the disease up to 20–40% [83, 92]. In European protocols radiotherapy is typically delivered focal radiation to the tumour bed for the treatment of NGGCT. On the other hand, Japanese protocols favour the use of CSI for NGGCTs [88]. In Europe treatment decision is based on age (> or < 6 years) and the CSF AFP level (> or < 1000 ng/ml) optimal treatment is high intensity chemotherapy, followed by surgical resection and then focal RT to the primary tumour site (54 Gy in 30 fractions to the tumour bed) [88].

In addition, salvage surgery could be the third step of treatment in NGGCT when there is radiological residual disease after chemotherapy and radiotherapy, as all residual tumours is to be resected [83] [83, 89]. The SIOP GCT 96 study showed 68% of the patients with localised NGGCT that received chemotherapy and focal radiotherapy remained in remission at a median follow-up of 35 months (10-year overall survival 67%). In this study, 25 relapses among 102 patients with localised NGGCTs, 17 were focal, two ventricular, one distant and five combined [83].

In the SIOP GCT II study, patients with localised NGGCTs offered neoadjuvant chemotherapy followed by surgical resection if residual disease was present followed by focal radiotherapy (54 Gy in 30 fractions to the tumour bed). The chemotherapy treatment is based on two risk groups: the standard risk (diagnostic serum or CSF AFP 1000 ng/ml and age 6 years) and high-risk (AFP > 1000 ng/ml or age < 6 years). COG ACNS0122 reported a 5-year PFS of 84% and an overall survival of 93% in patients with NGGCTs that received 3 cycles of (three cycles of carboplatin and etoposide alternating with three cycles of ifosfamide and etoposide) followed by craniospinal radiotherapy (36 Gy) and focal boost (18 Gy) [93].

The ACNS1123 study, was outlined to assess the volume of the radiotherapy field reduction from Whole Brain Radiotherapy (WBRT) to WVI (30.6 Gy) with focal boost (23.4 Gy) for patients with localised NGGCTs. All patients received adjuvant chemotherapy and achieved a complete/partial response after the chemotherapy with or without second-look surgery. The study has now closed prematurely due to an excess of outside field recurrences [85]. In Japan, patients with localized malignant teratoma and mixed tumours, mainly composed of germinoma or malignant teratoma (intermediate prognosis), receive concurrent chemo-radiotherapy followed by response-based adjuvant chemotherapy. The current treatment recommendation in localised NGGCTs is chemotherapy followed by focal radiotherapy.

In disseminated non- germinomatous germ cell tumours, according to the results of the SIOP CNS GCT 96 study, it is recommended that patients receive chemotherapy followed by craniospinal radiotherapy (30 Gy) and focal radiotherapy to the primary tumour and macroscopic metastases (24 Gy) [83]. Another study (SIOP CNS GCT II) will evaluate the addition of dose intensification for high-risk patients for localised disease [48]. The current recommended treatment in disseminated NGGCTs is chemotherapy followed by craniospinal radiotherapy and focal boost to primary and metastatic sites.

52.8.3 Proton Beam Treatment

One study of 22 patients treated with conformal proton therapy showed a PFS of 95% and an overall survival of 100% at a median follow-up of 28 months [66]. In another study of 20 patients, the 5-year PFS and overall survival rates were 89% and 100% for germinomas and the corresponding figures for NGGCTs were both 82% [32]. A phase III trial comparing conventional radiotherapy with proton radiotherapy in intracranial germ cell tumours (icGCTs) has not been reported to date. In recurrent or progressive icGCTs, a currently open phase II trial (NCI-201301195) is evaluating the role of combination of chemotherapy and stem cell transplant [94].

52.9 Side Effects of the Radiotherapy

Radiotherapy is one of the cornerstones in the treatment of pediatric brain tumours. This effective treatment improves clinical outcomes in terms of overall survival, however, it can reduce the quality of life due to the late effects that are stemming from RT. Long-term side effects are related to the fact that dose and fractionation are often multifactorial influenced by age, extent of tumour and anatomic location of the radiation target. For pediatric brain radiotherapy there is no optimal dose fractionation response effect, since there is no data from randomised trials. However, the

patients that received higher dose had a lower level of functioning and more symptoms (fatigue and insomnia) following radiotherapy [95, 96]. The dose that is generally accepted ranges between 45 and 54 Gy in 1.8 Gy fractions. Retrospective data, however, indicate that a dose of 50.4 Gy could be equally effective as 54 Gy [97].

Long-term side effects can include neurocognitive dysfunction, neuroendocrine dysfunction, ototoxicity, brainstem toxicity, alopecia, and second malignant and non-malignant neoplasms [28, 51, 65, 98].

52.9.1 Neuro-cognition

Long sequelae of radiotherapy can range from a decline in processing speed up to decline in full-scale intelligence [24] In addition, other factors can contribute to neurocognitive dysfunction are the tumour itself, the presence of NF-1, the hydrocephalus, the extent of resection, genetics and chemotherapy [24, 99, 100]. Recently, in a study with medulloblastoma patients treated with radiotherapy, either photons or with protons, assessed of cognitive function (e.g perceptual reasoning and working memory) used global IQ scores. Patients treated with PBRT, all tested IQ domains were stable over time, except for processing speed [60]. Another study included patients with LGGs treated with protons and the outcome suggested no significant decline in full scale IQ in children >7 years and those who received a lower dose to the left temporal lobe/hippocampus [80]. However, evaluation of the clinical benefit from proton therapy requires further clinical studies with measures of long-term physical and neurocognitive outcome.

52.9.2 Neuroendocrine Function

Radiotherapy can lead to a risk high risk of hormone deficiency related to the radiation dose received by both the hypothalamus and pituitary gland. The results of a recent study showed that cumulative dose is the independent risk factor for growth hormone deficiency. Following a dose of more than 18 Gy to the pituitary, growth hormone reduction is the most common (40–80%) abnormality [99]. Growth hormone deficiency and early puberty can contribute to impaired growth [36]. In a recent study 222 patients presented with hypothyroidism as the second most common endocrinopathy, with a 5-year actuarial rate of 4.2%, 24.5%, and 42.8% after hypothalamic and pituitary doses of $\leq$20 GyRBE, 20 to 40 GyRBE, and $\geq$ 40 GyRBE, respectively. Hypothyroidism is mostly expressed as TSH deficiency and there is a need of thyroid hormone replacement [101]. On the other hand, cortisol and sex hormones can be less affected. When the dose to the hypothalamus and pituitary ranges at $\geq$40 Gy it places patients at a significant risk of developing hormone deficiency in the years following therapy.

52.9.3 Hearing

Ototoxicity is a common side effect and is related to the proximity of the tumour to the cochlea. Other risk factors that can contribute to ototoxicity are i) the location the tumour, most common to ones located near to posterior fossa, ii) the dose >40 Gy which can increase the risk of hearing loss, especially at high frequencies and iii) the platinum based treatments specially when delivered with the radiotherapy. The rates of ototoxicity after photon RT range from 18% to 24% [101, 102], while a study using PBRT demonstrated a lower rate (16% for grades 3 and 4 on the Pediatric Oncology Group scale) five years after treatment [98]. Although there was no direct comparison between proton and photon, the retrospective study of patients treated for medulloblastoma, showed that there was no difference in the outcome between photon RT and proton modalities despite a lower mean cochlear dose achieved when using protons [102].

52.9.4 Cerebrovascular Effects (Stroke)

Radiotherapy can cause vasculopathies of brain arteries, which lead to abnormal architecture and formation of collateral vessels and reduced blood supply. This pathology develops in 3–4% of the patients receiving radiotherapy usually 12 months after the completion of the treatment [68, 103]. Factors that can increase the risk further are neurofibromatosis type 1, Down's syndrome, hypertension and diabetes mellitus. Vasculopathy is a dose related effect so patients who receive RT dose ≥50 Gy near to the optic chiasm have a 4–10% risk [68, 103]. Stroke risk is dependent on tumour location, radiation dose, and time since RT. In a study of Indelicato et al., with a median follow up of 3 years, the risk of stroke after RT was estimated to 1.2% (7 out of 664 patients) experiencing permanent neurological deficits and 4 of them treated with revascularization surgery [81].

52.9.5 Alopecia

The potential for permanent radiation-induced alopecia (RIA) is significant in peripherally located tumours when radiation doses of 50–60 Gy are needed. This happens more commonly in the paediatric glioma population. The dose tolerance of hair follicles varies by patient and chemotherapy exposure but is approximately 40 Gy. Similar scalp dose constraints to limit the risk of permanent RIA have been reported for photon and proton treatment modalities [65]. Importantly, RIA has been associated with increased anxiety in childhood cancer survivors. Both photon and proton modalities can be manipulated to spare dose to the skin follicles.

52.9.6 Secondary Neoplasms

A recent meta-analysis of six studies (total 1114 patients) reported a 10-year cumulative incidence of 6.1% for secondary neoplasms [104]. Fifty-eight per cent of secondary neoplasms were malignant, with high-grade glioma being the most common (45%). The most common secondary benign neoplasm was meningioma (67%). A significant proportion of secondary neoplasms occur in the areas of radiotherapy exit dose. It is not clear whether widespread adoption of proton therapy for children with medulloblastoma might lead to a decline in second neoplasms.

52.10 Paediatric Normal Tissue Effects in the Clinic (PENTEC)

In 2010, the international QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) consortium recommended radiation dose constraints for normal tissues in adults and illustrated the uncertainties in those constraints [105]. However, the above cannot be applied to pediatric oncology as stated by Constine et al. The methodological approach of the international collaboration on Paediatric Normal Tissue Effects in the Clinic (PENTEC) has been outlined recently [106]. A better holistic approach of the optimal use of multimodality treatments is needed to help understanding the adverse consequences. . New patterns of late morbidity and mortality may emerge as survivors continue to age, and it is only through continued study that such patterns will be identified and interventions for treatment and prevention of adverse effects can be designed. PENTEC seeks to clarify complexity and define normal tissue tolerance in developing children as a function of radiation dose/volume, type and scheduling of chemotherapy, and surgery. Ideally, this information be used to inform radiation oncologists, patients and parents on the risk-benefit of multimodality therapy involving radiation therapy, define treatment planning radiation dose constraints and propose new research directions.

52.11 Conclusion

Advances in radiation therapy and chemotherapy have increased the survival rate for almost all paediatric malignancies. However, they may be associated with long-term adverse outcomes that may affect the individual's quality of life. So far, the range of the side effects is well documented in the literature. However, there is still a lot of research to be done in order to quantify the dose-volume-effect, as well as the impact of risk/patient factors such as developmental status and genetic susceptibility.

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Chapter 53
Rehabilitation of Children with Traumatic Brain Injury

Eleftherios-Spyridon Alexiou and Jiolanda Zika

53.1 Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability in children and adolescent. The majority of TBI is of mild severity. Severe TBI comprise approximately 10% of all TBI cases. Children younger than eight years of age more frequently suffer from moderate and severe intracranial injury from trauma [1]. The cause of TBI differs by age. Falls and abusive head trauma is the most frequent cause of TBI in infants and toddlers. For children 0–14 years the most common causes are falls and being struck by an object and in older children are motor accidents and falls. Symptoms of TBI involve headache, dizziness, memory deficits, sleep disruption, and mood changes. Presence of intracranial hemorrhage and skull fracture is associated with longer rehabilitation length of stay. Especially, children with traumatic axonal injury are associated with longer rehabilitation. Apart from TBI severity several other factors have been associated with outcome such as socialeconomic status. Glasgow Outcome Scale- Extended, Pediatric Revision (GOS-E Peds) has been used in several studies as a main outcome measure. These children also have cognitive fatigue even in mild TBI. There is an unexplained heterogeneity in outcomes following pediatric TBI.

Several motor deficits may occur after TBI and depend on the brain injury loci. Depending on the extent of damage hemiparesis may be more pronounced in the

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lower or upper extremities. In general, focal injuries have a better prognosis than diffuse brain damage.

53.2 Rehabilitation

The goals of rehabilitation are to reduce disability and to help the child to gain independence in physical, cognitive, social and emotional areas. Rehabilitation of a TBI patient is a slow process that can take months or years. GCS at presentation is of prognostic significance and there may usually be some degree of disability even in mild TBI. Patients with post-traumatic epilepsy, depression, and post-traumatic amnesia have unfavorable prognosis [2, 3]. Six months post TBI is indicative of the outcome, however, waiting a year after the injury is considered appropriate before important decisions are made on the outcome.

Rehabilitation of the patient with TBI involves three stages. The first stage is in the intensive care unit (ICU), the second is usually in a Neurosurgical clinic and the third in the rehabilitation center or at patient's home. Rehabilitation should start early while the child is still in the ICU. The goals at this stage are to diminish complications of immobility, such as pressure ulcers, compression neuropathies, and contractures. Thus, frequent patient's repositioning, foams, air, water or elastomeric mattresses and padding bony prominences are needed. Furthermore, prevention of secondary complications such as pneumonia or muscle dysfunction, improvement of consciousness and sensory perception are important. Apart from that chest physiotherapy, passive kinesiotherapy, massage, skin care and listening to music are also of equal importance.

After discharge from the ICU the patient starts a rehabilitation program, depending on his abilities and the general state of health. At first stage there is an intensification of rehabilitation program with physiotherapy, psychotherapy and speech therapy. When the patient is referred to a rehabilitation unit then a more specific rehabilitation program starts that focuses on both patient and his family, in order to maximize the patients' independence. The daily treatment should last at least 3 h.

Motor disorders are common in patients with TBI. Weakness requires strengthening exercises. In case of hemiparesis apart from physical therapy other interventions exist such as therapy aided by a robotic exoskeleton and constraint-induced movement therapy. Muscle tone disorders such spasticity and rigidity may require specific treatment when producing functional limitations. Treatment has been extensively presented in the chapter of spasticity and usually involves drugs such as diazepam, clonidine, tizanidine, and dantrolene, chemical denervation using botulinum toxin and also surgical treatment.

Dysphagia is another common disorder after TBI and is associated with oral-motor musculature and patient's cognitive status. In children with severe TBI dysphagia can be found in 68–76% of patients [4]. Resolution of swallowing impairment is typically achieved after 3 months in patients with cortical injury. Thus, gastrostomy might not be indicated before this time period [4].

53.3 Neuropsychiatric Effects of TBI

Depression is a common finding in TBI patients with an incidence ranging between 33% and 50% [3]. Injury-associated factors such as lesions in the brain and chronic pain, as well as other contributing factors such as older age at injury and low socioeconomic status, are related to more frequent depressive symptoms. The most common reported symptoms were lack of energy in everyday life, concentration difficulty and irritability. Traumatic axonal injury is a common finding in MRI on these patients. Post-traumatic stress disorder (PTSD) is also common in these patients ranging from 3.3% to 48.5%. PTSD is associated with long-term disability, cognitive and emotional disturbances and one fourth of patients do not recover even 10 years after TBI [5]. Bipolar disorder, psychosis, anxiety disorder and sleep disturbances are less common. Adult patients with moderate to severe TBI have an increased risk of developing dementia or Alzheimer's disease.

53.4 Future Perspectives

Technological advances provide new opportunities for rehabilitation of children after TBI. Virtual reality has an increasingly important role in rehabilitation practices. By creating an artificial environment there was a positive effect on physical outcomes such as balance and flexibility among children with TBI [6]. The incorporation of electronic gaming systems into rehabilitation therapies of children is another promising approach. In a multi-centre, observational proof-of-concept study of a 12-week intervention with the Nintendo Wii in 50 patients there was significant positive changes in physical activity, speed of information processing, attention, response inhibition and visual-motor coordination [7].

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Index

G. Alexiou, N. Prodromou (eds.), *Pediatric Neurosurgery for Clinicians*,
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