Christos P. Panteliadis
Editor

Cerebral Palsy

A Multidisciplinary Approach

Third Edition

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Preface to the Third Edition

Six years has passed since the release of the second edition of the book *Cerebral Palsy: A Multidisciplinary Approach*. There was a good response from the readership, and the text was also translated into the Turkish language. As the scientific knowledge of the early diagnosis, management and rehabilitation of cerebral palsy has expanded since 2011, the production of the third edition of this book was inevitable as a means of incorporating all of the latest data and nuances.

New distinguished authors from around the world, along with many authors of the second edition, have provided sharper and more acute dimensions to the overall upgraded version of this book. All of the chapters have been revised and updated, and new chapters have been added.

The editor would like to thank all of the expert authors for their invaluable input, cooperation and patience towards the successful realization of this project and the publisher Springer Medicine Books, Continental, Europe & UK for the unwavering commitment in disseminating medical knowledge. Special thanks to Christos Livanos from Thessaloniki, for his relentless administrative assistance.

Thessaloniki, Greece — Christos P. Panteliadis

Preface to the Second Edition

Brain damage of the foetal and early infant brain, clinically presented as cerebral palsy, results from a diversity of aetiologies, manifesting as different clinical pictures, and follows different clinical courses demanding for an interdisciplinary treatment. This book systematically reviews the recent developments of diagnosis and treatment of cerebral palsy. It was written by an international team of specialists, including neuro-paediatricians, orthopaedics, psychologists, epidemiologists and others who work in the field of cerebral palsy.

Six years has passed since the first edition of *Cerebral Palsy* was published, and I would like to take the opportunity to thank all the readers for their feedback, which helped to improve the text. The updated manuscript has been thoroughly edited for language usage and grammar. New chapters have been included covering additional aspects of this multifaceted disorder.

Finally, I would like to thank all authors of the present edition for sharing their expertise, as well as the publisher for their professional support and patience for listening to all of the wishes of the editor.

Thessaloniki, Greece — Christos P. Panteliadis

Preface (Parts from First Edition)

Cerebral palsy (*CP*) institutes a nosologic entity with multiple diagnostic and therapeutic dilemmas. It also specifies a scientific issue with particular social, ethical and economic extensions.

CP has been shown to be one of the most frequent problems which occupy paediatricians, paediatric neurologist, orthopaedist and physicians of other specialities. The delay in kinetic operation, which characterizes *CP*, becomes even more serious when accompanied by other problems. Thus, the rehabilitation programme becomes multidimensional. The consequences on family, education and society are very important.

After diagnosis, the biggest burden is undertaken by the rehabilitation group, along with family cooperation. The insecurity and the uncertainty for the child's future dominate each family. In time, signs of deterioration appear on the collective attempt.

This book is a complete effort of Greek and German authors who have been engaged for many years with CP and the problems related to it. A great effort has been put in by all the authors: everyone in his/her own field has better approached the multidimensional issue of cerebral palsy.

Modern views are expressed on the explanation, clinical demonstration, prompt diagnosis and the related problems and ways of confronting them. We hope that in this new edition we could improve the weaknesses which might appear in this first edition.

Thessaloniki, Greece — Christos P. Panteliadis
Wuerzburg, Germany — H-M Strassburg

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Cerebral Palsy: A Historical Review

1

Christos P. Panteliadis and Photios Vassilyadi

Abstract

Cerebral palsy (CP) is a term that has been applied over the years to a group of children with motor disability and related service requirements. The first conceptions of cerebral palsy and our knowledge about etiology and pathogeny allow us to assume that cerebral palsy existed in the Ancient World. Although there is lack of detailed medical descriptions from before the nineteenth century, mentions to cerebral palsy can be found in representational art, literary sources, and paleopathology; however, because of the poor medical documentation, the diagnosis of cerebral palsy must remain a more or less well-justified supposition.

In the Ancient World, the first medical description of cerebral palsy was made by *Hippocrates* in his work *Corpus Hippocraticum*. Concrete examples and definitions of cerebral palsy, however, did not emerge until the early nineteenth century with observations by *William John Little*; thus, Little was the first personality to intensely engage cerebral palsy. Toward the end of the nineteenth century, two more personalities emerged, adding to the historical hallmarks of cerebral palsy: *William Osler* and *Sigmund Freud*. The significant developments that have followed since then are all due to the contributions of these three personalities in the field of cerebral palsy.

1.1 Introduction

Cerebral palsy (*CP*) has been recognized and described since the fifth to fourth century B.C. *Hippocrates* was the first to discuss the association of prematurity, congenital infection, and prenatal stress in relation to the pathogenesis of brain damage. In his work *Of the Seven-Month Foetus* and *Of the Eight-Month Foetus*, *Hippocrates* refers to children born from "intrauterine dis-

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ease" as having increased morbidity and mortality. He was the first to mention that "women who gave birth to lame, blind or children with any other deficit, had foetal distress during the 8th month of pregnancy" and also that "pregnant women who have fever or lost too much weight, without any obvious cause, gave birth to their child with difficulty and dangerously, or they would abort dangerously" [1, 2].

The word "palsy" undoubtedly has its roots in Ancient Greece. It may be derived from "paralysis," which was used by *Galino* (a physician during the period 130–199 A.D.) to mean "weakness and total or partial necrosis of the nerves of the extremities" or perhaps more appropriately from "paresis," denoting weakness. In Ancient Greece, this topic was described by *Soranos* from Ephesos (98–138 A.D.) using such terms as apoplexia, paralysis, paresis, paraplegia, and paralipsis. Paralysis has also been described as motoric or sensible, making the distinction between nerves involved in movement and sensation, respectively.

1.2 Before the Common Era

Prior to *Hippocrates*, suspicions of CP were detected in hieroglyphic figures of people found on Egyptian monuments and by studying mummies. The *mummy* of Pharaoh Siptah (1196–1190 B.C.), a ruler of the 19th Dynasty, was described by the Egyptologists *Ikram and Dodson* [3] as having its left foot in an extended position due to a shortened Achilles tendon. This was seen as an indication of CP; however, the interpretation has been questioned because of its resemblance to poliomyelitis [4]. The claim of CP was supported by photographs from the book of *Smith* and *Dawson* [5] entitled *Egyptian Mummies* (first published in 1924). In addition, photographic plates in Smith's *Royal Mummies* show that Siptah's arms were crossed in a rather awkward position, which may have also been as a result of CP, affecting the arm muscles [6]. *Kolta* and *Schwarzmann-Schafhauser* [7] stated that "we cannot be certain whether these defects were neurological impairments due to poliomyelitis, spastic paresis or a post-mortem artefact." *Sandison* [8], on the other hand, believes that the defects were probably due to a congenital abnormality instead of poliomyelitis, based on his reports on *Siptah* and a mummy of the 12th Dynasty named Pharoah Khnumu-Nekht's. *Brothwell* [9] further illustrate the following about the mummy of Siptah: "... as in the previous case, the left foot only is involved. Previously, consensus of opinion has been in favour of equinovarus deformity, although an alternative diagnosis of poliomyelitis has been ruled out…" [10]. In addition, some medical details are provided by *Whitehouse* in his book *Radiologic Findings in Royal Mummies*. He states: "The deformity of the left lower extremity of Siptah has in the past been described as clubfoot or talipes equinovarus; however, it strongly resembles a post-poliomyelitis deformity, with underdevelopment of the entire extremity and hyperextension of the foot and the ankle to compensate for the resulting inequality in the leg length."

The earliest visual record of poliomyelitis was also reported in Egypt. It is found on the steel plaque dedicated to the Syrian *Astarte* (or Aphrodite), dating back to the 19th Dynasty (1580–1350 B.C.). This plaque records the handicap of *Roma* (or Ruma), a priest and doorkeeper of the Temple of Astarte at Memphis. *Roma* had been crippled by a disease that made him use a walking stick, causing his right leg to atrophy [11]. The Department of History of Egyptian Medicine at Indiana University asserts that "... some favor the view that this is a case of poliomyelitis contracted in childhood before the completion of skeletal growth. Alternatively, the deformity could be the result of a specific variety of club foot with a secondary wasting and shortening of the leg."

An example of cerebral palsy from Hellenistic art has been provided by *Temple Fay* (an American neurosurgeon and neurologist). After a careful morphological examination, he recognized a spastic hemiplegia in a sculpture of a man's head (possibly the Athenian comedy writer *Menander*) which depicted facial asymmetry.

Mirko Grmek, a pioneer of medical history [12], and *Martha Rose* [13] mention further examples of cerebral palsy in her book *The Staff of Oedipus*. This manuscript looks at a wide range of writings on disability within the framework of ancient social history; nevertheless, the cases described are not convincing.

1.3 The Common Era Prior to the Nineteenth Century

In the Roman era, the Emperor *Tiberius Claudius Nero* (10 B.C.–54 A.D.) suffered from cerebral palsy. According to historical sources [14–16], he suffered from multiple physical and behavioral peculiarities. The Roman historian *Suetonius* (70–130 A.D.) describes the many health problems suffered by the Emperor in the manuscript *The Twelve Caesars* [17], while *Robert Graves* in his 1934 novel *I, Claudius* describes the Emperor's head as having a "tremulum" which is Latin for "trembling," insinuating nervous tics. Today, these peculiarities can be interpreted as asymmetrical gait disorder, abnormal movements of the head and hands, dysarthria and dysphonia, salivation, hypertrophy of the anterior neck muscles, unseemly and uncontrolled laughter, and an increase of symptoms under the stress of anger. *Pearce* [18], in his article "The emperor with the shaking head," diagnosed the Emperor with the athetoid variant of cerebral palsy and further noted that the Emperor's high intelligence is consistent with this variation of CP. In a more recent article entitled "A neurological mystery from history: the case of Claudius Caesar," *Murad* reexamines ancient historical sources and concludes that along with cerebral palsy, another likely diagnosis of the Emperor's neurological problems can be Tourette's syndrome [19].

It was not until many centuries later that the medical community started to see physical disabilities from people depicted in paintings. Around 1510 in Frankfurt, *Matthias Grunewald* (1470–1528) painted the Heller Altarpiece in which one of the four saints painted was Saint Cyriacus who was depicted as "exorcizing" the Emperor Diocletian's daughter (Fig. 1.1). Around 1516 in London, *Raphael* (Raffaello Sanzio, 1483–1520) painted what is known today as the Raphael Cartoons, where in one (of the seven) tapestries he depicts St. Peter in the "The Healing of the Lame." The most impressive painting depicting physical disability, though, was done in Naples in 1642 by *Jusepe de Ribera* (1591–1652): his painting of "The Clubfoot" is now found in the Louvre in Paris (Fig. 1.2). In the monasteries of Mount Athos, there are several icons on exhibit that depict paralyzed persons (Fig. 1.3).

Fig. 1.1 Matthias Grunewald (about 1470–1528) painted Saint Cyriacus who was depicted as "exorcizing" the Emperor Diocletian's daughter

Fig. 1.2 J. De Ribera (1591–1652). The young child with the clubfoot. Left spastic hemiparesis (Louvre, Paris)

Fig. 1.3 Icon "The Paralytiker" from monk Merkurius (about 1613–1620) in monastery Holy Dionysios, Mount Athos/Greece

1.4 The Nineteenth Century

The history of CP in the early to middle nineteenth century began with publications by *Johann Christian Reil* [20] and *Claude Francois Lallemand* [21]. In 1827, *Jean-Baptiste Cazauvieilh* reported cerebral atrophy in individuals with congenital paralysis and tried to distinguish lesions in the developing brain with those related to trauma [22]. One year later (in 1828), *Charles-Michel Billard* [23] described pathological changes in the infant brain; however, it was the works of *Jean Cruveilhier* [24] and *Carl von Rokitansky* [25] that first reported isolated cases of cerebral atrophy in children. Later, *Eduard Heinrich Henoch* in his 1842 dissertation, "Die Atrophia Cerebri," described cerebral changes associated with infantile hemiplegia [26].

William John Little (1810–1894), the founder of orthopedic surgery in England, was the first personality to intensely engage cerebral palsy. At the age of 16, he worked as an apothecary's apprentice [27]. Two years later, he commenced medical school at the London Hospital. In 1836, 4 years after completing his studies, he underwent successful correction of his own clubfoot, having convinced the noted *Georg Friedrich Louis Stromeyer* (1804–1876) of Hannover, a pioneer in the technique of subcutaneous tenotomy, to undertake the operation. It was the cure of his deformity that stimulated him to pursue his surgical career [28]. *Little*, then, undertook the same procedure on 30 patients with clubfoot, detailing the results in his doctoral thesis in 1837.

In 1843, *Little* delivered nine lectures entitled "Deformities of the Human Frame," which were published in the Lancet between the 1843 and 1844 [2, 29–31]. He detailed: "a peculiar distortion which affects newborn children which has never been elsewhere described, the spasmodic tetanus-like rigidity and distortion of the limbs of

newborn infants, which traced to asphyxia neonatorum, and mechanical injury to the foetus immediately before or during parturition." He described CP in this lecture series as "... in many instances the spasmodic affection is produced at the moment of birth or within a few hours or days of that event" [29, 30]. After extensive deletions, rearrangements, and the addition of a number of illustrations and several detailed case histories, the lectures became the basis for the 1853 monograph "On the Nature and Treatment of the Deformities of the Human Frame." In this monograph, *Little* tabulated data on 24 patients with generalized spasticity, noting associations with varying degrees of prematurity in 12 cases, difficult protracted labor requiring forceps delivery in 7 cases, and severe asphyxia with convulsions in 7 cases [32].

Neither the clinical description nor the etiological conception of CP changed significantly from 1843 to 1853, and *Little's* initial enthusiasm for subcutaneous tenotomy had been dampened somewhat. In 1843, he wrote "tenotomy had now been successfully applied to every part of the frame," but in 1853 he added "...from which has resulted its indiscriminate use by some too sanguine practitioners." His years of experience in operating to alleviate the effects of aberrant neuromuscular development had taught him the limits of surgery; tenotomy was a last resort that sometimes increased deformity and often only helped transiently. In 1850, *Bednar* described leukomalacia as a distinct disorder of the newborn [33]. In 1853, *Little* described the condition of spastic diplegia (*Little's Disease*) which he ascribed to prematurity and birth asphyxia. Cerebral palsy, by the end of the nineteenth century, was widely known as "Little's Disease."

In 1861, after 20 years of experience and nearly 200 cases, *Little* defended his theory that asphyxia at birth could cause permanent central nervous system damage, in front of the London Medical Society [34]. *Little* postulated an entire spectrum of long-term deformities and disabilities that were secondary to "interruption of the proper placental relation of the foetus to the mother, and non-substitution of pulmonary respiration, 'rather' than from direct mechanical injury," acting on the brain of "too early and unripe-born foetuses." An appendix tabulated 47 cases of spastic rigidity: hemiplegic (affecting one side only), paraplegia (affecting both legs more than arms), and generalized rigidity. *Little* also noted the varying susceptibility of the developing nervous system to damage at different stages of gestation and that many patients exhibited a delay in the appearance of the classical signs, thus, the original term "cerebral paresis" [35].

Little's work appeared at about the same time as that of *Jakob von Heine* (1799–1879). In the second edition of his manuscript *Spinale Kinderlaehmung*, he reported that the symmetrical paralyses of the lower extremities resulted from cerebral, rather than spinal, disease [36]. In 1867, *Virchow* described white, softened areas around the ventricles of infants examined postmortem [37]. *Parrot* [38] later identified this as an affliction of prematurity and postulated that it was caused by immature white matter. *Richard Heschl* first introduced, in 1859, the term "porencephaly" to designate brain lesions characterized by focal cerebral atrophy, and, in 1871, *Hammond* defined "athetosis" as "adults being affected with hemiplegia" [39].

In 1868, *Jean Louis Cotard* [40], under the guidance of *Jean-Martin Charcot* (1825–1893), a French neurologist, analyzed the different etiologies of cerebral paralysis (especially trauma) and described partial atrophy of the brain in these conditions. These were documented in his dissertation "Etude sur l'atrophie cerebrale" and coined the term *cerebral sclerosis* in children [41]. A large series of cases were reported by *Hans Kundrat* in 1882 [42], 103 cases by *Jean Audry* [43] between 1888 and 1892, 80 cases by *Ernest Gaudard* on infantile hemiplegia in 1884 [44], and 160 cases by *Adolf Wallenberg* on pediatric cerebral paralysis in 1886 [45]. *Joseph Parrot* in 1873 and *Victor Hutinel* in 1887 suggested that congenital hemiplegia might result from localized encephalomalacia, which is secondary to venous congestion, stasis, thrombosis, and hemorrhage [35, 46].

In 1882, *James Ross* championed the idea that most, if not all, cases of spastic paraplegia in infancy were due to "... a porencephalous defect of the cortical motor centers." In 1885, *Ernst Adolf Strumpell* provided a fresh impetus to the

study of these disorders by claiming that they were a form of central nervous system infection, which he termed polioencephalitis [47]. The same year, *William Richard Gowers* (1885–1888) of England mentioned eight cases of seizures occurring soon after birth "... the labor in several of these cases having been difficult, and in some forceps applied"; he used the theory of "Little's Disease" in his lectures on paralysis [48]. In France, *Jules Dejerine* used the term "Maladie de Little." In 1885, *Sarah McNutt* continued to raise the profile of the risks of long-term disability arising from birth trauma [49].

Little was the first to propose a direct relationship between various neuromuscular disabilities of neonates and children with difficult delivery, neonatal asphyxia, and prematurity. He reached the conclusion that "Richard's deformity" was secondary to birth asphyxia [50]. This hypothesis was also supported by *Sir Thomas More's* statement that King Richard was born in the breech position "feet forward" [50]. *Gower* and *Little* found that more extensive motor involvement was correlated with greater intellectual deficiency. Erratic learning, short attention span, irritability, destructiveness, aggression, hebetudes, weakness of every intellectual facility, and even complete idiocy were also described.

In 1888, the eminent *William Osler* (1849–1919), a Canadian professor of clinical medicine in Pennsylvania, wrote a book monograph entitled *The Cerebral Palsies of Children*. *Osler* was the second great personality (after *Little*) who worked toward cerebral palsy. He reviewed 151 cases, both his own and those from the literature (120 with infantile hemiplegia, 20 with bilateral spastic hemiplegia, and 11 with spastic paraplegia), classifying them by distribution and location and correlating them with neuroanatomical pathology (Fig. 1.4). Many of these cases were from the Pennsylvania Institution for Feeble-Minded Children, where patients showed severe mental retardations. *Osler* credited *Strumpell's* paper in 1885 for sparking his interest toward this problem. *Osler* noted the association between difficulties during delivery, asphyxia, prolonged resuscitation, and seizures. His review of the literature addressed arachnoid and subarachnoid hemorrhages but not intraventricular hemorrhage [51–54]. *Osler* believed that *Strumpell's* theory of polioencephalitis (a cerebral counterpart of the spinal variety) was plausible and supported by the occurrence of this disorder following infectious diseases. Nonetheless, he cautioned that the pathological changes seen were, in most instances, necrotic rather than inflammatory. He also commented on the need to study the pyramidal tracts in the spinal cord and spinal centers in an effort to ascertain the causes of paralysis and rigidity in these cases.

Fig. 1.4 First photography of a child with the symptoms of spastic diplegia by Osler

Concerning the pathology, *Osler* recorded "we are impressed" with the extent to which sclerotic and other changes may exist without symptoms if the motor areas are spared; however, there may be a degree of permanent disability which may exist with even slight affliction of this region. *Osler* concluded that the pathogenesis of

these palsies associated with birth was strongly related to intracranial hemorrhage. *Osler* was the first to mention jaundice in infancy as a possible etiological factor of CP. However, as noted by *Ingram*, it is likely that *Osler* may not have realized its significance, as he had only quickly mentioned it: "... had jaundiced when 1 day old after which the paralysis occurred" [55–57].

A few years later, *Sigmund Freud* (1856–1939) wrote several volumes entitled "Cerebral Palsy." *Freud* was the third major personality to have a historical contribution to cerebral palsy in the nineteenth century. His contribution was threefold: (1) he developed a classification system that is still in use today and essentially unchanged, (2) he documented a poor correlation between clinical syndromes and neuropathologic lesions, and (3) he contributed extensively to the description of various movement disorder syndromes in children.

Freud described the relationship between the location of the lesion and the degree of the contracture; the more superficial the lesion, the more likely it is to affect the lower extremities. *Freud* was the first to derive a classification system based on the etiology of cerebral palsy: congenital (*antepartum*), acquired during birth (*intrapartum*), and acquired postnatally (*postpartum*). In his papers, he used the term "infantile Zerebrallaehmung" and proposed the classification was based on the clinical types of hemiplegia, total cerebral spasticity, paraplegic spasticity, central chorea, bilateral athetosis, and finally bilateral spastic hemiplegia [58].

Freud established that all diplegias that originated from birth and had been attributed to birth abnormalities actually had their pathological origin during intrauterine life. *James Stansfield Collier* (1870–1935), a British neurologist who also had a deep interest in cerebral diplegia, referred to *Freud's* 1897 [59] monograph as "the most complete and authoritative exposition of the subject." *Collier* quotes *Freud* as follows: "... premature, precipitate and difficult births and asphyxia neonatorum are not causal factors in the production of diplegia, development of the fetus or the organism of the mother [60, 61]" *Bernard* (Barney) *Sachs* (1858–1944), the great New York neurologist and former student of *Freud*, characterized *Freud's* book as "masterly and exhaustive" [62].

By this time, however, *Freud's* interests had already shifted toward psychiatry, and it was with some effort that he completed his previous work on CP. In a letter to *Wilhelm Fliess* (1858–1928), he complained, "I am fully occupied with children's paralysis, in which I am not the least interested … the completely uninteresting work on children's paralysis has taken all my time" [63].

In 1890, *Sachs* and *Peterson* admitted to a persistent confusion between cerebral palsy and poliomyelitis [64]. *Osler* and *Freud* (as well as *Sachs*) debated whether convulsions by themselves could cause cerebral palsy. *Freud* in his 1891 monograph disagreed, believing that although there might be a temporal relation, it did not provide sufficient proof of causation. An interesting theory on the etiology of diplegia was presented by *Brissaud* in 1894 [65, 66]. He believed that diplegia was due to prematurity and a lack of postnatal development of the pyramidal system. *Brissaud*, a student of *Charcot*, believed that the origins of cerebral palsy were due to spinal disease (based on *Charcot's* work on amyotrophic lateral sclerosis and progressive spastic paraplegia). *Freud* argued against *Brissaud's* theory that diplegia was due to a form of developmental arrest that occurs with prematurity.

1.5 The Early Twentieth Century

At the end of nineteenth century through to the mid-twentieth century, there grew a marked medical disinterest toward cerebral palsy because of a lack of clinical classification and neuropathological correlation. In 1903 and 1906, *Batten* [67, 68] described ataxia as a type of cerebral palsy, which was later corroborated by *Forster's* work in 1913 [69], "Der Anatomische Astatiche Typus der Infantilen Zerebrallaehmung."

Following *Osler's* footsteps, *Winthrop Phelps*, an orthopedic surgeon in Baltimore, became interested in cerebral palsy in the 1930s and developed a treatment regimen that was principally concerned with the peripheral muscular

skeletal system. In a historic lecture in 1932 to the New York Academy of Medicine (Orthopedic Section), he described cerebral birth injuries from an orthopedic point of view, rather than a neurological one, in order to facilitate therapy [70]. In 1941, *Phelps* published an impressive paper entitled "The management of cerebral palsy" [71].

Normal motor development had been described in great detail by *Schaltenbrand* [72], *McGraw* [73], *Gesell* and *Amatruda* [74], *Illingworth* [75], and others. The abnormal postural reactions of the body during CP are attributed to the tonic reflexes described by *Walshe* [76] and *Magnus* [77]. In 1947, *Strauss* and *Lehtinen* noticed (for the first time) that behavioral and emotional abnormalities are common in children with cerebral palsy [78].

In the early 1940s, *Berta Bobath*, a German gymnast, and her husband *Karel*, a psychiatrist from Czechoslovakia, suggested that the aim of therapy was to inhibit the abnormal postural reflex activity and to facilitate normal automatic movement in a sequence based on normal neurological development [79, 80]. According to *Perlstein* and *Shere* [81], about 75% of children with CP were found to have speech defects and, of those, 50–75% wanted/required speech therapy [82].

1.6 The Mid-twentieth Century

In the 1950s, *Temple Fay* developed a theory that the central nervous system is comprised of evolutionary layers from the upper end of the spinal cord to the cerebral cortex. Each layer coincides with a stage of locomotion based on the sequential hierarchical classification of species and that neurological organization is possible if each sequence is perfected before progressing to the next one [83]. At this time, conductive education had already been developed by *Andras Peto* (1893–1967), a physician and neuropsychologist. *Peto* followed in the footsteps of *Freud*, with the objective to enable children with cerebral palsy to walk in order to be able to integrate them into the regular educational system in Hungary [84]. *Carl Delacato* and *Glenn Doman* [85, 86], in Philadelphia, and *Vaclav Vojta* [87], a neurologist from Prague, became interested in cerebral palsy in the 1960s. *Doman's* and *Delacato's* ideas were an extension of *Temple Fay's* work. *Vojta's* main goals of therapy were to: "correct abnormal postural reflexes, especially in very early life, by treatment and to induce storage in the brain of normal therapy-influenced reflex pattern which will allow normal patterns of locomotor function to emerge by the use of manual pressure on trigger zones, eliciting normal patterns of reflex motion."

In 1955, *Virginia Apgar* [88] generated a scoring system that forced obstetricians to examine the condition of newborns at birth and assess the need for treatment. The *Apgar score* was the first to standardize the "language of asphyxia": newborns with low scores would have a lesser chance of any brain damage later in life. Later, in 1961, *Erich Saling* and *Damaschke* developed the micro-assay for sampling blood gas [89]. This allowed the diagnosis of acidosis and hypoxia using small quantities of blood; however, at that time, there was no established relationship between hypoxia and acidosis, tissue perfusion, shock, and death.

In England, *Mac Keith* and *Polani* [90] convened the *Little Club of CP* and in 1959 published its definition: "a permanent but not unchanging disorder of movement and posture, appearing in the early years of life and due to a non-progressive disorder of the brain during its development." *Banker* and *Larroche* [91] coined the term "periventricular leukomalacia" and, in 1967, *Christensen* and *Melchior* published the first book on CP, which concentrated on clinical and neuropathological studies [92].

Since the beginning of the 1990s, there has been a growing use of botulinum toxin A in spastic movement disorders in children. It has been used therapeutically in humans for a variety of conditions since 1980. Historically, the first indication of therapy was performed by *Scott* in 1981 for strabismus. In 2006, a consensus was developed on the best practice for the treatment of CP using the botulinum toxin [93].

The mid-twentieth century ushered in a better understanding of the pathophysiology of fetal

neurological injury with the aid of direct monitoring and visualization of the fetus, along with experimental studies and statistics. However, the first development of direct monitoring was in 1821 by *Jean Alexandre Le Jumeau* and *Vicomte de Kergaradec*. By using auscultation to hear the amniotic fluid of a pregnant woman, he was astute enough to auscultate the fetal heart and, more significantly, to envision the practical possibilities of auscultation. His observation was the following: "from the changes occurring in strength and rate of foetal heart beats, wouldn't it be possible to know about the status of health or sickness of the foetus?"

1.7 The Late Twentieth Century to Early Twenty-First Century

Crothers and *Paine* [94] were pioneers that used a multidisciplinary approach for the evaluation and treatment of children with CP. Progress has been made in this respect, especially in the field of physiotherapy with such applied methods as comprehensive physiotherapy, neurodevelopmental therapy (*NDT*), and constraint-induced movement therapy (*CIMT*). These methods used alone or in combination can be applied depending on the severity of CP. For example, CIMT is the most appropriate therapy for the upper extremities. The hand-arm bimanual intensive therapy (*HABIT*) is also appropriate to use and highly effective, as well as locomotor training. Surgical procedures include the implantation of programmable pumps for the delivery of intrathecal baclofen, selective dorsal rhizotomy, and orthopedic surgery such as tendon releases (for more see Chaps. 19–22, 25, and 26).

The gross motor function classification system (*GMFCS*) developed by *Palisano* and his colleagues [95] classifies the severity of movement disability in children with CP in five levels according to the extent of impairment across four age groups. It describes gross motor function in terms of self-initiated movements with the emphasis on function in sitting and walking. The benefits of this classification are that it incorporates both the concepts of disability and of functional limitation, and the assessment obtained in early childhood can predict the level of disability later in life. Recently, a revised GMFCS (*GMFCS—ER*) was developed and subsequently validated in 2008 ([96]; see Chap. 22).

In 1998, the group for the Surveillance of Cerebral Palsy in Europe [97] was established. It started with 14 centers from 8 countries, publishing their standardized protocols for registers and database collection and providing information for service planning and a framework for research projects in the field of CP. In 2004, *Graham*, an orthopedist, described the Functional Mobility Scale (*FMS*) [98], a system used to measure changes in walking ability. In 2006, *Eliasson* et al. published a new method, "The Manual Ability Classification System (*MACS*)," which is analogous to GMFCS (see Chaps. 17 and 22).

The advent of new imaging techniques signaled a revolutionary approach in the diagnosis of CP (see Chaps. 12–14). The range of possible imaging modalities for evaluating brain pathology had evolved since the first computed tomography (*CT*) scan to the addition of magnetic resonance imaging (MRI), functional MRI (f*MRI*) , fetal MRI, as well as positron-emission tomography (*PET*) and single-photon emission computed tomography (*SPECT*). Technologies were also used for prenatal diagnoses, including sonography, amniocentesis, and fetoscopy.

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The Definition of Cerebral Palsy

2

Eve Blair and Christine Cans

Abstract

Cerebral palsy (CP) should not be considered as a diagnosis but as a label; it is an umbrella term. The definition is not sufficiently precise to guarantee agreement as to which patients to include under this label, but the additional inclusion criteria required are not yet internationally standardised.

2.1 Definitions

Cerebral palsy (*CP*) is the term applied to a group of children with motor impairment and related service requirements. Since this group is heterogeneous with respect to clinical signs, aetiology and pathology, it has frequently been suggested that it is more appropriate to refer to the cerebral palsies, in the plural.

The word *palsy* undoubtedly has its roots in ancient Greek. It is most likely derived from paresis (πάρεση in Greek) denoting weakness [1]. However the term 'cerebral palsies' was probably not coined until the late 1880s by *William Osler*, a Canadian physician (*see* also Chap. 1) [2, 3]. Between 1950 and 2000, several authors published rather similar definitions of CP [4–8]. The Mutch et al. [7] paper, commissioned by the UK Spastic Society, was the result of several meetings held in Europe and America. On account of the well-recognised heterogeneity seen in CP, it was agreed at these meetings that it did not refer to a unique disorder but that it was nonetheless a useful umbrella term. A European consortium of professionals involved in the CP field were responsible for the SCPE [8] paper in which we read: '*Cerebral Palsy* is a group of permanent, but not unchanging, disorders of movement and/or posture and of motor function, which are due to a non-progressive interference, lesion, or abnormality of the developing/immature brain'.

At a 2004 workshop held in Washington, the utility of retaining the term CP was discussed at length since the label does not inform aetiology, severity or even prognosis, given that should the cerebral pathology progress, it is the label that is retrospectively removed. However it was agreed to retain the term since in an age of electronic databases, it is a conveniently

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unique, well-recognised and understood search term. Following this workshop, Rosenbaum et al. [9] published the following: '*Cerebral palsy* describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems'. This definition is followed by an annotation concerning the terms used and was accompanied by several commentaries (e.g. [10]).

The differences between the SCPE [8] and Rosenbaum [9] definitions lie primarily in the choice of words: *motor function* is replaced by 'activity limitation' and 'developing/immature brain' by *developing fetal or infant brain*. The latter definition also expresses the possibility that additional impairments coexist, a fact that was neither excluded by earlier definitions nor necessary for acquiring the CP label.

All definitions have four elements in common: (1) disorders of movement or posture leading to motor impairment that (2) develop very early in life (3) can be attributed to cerebral abnormality, and (4) although the clinical signs change with the child's development, the cerebral abnormality neither resolves nor deteriorates.

These four elements make it clear that CP is a man-made construct defined by clinical description rather than by any objective biological, aetiological or anatomic criteria; other than that the primary responsible pathology is sited in the brain and not in other elements contributing to motor function such as the spinal cord or muscles. Thus CP should not be considered a diagnosis but as a useful label to group patients likely to benefit from related management strategies, an umbrella term for many different pathological and aetiological diagnoses, not all of which are yet recognised but middle cerebral arteria infarctus, CMV maternofetal infection, periventricular leukomalacia due to very preterm birth, lissencephaly, cardiovascular accident and kernicterus represent some examples.

Although these definitions for CP are useful, they are not sufficiently precise to guarantee agreement as to which individuals to include under the label. Observers of CP have therefore had to formulate their own sufficiently precise inclusion criteria, which has resulted in there being variations between them.

2.2 Elements Varying Between Sets of Inclusion Criteria for CP

Consensus with Freud's phenomenological approach that CP is defined exclusively by clinical description [11] is gaining greater acceptance [8, 12]. However this was not always the case. In the past CP was often considered a 'diagnosis of exclusion'. If aetiology was known, then it was argued, the individual could not also be 'diagnosed' as CP. This led to the exclusion of the most easily recognised aetiologies (e.g. those with a genetic cause or known syndrome or with chromosomal anomaly), even when the clinical criteria for inclusion were met [13]. With this approach, increasing diagnostic power would decrease the reported prevalence of those labelled CP even in the absence of any change in prevalence of symptoms. However, for long-term registers that had continued to exclude historically excluded diagnoses, embracing the phenomenological approach in its entirety risked artificially increasing apparent prevalence in their estimation of time trends, leading to the publication of 'What constitutes CP?' [14] which tried to define which diagnoses were and were not included. With the recognition that the proportion of CP with such historically excluded diagnoses was very small and the increasing number of new registers for whom this was not an issue, the subsequent 'What constitutes CP?' paper [12] fully embraced the phenomenological approach.

There are a number of characteristics to be considered when deciding whether to include a person under the CP umbrella, and algorithms have been found useful to increase reliability of labelling [8, 12], but controversy remains concerning a few issues.

2.2.1 Type of Disorder of Movement or Posture

Spasticity, dyskinesia and ataxia are always included but the rarely encountered isolated hypotonia is excluded by European but included by many Australian and US workers, though frequently with caveats. In Western Australia isolated hypotonia is only included if not attributable to cognitive deficits and contributes only 1% of congenital CP [15].

2.2.2 Severity of Disorder of Movement or Posture

In the past, the severity of CP has been considered to be that of the primary motor impairment (e.g. the degree of spasticity or dystonia) but is now usually assessed from motor functional ability. Of 24 CP surveillance programmes surveyed, only 9 included a criterion purporting to address minimum severity in their definitions of CP [16]. Four programmes required *activity limitation* clarified as 'difficulties an individual may have in executing activities' [9] with only one stipulating that the limitation must be due to motor impairment. Since the activities are not defined and everyone has difficulty, for want of strength, flexibility or practice, in executing some activities that others may accomplish with ease, it remains a subjective criterion for severity, the necessity of motor impairment making it somewhat more objective. Five further programmes require a minimum Gross Motor Function Classification System (GMFCS) level of I [17] despite it reflecting only lower limb function. GMFCS level I children can run and jump in late childhood but with suboptimal speed, balance and coordination, the same activity limitations observed in the clumsy child, yet it is generally agreed that 'merely' clumsy children are excluded. One further population based register specifies that abnormal neurological signs are required but that functional impairment is not required to be described as minimal CP.

Defining the boundary of the milder end of the CP spectrum remains problematical, particularly since in some jurisdictions, the CP label may be allocated in order to gain access to medical services such as botulinum toxin.

2.2.3 How Early in Life Can the Disorder of Movement or Posture Be Reliably Recognised?

The earlier that CP can be recognised, the better in terms of providing optimal care for the child, informing parents and maximising the information that can be retrieved for epidemiological purposes. Signs of disordered motor control may be present very soon after birth, and satisfactory prediction of CP from abnormal *general movements* has been demonstrated by 20 weeks postterm age by trained observers in high-risk infants either born very preterm or with neonatal neurological signs (e.g. [18–20]). These high-risk infants contribute almost half of congenital CP, and the increasing availability of trained observers allows the 'at high risk of CP' label to be assigned before, even well before, 5 months postterm age. However, the motor disorders that define CP neither resolve nor deteriorate and are generally considered to refer to voluntary movement and posture. Since verification of these characteristics must await development, 10 of 24 surveillance programmes include only children who survive to a specified minimum age which varies between 1 and 16 years [16]. However excluding early deaths risks excluding the most severe end of the CP disability spectrum, children who would uncontroversially have exhibited severe CP had survived. If severity of impairment correlates with severity of the causal factors, this would exclude those in whom causal factors may be most easily recognised and is the reason that a narrow majority of surveillance programmes do not define a minimum age of survival but accept any definite description of CP by 'a suitably qualified person'. It is not clear if or when observers trained in recognising abnormal general movements will be considered 'suitably qualified persons'.

2.2.4 Progression or Resolution of the Cerebral Abnormality

All definitions make it clear that to meet criteria for the CP label, the cerebral pathology neither resolves nor progresses. Should this occur in a child labelled as CP, the CP label is removed as the defining criteria are no longer met. So, although the initial categorisation as CP is based on neurological examination, the continued appropriateness of that label is not assured. With increased diagnostic capabilities, aetiological diagnoses for children with the CP label are now identified more frequently, and it may be possible to exclude a child from the CP category on the grounds of having an aetiological diagnosis that is known to be progressive, even before that progression becomes apparent, for example, with genetically diagnosed Rett syndrome [21]. Such diagnoses apply only to the minority, so to increase the objectivity of this criterion, most registers define a cut-off age (typically the age of ascertainment) by which resolution or progression must be identified if a potential registrant is to be excluded.

An associated conundrum is the differentiation between degeneration and repeated insults. Some vascular or metabolic defects create a vulnerability to brain damage which may occur once or repeatedly depending on environmental circumstances, including treatment. Smithers-Sheedy et al. propose that such conditions be included since they are not inherently progressive despite the possibility that they may appear progressive and, in the absence of the diagnosis being recognised, may well have been excluded [12].

2.2.5 How Early in Life Must the Cerebral Abnormality Be Acquired?

It is agreed that cerebral pathology acquired prenatally and intrapartum is included. Since the precise timing of perinatally acquired brain damage may be difficult to identify and often has its origins in the prenatal or intrapartum periods, all relevant cerebral pathology believed to be acquired before 28 days of life is usually, though not always particularly in developing countries, grouped together. Even in developed countries, there are exceptions such as term or near-term infants who suffer traumatic accidents days or weeks after being discharged from the birthing location as neurologically intact. Such an infant may be included with infants meeting the criteria for CP after acquiring brain damage postneonatally. These have been reported to contribute between 4.6% and up to 60% of all CP in developing countries, the proportion correlating with social disadvantage [22]. The upper age limit of acquisition of cerebral damage, after which any resulting impairment is not included as CP, varies between 2 and 10 years, with 2 and 5 years being the most popular choices [16]. However since most postneonatally acquired CP is acquired by 2 years of age [15], variations in upper age limit have little effect on estimations of prevalence.

Despite extensive research, the causal pathways to CP are not well understood, at least in part because there are so many such causal paths, each responsible for only a small proportion of all CPs. However the majority of the more than 800 CP-related research papers published annually are devoted to the management of CP. This plethora of literature, sometimes with conflicting conclusions, complicates the work of the physician and is the reason for this book. The spectrum of CP management has many factors that demand new and up-to-date knowledge by a group of experienced doctors, nurses, physiotherapists and others that work with individuals with *CP* in order to achieve the best possible outcomes.

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3 Epidemiology of the Cerebral Palsies

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Abstract

Epidemiology of CP aims to describe the frequency of the condition in a population and to monitor its changes over time. Also it studies the determinants of this condition which responsible for some changes over time. Classification of CP is an important step toward describing more homogenous subgroups of persons with CP. Several classifications exist based on neurological signs and topography, on motor function loss, on associated impairments, on severity of the clinical pattern and on the neuroimaging findings. Overall prevalence of CP is around 2 per 1000 live births in developed and in developing countries, with a trend toward a decrease during the last decade, at least for the more severe subgroups and the more tiny babies. Caution should be paid when interpreting changes in prevalence rates since factors that may influence these estimates are numerous.

Cerebral palsy (*CP*) is an umbrella term for a collection of conditions resulting in lifelong motor disability. Together they constitute the most common cause of physical impairment in children and are responsible for permanent activity limitation and lifetime participation restriction [1]. CP is defined by motor impairment due to maldevelopments of, or injury to, the immature brain, the latter being a phrase open to variable interpretation but often taken to be before 2 postnatal years; see Chap. 2. Children and adults included under the *CP* umbrella have very heterogeneous clinical presentations. In addition to motor impairments, they may also have impairments of

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cognition, vision, hearing, communication, proprioception, behaviour and/or epilepsy that may exacerbate or even overshadow the disability due to the motor impairment. By definition the responsible cerebral pathology is not progressive, but the clinical manifestations change over time with development and the long-term deleterious effects of motor impairment on the musculoskeletal system. Those with severe CP tend to have significantly lower survival rates, especially if oromotor impairment is present.

Epidemiology is the study of the distribution and of the determinants of disease frequency in a population. The aims of epidemiology of *CP* are multiple. *Firstly* it aims to evaluate the burden of a disease by describing its frequency according to its clinical characteristics. *Secondly* it monitors trends in prevalence over time in the search for clues regarding aetiology and prevention. These trends are considered an important measure of the impact of developments in pre-, peri- and neonatal care since more than two thirds of CP cases are considered to have aetiologies involving these periods [2, 3]. *Thirdly* it seeks specific risk factors and combinations of risk factors associated with CP or different subtypes of CP.

Following the first step of defining and describing CP (see Chap. 2), two other major steps are (1) to collect information in order to be able to study the frequency of the disease and (2) to seek explanations for any changes in frequency.

3.1 Definitions About Rate and Trends, Methodological Issues

Prevalence refers to the proportion of a population with a condition and is most relevant for service provision. It is calculated as the number of persons with a condition (the numerator) divided by the number of persons in the population from which the numerator arose (the denominator). Since both numerator and denominator change over time, prevalence must be estimated at one point in time (referred to as *point prevalence*) which may or may not be stable over time. A trend in prevalence refers to a systematic change in prevalence over a period of time.

Incidence refers to the number of new cases of a condition arising per unit time. However since this is of little epidemiological interest (unless the size of the source population is known), *incidence* is often used as a shorthand for *incidence density rate* which is the ratio of new cases of a condition to the number of person-time units at risk, where time is usually measured in years. *Incidence (density rate)* is therefore more relevant to aetiological investigation.

The relationship between prevalence and incidence is simplified for a lifelong condition, since an individual contributes only once to incidence and will contribute to prevalence for the duration of their survival. The problem with a condition such as CP, which may not be recognised at the point of acquisition, is that death may precede recognition. This is of little interest to service providers who routinely divide the number of persons surviving with the CP label, typically to 2 years of age, by the number of births from which they arose, a ratio sometimes termed "birth prevalence". This will not estimate true prevalence if any losses or gains occur in the source population before the age at which the numerator is ascertained (due to death or migration) but is nonetheless the method used by the majority of CP surveillance systems [4] which typically exist in developed countries where neonatal and infant mortality is low.

3.2 Factors Affecting the Ascertainment

Cerebral palsy registers have been established around the world with the aim of estimating prevalence rates of CP in a population [5]. The first *CP* registers set up in *Europe* were in *Sweden* (1954), *England* (1966), *Ireland* (1966) and *Denmark* (1967). Then, other registries were created in other *European countries*. In 1999, a network of registers was established—gathering 14 registers or population-based surveys from 8 different countries [6]. After harmonisation of their data, these registers set up a common database. At present, the network includes 24 active registers. *In Western*

Australia, a *CP* register was created in 1975, followed by registers in the States of South Australia and Victoria. Recently, new registers were implemented in other parts of Australia, and a common database, the Australian Cerebral Palsy Register (*ACPR*), has been created, gathering data from all registers [7] and assisting in the creation of compatible registers in New Zealand and Bangladesh. In Japan, a CP register has been collecting data for children born since 1988 in the Okinawa Prefecture [8]. In the USA, the Autism and Developmental Disabilities Monitoring Network (*ADDM*) [9] includes three sites where population-based surveys of CP are periodically held. Several excellent surveys have been conducted in other parts of the world including house-to-house data collection in developing countries, demonstrating that the childhood prevalence of CP does not differ greatly throughout the world; see Table 3.1. However detailed examination of these surveys is beyond the scope of this chapter.

Registers are population databases utilising information from multiple sources, relying on a clear definition and inclusion and exclusion criteria of CP [5]. The use of multiple sources seeks to maximise the accuracy and completeness of data collection in a defined area (county, region or country) and minimise selection bias that may arise from hospital- or clinic-based studies. Population-based studies also use multiple sources but differ from registers in that the inclusion of cases is not continuous over time but limited usually to a predefined span of birth dates. Although independently created registers vary in methodology, similarities exist regarding their aims, definitions and the data they collect creating the possibility for

Table 3.1 Most recent prevalence estimates of cerebral palsy in different geographical locations

Reference	Location	Study population	Children with CP (*n*)	Birth cohort	Denominators	Prevalence rate
Sellier et al. [10]	20 registers in Europe	At least 4 years old	10,756	1980–2003	Per 1000 live births	1.90 in 1980 to 1.77 in 2003
ACPR [7]	3 registers, Australia	5 years old	3662	1993–2009	Per 1000 live births	2.0 in 1993–1994 to 1.6 in 2007–2009
Van Naarden Braun et al. [11]	Metropolitan Atlanta, USA	8 years old	766	1985–2002	Per 1000 1-year survivors	1.9 in 1985 to 2.2 in 2002
Touyama et al. [8]	Japan	>2 years old	639	1988–2007	Per 1000 live births	1.8 in 1988–1997 and 2.0 in 1998–2007
Liu et al. [12]	China, seven cities in Jiangsu	<7 years old	622	1990–1997	Per 1000 children <7 years old living in surveillance areas	1.6
Yam et al. [13]	Hong Kong	6–12 years old	578	1991–1997	Per 1000 children enrolled in the education system in the school year 2003/2004	1.3
Smith et al. [14]	British Columbia, Canada	At least 3 years old	497	1991–1995	Per 1000 live births	2.7
Oskoui et al. [15, 16]	Quebec, Canada	9–11 years old	228	1999–2001	Per 1000 children living in surveillance areas	1.8
Oztürk et al. [17]	Turkey	2–16 years old	102	1990–2004	Per 1000 live births	1.1
Banerjee et al. [18]	Metropolis of Kolkata, India	<19 years old	48	1984–2003	Sample of 16,979 children <19 years old	2.8

valid data comparisons and research collaborations [4]. Numerous factors may affect the probability that a child will be identified by a CP register. These factors include eligibility criteria, age of ascertainment, consent requirements and methods used to identify new cases. Nevertheless, despite these limitations, *CP* registers constitute invaluable sources of detailed information for monitoring *CP* characteristics, rates and trends and for the planning of services. They are useful also in the endless search for causal pathways to *CP*.

3.3 Classification of Cerebral Palsy

Clinical presentation is very heterogeneous with examples found at all points of several continua, though clinical descriptions do tend to cluster. It is these clusters that are responsible for the traditional classification systems by type of motor impairment, bodily distribution and severity. For epidemiological purposes it is convenient to define subgroups of individuals with a significant degree of clinical homogeneity, but it must be appreciated that such divisions are somewhat artificial; clinical heterogeneity remains within subgroups, and examples exist that defy such classification.

3.3.1 Classification Based on Neurological Signs and Topography of Motor Impairment

The different classification systems based on clinical findings serve different functions, some of them having been proposed a long time ago [19]. The main differences between classifications in use are the number of the different CP types described. *CP* types have been given names such as diplegia, quadriplegia, double hemiplegia, triplegia, dystonic, dyskinetic, ataxic and mixed mainly spastic [20, 21]. All these *CP* types are quite useful for a clinician when describing the condition of one child; however, for comparison purposes (often required in epidemiology), it has been shown that the distinction between these terms, mainly between diplegia and quadriplegia, is not reliable enough [22, 23]. None of these categories have a standardised definition in terms of motor impairment, and their interpretation is further complicated by variable assumptions sometimes being made concerning non-motor impairments. For instance, some professionals will classify a child with CP diplegia type if the two lower limbs are "predominantly" involved, while others will classify the same child as quadriplegia because all four limbs are involved, and for yet others the choice between these two categories may be determined by cognitive ability.

One more simple classification system was proposed recently by the European *SCPE* network, with agreement between partners on the clinical findings required for each following *CP type*: bilateral spastic, unilateral spastic, dyskinetic and ataxic. In the SCPE database, half of children with CP have a bilateral spastic type, nearly a third a unilateral spastic type, and the others have either a dyskinetic or an ataxic type. When more than one type is present, i.e. spasticity with ataxia and/or dyskinesia, the child should be classified according to the dominant clinical feature [24]. This classification system had substantial to excellent interrater reliability [25] and is recommended for epidemiological studies.

3.3.2 Classification Based on Motor Function Loss

The impact of the brain lesion on the motor function is often assessed through the ability of the child to walk. It has been shown that walking ability is strongly associated with *CP* type [26]. However, *walking ability* might mean walking outdoors in everyday life, being able to walk just a few metres or able only to walk indoors. During the last decades, scales have been devised specifically for children with CP to assess the loss of motor function in both the lower and the upper limbs, with the aim of increasing the comparability of assessments between professionals and geographically diverse research groups. *A five-point scale* for the trunk and lower limb motor function, i.e. the Gross Motor Function

Classification System (*GMFCS*) (*see* also chapter "Integrated management with Botulinum Neurotoxin A"), was proposed and validated by the Canadian research group CanChild ([27], www.canchild.ca). It was subsequently extended and revised [28]. Similarly, two five-point scales for fine motor abilities of the upper limbs have been proposed: the Manual Ability Classification System (*MACS*) and the Bimanual Fine Motor Function (*BFMF*) scales [29, 30]. It is possible to take into account the asymmetry of the upper limb function with the *BFMF* scale which also provides complementary information about the fine motor capacity [31]. Within these broad categories, human functional abilities are multidimensional, so it should come as no surprise that the two scales that purport to measure upper limb function differ somewhat in which aspects of upper limb function are assessed, as do the two scales assessing communication. Moreover, both *GMFCS* and *BFMF* scales allow the level to be determined from medical records, and parents have been shown to be able to reliably assess their child's *GMFCS* level [32]. The use of these scales represents a great step forward in describing a child with CP and has greatly increased the validity of comparing results between registers and surveys.

3.3.3 Classification Based on Associated Impairments, Including Epilepsy

As mentioned in the most recent *CP* definition [33], a child with *CP* may present several other associated neurosensorial impairments. Many of them are well defined and quantified, and detailed descriptions are given in Chap. 10 on comorbidities. For some such as communication and speech disorders and feeding problems, standardised assessment tools have only very recently been proposed [34–36], and population-based studies assessing their frequency among children with *CP* are lacking. The use of these standardised tools to collect information on all these comorbidities is highly recommended both for epidemiological purposes and to achieve optimal outcomes in children with *CP* and their families [37].

Intellectual impairment is the most commonly associated impairment encountered among children with *CP*. It occurs in 30–40% when restricted to severe intellectual impairment (IQ level < 50) [38] and up to 60–70% if "mild" intellectual impairment or any specific learning disabilities are also included. On account of their other impairments, it is not always easy to appreciate the intellectual level in children with CP, and it is probably quite often underestimated [39].

The *second* most frequently associated impairment is epilepsy which may appear early in life or not until school age. Many studies report that about 30% of people with CP have active epilepsy varying in type depending on the type of the brain anomaly [40]. Some will require continuous long-term treatment in order to avoid repeated fits compounding the original cerebral anomaly.

The *third* most frequent associated impairment is visual impairment which can be a squint and/or a loss of visual acuity. Several studies report that about 15% of children with *CP* have a severe visual impairment (visual acuity below 0.01 on the better eye after correction) [41].

Severe hearing impairment, defined as a loss of 70 db or more in the better ear before correction, is rare in children with CP at around 2–3%.

Children with *CP* may also present with behavioural disorder, as a direct consequence of the brain lesion or as a consequence of their activity limitation and participation restriction. Severe psychiatric conditions such as autism are also infrequently observed in children with *CP* [42].

3.3.4 Severity Assessment in Children with CP

Using the classification systems described above, it may be possible to say that one child with CP presents with a more severe pattern of any particular facet of their impairments than another. This is very important when comparing study samples whether considering prevalence of CP, assessing medical or educational needs or

the appropriateness or efficacy of management interventions.

Clinicians usually consider severity in terms of loss of motor ability, possibly in combination with type of motor disorder [43], and the widespread use of GMFCS, BFMF and MACS have greatly increased the comparability of results between centres [44]. In Australia the Australian Spasticity Assessment Scale is used to categorise the severity of spastic impairment [45]. Another scale has been developed for dyskinesia based on the Barry-Albright Dystonia (BD) scale [46, 47]. In some studies motor function and intellectual impairment levels are used together to define mild, moderate and severe impairment [48–50], and in a study of life expectancy, the type and severity of motor impairment, together with impairments of intellect, epilepsy, sight and hearing, were combined into a 12-category overall disability score [51]. Ideally, the assessment of overall disability in the person with CP would be assessed by combining the standardised assessments of the many possible components of impairment. The challenge is to know how to weight the different components, since the contribution to disability of each individual component varies with the activities under consideration.

3.3.5 Classification Based on Neuroimaging Results

Following recent recommendations, [52] cerebral MRI is performed more frequently on children with CP, which together with improved image quality has allowed classification systems of brain images to be proposed, e.g. [53, 54]. Systematic classification is of great interest in epidemiological studies that seek to monitor trends over time for different groups of children with CP according to their cerebral pathology and also provides important information about the probable timing of the lesion responsible of the CP [53]. Not all children with CP receive cerebral MRI after the recommended 2 years of age; thus, a standardised classification has also been proposed for neonatal ultrasound imaging results (https://pehta.sites.innovatif.com/fib.scpenet/en/my-scpe/rtm/neuroimaging/neonatal-neuroimaging/). In both MRI and neonatal ultrasound imaging classifications, the main categories in the European system are maldevelopments, predominant white matter injury (PVL, IVH) and predominant grey matter injury (basal ganglia, cortical subcortical, arterial infarctions), while the Australian system separates out the focal vascular insults and reports that combinations of categories occurred rarely [54]. Population-based registers indicate a lesional pattern in more than two thirds of MRI results, more often predominantly in white than cortical or deep grey matter. Maldevelopments were observed in less than 10% of cases and normal findings in a bit more than 10% [53, 54]. Harmonisation of neuroimaging classifications and international consensus are important for the future [54], and training tools based on web imaging will be very helpful for the physicians and students [55]. Quantitative aspect may also be taken into account for neuroimaging classifications, and several have been proposed recently including one for unilateral spastic lesion [56] and a semi-quantitative one for all children with CP [57]; however these should currently be considered as research tools rather than tools for clinical practice.

3.4 Prevalence of CP and Time Trends

Prevalence estimates of CP are around 2 per 1000 live births (Table 3.1). Prevalence of CP is strongly associated with gestational age and birth weight. The rate is 1 per 1000 live births in children born at term, 7–10 times higher for children born moderately preterm (i.e. 32–36 weeks gestational age) and 60 times higher for children born very preterm (i.e. before 32 weeks gestational age) [15, 16, 58]. Prevalence is higher in males than female (rate ratio of 1.35) [59]. The prevalence is also higher for children born in multiple births, with risk increasing with increasing multiplicity. Multiples tend to be born more preterm than singletons, and their increased risk of CP is mainly related to the higher risk of

preterm birth in multiples even though there are also causal factors specific to multiple pregnancies such as cofetal demise and twin-twin transfusion [60]. The prevalence varies according to race/ethnicity with a higher prevalence rate for non-Hispanic black children than for non-Hispanic white children [11] and a higher rate for indigenous than for nonindigenous children [61]. Population-based studies on CP that have been conducted in developing countries [12, 18] surprisingly showed no large differences in prevalence rates between developed and developing countries. Nevertheless, disparities in methodology, age range, classification systems and populations make the studies difficult to compare to those made in higher-income settings [62].

The prevalence of CP of postneonatal origin, i.e. CP as a result of a recognised causal event occurring between the 28th day and 24 months, was estimated at 1.2 per 10,000 live births in Europe (birth years 1976–1998) [63] with a decrease over the period.

The oldest population-based registers have monitored the prevalence rate of CP since the 1950s. During several decades, no systematic time trend was observed apart from a slight increase in the 1980s [64]. In more recent years, SCPE has shown a decrease in CP prevalence for children born between 1980 and 2003 in Europe [10] with an important decrease for children born with a birth weight between 1000 and 1499 g (from 70.9 to 35.9/1000 live births), a significant decrease for children with a birth weight between 1500 and 2499 g (from 8.5 to 6.2/1000 live births) but no significant change for children born with a birth weight below 1000 g or over 2500 g. The decrease was observed primarily in bilateral spastic CP and concerned all levels of severity. In Australia, the ACPR reported, after a long period of stable prevalence at around 2–2.5/1000 1000 live births, a decline to 1.4–2.1/1000 in the 2007–2009 period [7]. Over the 2003–2009 period, the rate of CP/1000 live births reduced across all gestational age groups although there was a decrease in the proportion with co-occurring intellectual disability [11].

Moreover, studies on the different subtypes of CP suggest different time trends according to subtype. A decrease of bilateral spastic CP [65, 66] and an increase of unilateral CP were described for children born between 1983 and 1998 [66]. Prevalence of children with dyskinetic CP has also risen between birth years 1976 and 1996 [48].

3.5 Caution with Interpretation of Trends

Factors that may influence *CP* prevalence rates are numerous, and it is difficult to determine which ones are related to the observed changes in trends. Similarly, differences between estimated rates and overtime are not easily understandable even if we can suggest potential reasons. First, numerous methodological issues may have an impact on prevalence estimates including the type of ascertainment sources (e.g. schools, registers, administrative databases), the changes over time or between countries in the inclusion or exclusion criteria (e.g. inclusion of mild cases, postnatal cases or children with isolated hypotonia) and the denominators used. For a valid estimate of trend, each prevalence estimate contributing to the trend must be comparable. Even though registers attempt to maintain constant methods of ascertainment, changes in the external environment, such as privacy legislation or restructuring the provision of services for children with CP, necessitate "tweaking" ascertainment methods with the risk of affecting proportional ascertainment. Second, changes in the prevalence of determinants of *CP* are almost certain to result in changes in *CP* prevalence. For example, decreases in stillbirth and neonatal mortality rates are accompanied by an increase of the number of surviving children born extremely premature who remain at higher risk of CP than children born at term despite declining gestation-specific CP rates.

Since CP includes conditions resulting from many causal pathways together with the requirement for survival to an age at CP can be reliably recognised, the constant prevalence observed over many decades in developed countries and the equivalence of prevalence between developed and developing countries should not be interpreted as

constancy or equivalence of aetiological profile. The period of static prevalence in developed countries saw significant increases in the survival of compromised births and a consequent rise in their contributions to CP balanced by significant decreases in CP resulting from now preventable causes such as kernicterus secondary Rhesus incompatibility and maternal rubella and postneonatally to motor vehicle accidents and cerebral infections. In developing countries the aetiological profile may more resemble that which existed previously in developed countries: neonatal mortality removes compromised births, but the more technological preventive strategies may not be available, and unselected home births occur more frequently.

While lower CP prevalence is seen as most desirable from the human and service provision points of view, that desirability may be questionable if it comes at the cost of increased perinatal mortality.

Conclusion

The concept of cerebral palsy evolved recently with emphasis on the fact that it is very often accompanied by other neurosensorial impairments. Harmonisation in the way of describing CP led to improvements when monitoring *CP* rates and when comparing trends between countries and over time. However, several risk factors may also change over time, including those related to care delivered to pregnant women and care to the newborns. Thus, surveillance of *CP* should continue in both developed and developing countries.

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4 Philosophy, Epidemiology, and Cerebral Palsy Causation

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Abstract

In this chapter, I explore ideas from current philosophy of science in the context of cerebral palsy causation. Russo and Williamson suggest that causal claims in the health sciences require both difference-making (statistical) and mechanistic evidence. A recent account offered by Mumford and Anjum conceives of causation as the predisposition toward an effect. I review multiple aspects of this theory that would fit very well with our current concept of cerebral palsy causation. Dupré's theory of biological causation as a biological process is well aligned with the etiological model of causative factors that initiate the pathogenetic mechanism that culminates in clinical disease. Finally, I suggest to integrate the traditional epidemiological list of causal considerations provided by Hill in 1965 with Poston's recent explanatory coherentist theory.

4.1 Introduction

In this chapter I integrate findings (and opinions) published in the neuroscience, neuroepidemiology, and philosophy of science literatures from the perspective of cerebral palsy (CP) causation. I hope to spark the readers' interest, and perhaps even further research, at the intersection of these fields of inquiry. I am convinced that we can learn a lot from *current* philosophy of science about how we may want to conceptualize illness causation in general and cerebral palsy causation in particular.

Recently, philosophers of science have directed their attention toward causal explanation in the health sciences. To name only a few, Thagard [1], Williamson [2], Craver [3], Broadbent [4], Illari and Russo [5], and Reiss [6] have offered comprehensive discussions of causality in the health sciences. In what follows, I cannot offer an exhaustive review of their work. Instead, I have structured this chapter so that issues related to CP are explored in the context of pertinent recent philosophical ideas. Unfortunately, space constraints prevent me from offering the more detailed discussion the topic deserves.

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4.2 Etiology: Causes and Mechanisms

While some current online dictionaries define the term "etiology" as "(a) the study of the causes of diseases. (b) the cause or origin of a disease,"[1] others allow for a more comprehensive interpretation, e.g., "the cause, set of causes, or manner of causation of a disease or condition."[2] The latter version is in keeping with MacMahon and Pugh's definition, which conceptualizes etiology as "consisting of two parts: (1) causal events occurring prior to some initial bodily response, and (2) mechanisms within the body leading from the initial response to the characteristic manifestations of the disease" [7]. This distinction between causal initiators and mechanisms that connect causes and disease occurrence is not trivial (Fig. 4.1). While causes are studied by epidemiologists, who are interested in identifying causal risk factors for illness prevention, mechanisms are mainly studied by wet-lab biomedical scientists, who are interested in finding ways to interfere with the disease process. Achieving this twofold goal, to find causes of illness and to understand the disease process, requires consideration of knowledge from both areas of inquiry.

Illness causation research has received quite some attention in the philosophy of science arena in the past decade. Perhaps the most intense debate has revolved around what has come to be called the "Russo-Williamson Thesis" (*RWT*). Although not uncontended, the RWT holds that causal claims in the health sciences need support from both evidence of difference-making (i.e., statistical associations) and of mechanisms [9]. At least in part, this thesis might be rooted in the recognition that we need both epidemiological and pathogenetic evidence in order to generate a comprehensive etiologic understanding (see Chaps. 3 and 6). Alex Fiorentino and I have offered our epidemiological perspective that "exposure-outcome evidence (previously known as difference-making evidence) provides associations that can be explained through a hypothesis of causation, while mechanistic evidence provides finer-grained associations and knowledge of entities that ultimately explains a causal hypothesis" [10]. In the context of CP causation, this would mean that pathogenetic (biomechanistic) evidence that a certain experimental exposure *can lead to* perinatal brain damage explains the hypothesis that this exposure *does lead to* perinatal brain damage, which in turn explains epidemiological observations (once they are in fact made) that a similar exposure is associated with perinatal brain damage (see Chap. 3). Carmina Erdei and I have recently outlined how a classic epidemiological framework of illness causation [11] can be reinterpreted to include both talk about risk factors and talk about biomechanisms in the context of autism causation [12].

Of note, I take epidemiological studies to include both noninterventional "observational" (cohort, case control) and intervention studies (randomized controlled trials). Despite their "gold standard" status in medicine, philosophers

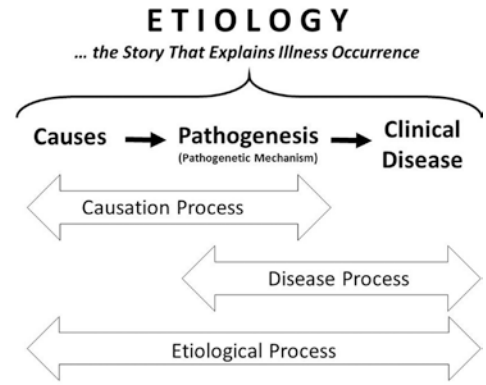

Fig. 4.1 The etiological stance (with permission from [8])

[1] http://dictionary.reference.com/browse/etiology; accessed 2/19/2016

[2] http://www.oxforddictionaries.com/us/definition/american_english/etiology; accessed 2/19/2016

are not entirely convinced that randomized trials are epistemologically superior to noninterventional studies [13, 14].

4.3 Causes: Risk Factors as Dispositions

At the core of cerebral palsy causation research is the recognition that the simple cooccurrence of a certain factor deemed the causal culprit, and the clinical phenotype of CP in an individual is *not* sufficient as a causal explanation. Beyond anecdotal data, we need statistical evidence that a purportedly causal factor occurs significantly more often in individuals with CP compared to controls. This frequentist comparative approach [15], enriched by statistical analysis, is the current state-of-the art methodology in the search for preventable risk factors. Part of the reason for the development of this methodology was the recognition that most risk factors do not occur in *all* cases, while not being absent in *all* controls. Instead of being deterministic predictors of CP, most risk factors are probabilistic antecedents of CP. I have previously, with Alan Leviton, discussed this misconception (and a few others) in the context of perinatal brain damage causation [16].

In philosophy of science, probabilistic accounts are at the forefront of biological models of causation. Spearheaded by Reichenbach, Suppes, and Eells, probabilistic theories of causation replace deterministic causal regularities with probabilistic ones. This has consequences for how we frame predictions. For example, the notion that "perinatal asphyxia leads to CP" is replaced with "perinatal asphyxia increases the risk of CP." In other words, we replace a rigid "always" with a deliberately wobbly "sometimes," and we replace fixed sequences of cause and effect with a sequence that can only be captured in probabilities.

Dispositional (or "power") theories fit notions of CP causation rather well are. For example, Mumford and Anjum's "pan-dispositionalist" theory holds that "a cause should be understood as something that disposes towards an effect" ([17], p. 19). In their language, asphyxia is a cause of CP because it disposes toward CP development, carefully circumventing deterministic terminology. Moreover, their theory allows for multiple kinds of causes in that what contributes to an effect is a cause of it ([17], p. 33). In this sense, preterm birth is not just a background condition of CP but a cause of it. This view is particularly helpful if one wants to identify causal background conditions that are potentially preventable. The dispositionalist view also agrees with the general notion that illness causation is multivariable: "powers (a.k.a., dispositions; OD) can partner with …any number of other powers to manifest an effect together" (17, p. 35). Finally, their approach agrees with the idea that causation is a process, which I discuss in the next section. In particular, they hold that the cause and effect coexist in time, thereby offering a philosophical model for the hypothesis [18] and subsequent observation [19] that systemic inflammation and the clinical CP phenotype are present and detectable at the same time.

4.4 Causation: From Insult to Process

The causation of CP was initially addressed by Osler, Freud, and Little (see Chap. 1). These earlier discussions must have led more recent scholars (Wigglesworth, Volpe) to the perception that CP is caused by *insults with immediate impact* on the structure of the immature brain. For example, main candidate insults discussed in texts published in the 1990s were "perinatal asphyxia" [20] and "hypoxia-ischemia" [21] (see Chap. 6).

The current view goes beyond the immediate consequences of insult view and favors a *process* view of CP causation [18, 22]. Although lack of oxygen may still play a role in CP causation among

term newborns, it is unlikely that hypoxia and/or ischemia are involved in CP causation in preterm infants [23]. A scenario involving exposure to inflammation appears to explain CP occurrence in both term and preterm infants [24]. Indeed, there is ample evidence that supports the notion that what Karin Nelson and Eve Blair suggest for children born at or close to term is also the case among infants born preterm [25]: "the chief antecedents of cerebral palsy […] are not single-cause events or injuries occurring at a specific point in time; instead, they are disordered developmental processes" [26].

Process causation is one of many ways how causality can be conceptualized ([5], pp. 111–119). While earlier process theories were mainly aimed at causal explanation in physics [27, 28], recent ones seem to be more relevant to biological systems. For example, John Dupré thinks that the equation of causation and mechanism is too simplistic; instead, he suggests that

> the entities that form the hierarchy of biological ontology are not stable. They are, rather, stabilized over a very wide variety of timescales, and the processes of stabilization are a fundamental part of the explanation of the activities of living systems. Living things are the explananda in biological sciences at least as much as they are the explanantia. What are stable and robust in biology are not things, but processes ([29], p. 30).

The view that biological causality is a process is mirrored in cerebral palsy causation research by notions of process like the one in the above quote from Nelson and Blair [26]. Whether and how such process views of biological causation differ from mechanistic accounts [30] has yet to be explored. In particular, it will be interesting to work out how multiple processes might interact in CP causation, thereby explaining the different pathways to CP [31].

4.5 Causal Inference: Explanatory Coherentism

In this final section, I want to respond to the second part of the question posed by perinatal epidemiologist Mervyn Susser, "What is a cause and how do we know one?" [32]. The answer will lead us from the metaphysical question of what constitutes a proper cause to an epistemological one, how do we detect causes?

The traditional model of causal inference in modern epidemiology was proposed by Sir Austin Bradford Hill in 1965 [33]. Hill's goal was to provide a list of characteristics of epidemiological studies that should be considered evidence that an observed association is causal: strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. Without going into further detail, these "viewpoints" (Hill's term) are sometimes called "criteria," which they are not, as readily acknowledged by epidemiologists [34, 35] and philosophers [4, 36]. Moreover, it has been suggested that they "are likely to fail in complex landscapes (causal systems)" [37]. This notion is contradicted by the facts that all illness causation is complex in the sense of having a multivariable etiology and that the Hill viewpoints are still around half a century after their publication.

Paul Thagard suggests that "the inference that a factor is a cause of a disease is based on explanatory coherence: We can infer that the factor causes the disease if this hypothesis is part of the best explanation of the full range of evidence" ([1], p. 129). Thagard anticipated the RWT (vs.) multiple years before it was published; he suggested that mere correlation is not enough to establish causal claims and that causal confidence is increased by mechanistic evidence ([1], p. 129). Currently, I work with Thagard and Ted Poston, a defender of explanatory coherentism [38], on a project that envisions Hill's viewpoints as both a concise explanatory coherentist framework for epidemiologists and as one component of a larger explanatory coherentist framework for medical bioscientists in general. In my future work, I will attempt to demonstrate that Hill's viewpoints (and how well evidence fits them) may be used as the theoretical basis for the computational formalization of causal inference and explanation in public health informatics [39].

Conclusion

In this chapter I have shown that some recent ideas and proposals from philosophy of science can help structure and clarify our thinking about CP causation. I propose that it will

be helpful to develop an integrated concept of etiology as including purported causes (epidemiological risk factors) and (pathogenetic mechanisms see Chaps. 3 and 6). It makes sense to view risk factors as dispositions toward CP development, to view CP etiology as a process, and to embrace explanatory coherentism as a potentially fruitful way to integrate causal evidence. I hope to further develop these ideas in a general theory of systems causation of illness that will help with causal inference and explanation in the health sciences.

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Neuropathology of Cerebral Palsy

5

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Abstract

The clinical picture of cerebral palsy (CP) develops subsequently to hypoxic/ischaemic or inflammatory/toxic injury of the developing central nervous system in the pre-, peri- or postnatal period. The distribution of lesions reflects peculiarities of foetal vascular development, increased vulnerabilities of developing cells or supply territories of the basal cerebral arteries. The present chapter focuses on pathophysiological aspects and the neuropathological alterations observed in CP. The pathologies described comprise (a) periventricular leukoencephalopathy which is predominantly seen in preterm births and may impress as small infarcts or gliotic foci, (b) germinal/ventricular haemorrhage mainly affecting preterm neonates presumably resulting from hypoxic damage to the endothelium of immature vessels in the germinal layer, (c) por-/hydranencephaly developing in the 5th gestational month following systemic hypotension, (d) pontosubicular neuronal apoptotic necrosis observed between the 30th gestational week and the 2nd postnatal month after severe systemic hypoxia, (e) cortical border zone infarction/ulegyria, (f) territorial infarction due to occlusion of a basal cerebral artery in mature neonates up to infant age, (g) marbled state referring to bilaterally abnormally myelinated scars in the basal ganglia and thalami due to lesioning in the perinatal period until an age of 6–9 months, and (h) multicystic encephalopathy, a global hemispheric necrosis developing postnatally up to an age of 18 months. The neuropathological findings particularly underline the importance of localization, extent and timing of brain injury for the clinical picture, whereas data on brain development may indicate possible time windows for therapeutic intervention.

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5.1 Introduction

Hypoxia-/ischaemia-related brain damage is a major factor for morbidity and mortality not only in the adult but also in the pre- and perinatal period where it clinically frequently presents as cerebral palsy (CP). Despite considerable progress in obstetrics, the prevalence of CP has remained stable for more than four decades with two to three cases per 1000 live births of which about half are born premature and half at term [1]. The present chapter describes pathophysiological aspects of CP in relation to brain development and delineates the morphological alterations in CP. The neuropathological findings particularly underline the importance of localization, extent and timing of brain injury for the clinical picture, whereas data on brain development may indicate possible time windows for therapeutic intervention (see also Chaps. 6 and 7).

5.2 Brain Development and Pathophysiology of Cerebral Palsy

The insult on a developing system has its own special risk factors, pathophysiology and morphology. Depending on the developmental stage of the brain, different regions and cell types may show an increased vulnerability to injury leading to defined tissue defects and developmental alterations. Table 5.1 gives an overview of the ontogenesis of the brain.

As depicted in Table 5.1, the vascularisation of the brain starts at the time of the closure of the neural tube around day 28 of gestation. The primordial vessels present as an indistinct meshwork, also called the head plexus. One to 2 days later, the internal carotid arteries can be recognised which join at their caudal divisions to form the posterior communicating artery at day 29. By day 32 the basilar and vertebral arteries are formed, and at day 35 the anterior cerebral arteries become distinguishable at the anterior divisions of the internal carotid arteries, and the medial cerebral arteries evolve as lateral branches of the proximal anterior cerebral arteries. As dorsal branches of the mesencephalic arteries extend, they take over the territories of the posterior cerebral arteries which are supplied by the internal carotid arteries at earlier stages of development. Between day 44 and 52, the mature pattern of vascularisation with the circle of Willis and the cerebral arteries is completed [2].

Table 5.1 Ontogenesis of the brain

Brain structure	
Neurulation	3rd–4th gestational week
Pons	5th gestational week–3rd trimester
Cerebellum	4th gestational week–15th postnatal month
Basal ganglia	13th gestational week–12th postnatal month
Induction of the telencephalon	5th gestational week
Cortical lamination	2nd–3rd trimester
Cortical gyrification	14th gestational week–2nd year of life
Corticospinal tract	Starts 1st trimester–reaches spinal cord 2nd trimester–postnatal refinement until mid-adolescence
Neuronal development of the telencephalon	
Proliferation of neuroblasts	5th–30th gestational week
Migration of neuroblasts	6th–35th gestational week
Axonal/dendritic growth	10th gestational week–end of 5th year of life
Neurotransmitter synthesis	From 8th gestational week
Formation of synapses	From 8th gestational week
Glial development	
Mature astrocytes	From 15th gestational week
Myelination	14th gestational week–adolescence
Vascular development	
Circle of Willis	End of 4th gestational week–8th gestational week
Vascularisation of basal ganglia and diencephalon	5th gestational week to 24th–28th gestational week
Long penetrating arteries supplying the deep white matter	16th–23rd gestational week
Short penetrating arteries supplying cortex and subcortical white matter	23rd gestational week–postnatal period

Like in adults a complete occlusion of a cerebral artery may occur leading to cerebral infarction and consecutively to congenital hemiplegia. The lesions are mainly seen in mature infants [3]. The causes for the development of thromboemboli are manifold and include among others disorders of the heart (patent ductus arteriosus, pulmonary valve atresia, etc.), alterations in composition of the blood (homocysteine, lipids, polycythaemia, Factor V Leiden, Protein S and C deficiency, abnormal prothrombin, etc.), infections, vascular malformations, trauma, birth asphyxia, dehydration, diseases of the mother and placental alterations.

The border zones or *watershed regions* between the main basal cerebral arteries play an important role in hypotensive brain injury occurring around term. On the brain surface, these border zones form a parasagittal line, whereas in the parenchyma, the borders of the anterior and middle cerebral arteries run anterior to the frontal horns of the lateral ventricles, and the borders between middle and posterior arteries are located in the white matter around the occipital horns [4]. Parasagittal cortical border zone infarctions in term infants may appear as so-called ulegyria (gyral scarring) [5]. Clinically the patients may present with mental retardation, motor deficits and epilepsy. However, ulegyria may also occur within the territory of one major cerebral artery.

The intrinsic vasculature of the brain develops around week 5 of gestation with large penetrating arteries running as branches of the middle cerebral arteries from the base of the brain to the basal ganglia and diencephalon as well as to the germinal matrix of the subependymal periventricular zones. The germinative zones show a high angiogenesis and high levels of cyclooxygenase and vascular growth factor [6]. The vascularisation of the basal ganglia and the diencephalon is completed by 24–28 weeks of gestation.

Regarding the maturation of the vascular walls, an arterial muscular layer appears at 20 weeks in striatal vessels, at 24 weeks in the putamen and at 26 weeks in the caudate nucleus. A clear arteriovenous differentiation of extrastriatal parenchymal vessels is apparent only in the last weeks of gestation [2]. Hence, the penetrators ending in the germinal matrix only consist of a single layer of endothelium. Direct damage to the endothelium due to hypoxia possibly aggravated by hypercarbia-induced increase in blood flow has been proposed as cause for periventricular and intraventricular haemorrhage [7] which originates from the germinal layer in the vicinity of the terminal vein between the thalamus and caudate nucleus. In accordance injections into the carotid artery of preterm infants resulted in leakage of injected material into the capillary bed of the germinal layer, suggesting that the capillaries, which are supplied with blood by Heubner's artery, may rupture by a rise in arterial pressure, particularly in conditions of hypercapnia and hypoxia [8]. Minor maternal trauma was proposed as possible cofactor for the development of subependymal and intraventricular haemorrhage [9]. Tissue necrosis as possible cause of the haemorrhage was suggested by Towbin [10], which is in accordance with the observation that the two conditions may coexist in up to one third of patients, although in different locations [11].

Blood supply of the white matter occurs from the surface of the convexity through long penetrating thin vessels which descend between the 16th and 23rd week of gestation followed by short penetrating arteries which become recognisable from the 23rd gestational week onwards and supply the cortex and subcortical white matter [12]. The development of the short penetrating vessels accompanies the rapid cortical organisation, axonal outgrowth and formation of synapses that takes place in this period [13]. The short cortical arteries are not fully developed until post-term period resulting in relatively low blood supply of the subcortical white matter [14]. This area is typically affected in the diffuse and subtle type of periventricular leukomalacia (PVL) which nowadays accounts for 90% of PVL patients. The regions corresponding to the endpoints of the long penetrating arteries match with the focal necrotic type of PVL mainly observed in very low birthweight survivors [15]. In fact, PVL appears to be the most important factor for neurologic morbidity in very low birthweight infants (<1500 g). In a series reported by Banker and Larroche [16], periventricular infarcts were

found in 19% of infant autopsies, and 64% of these cases were premature infants. In an investigation by Shevell et al. [17], 24.9% of a total of 217 patients suffering from CP had a history of periventricular leukomalacia. The most important factor for the development of periventricular infarcts is a severe perinatal anoxia necessitating resuscitation.

The white matter, which is injured in PVL, comprises oligodendroglial progenitors, growing axonal pathways and the subplate zone. The latter harbours a variety of axonal guidance molecules making it both a substrate and a gradient zone for the navigation of thalamocortical axons [18]. Focal hypoxic-ischaemic damage of the periventricular regions supplied by long penetrating arteries affects crossroads of projection, associative and commissural fibres, whereas injury of the *watershed regions* between short and long penetrators may also strike the subplate zone and disturb the formation of cortical connections.

Damage to oligodendroglial precursors between weeks 24 and 34 of gestation results in PVL. In vitro experiments showed margination of chromatin, nuclear condensation and DNA fragmentation in injured oligodendroglial precursors consistent with apoptosis as the mode of death [14]. In vitro studies further demonstrated that oligodendroglial precursors are vulnerable not only to oxygen/glucose deprivation but also to free radicals and cytokines [19]. The cells express lower levels of antioxidant enzyme manganese-containing superoxide dismutase which catalyses the dismutation of superoxide to hydrogen peroxide and oxygen. In addition, oligodendroglial precursors are more vulnerable to excitotoxic injury by kainate than mature oligodendroglia because they express α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA)-kainate receptors. Lastly, cytokines like interferon-γ are released in the context of intrauterine infections and may affect oligodendroglial precursors (for *review* see [7]). As possible source of toxic molecules, microglia was identified which may not only release these substances consecutively to asphyxia but also in infections and a number of other pathological conditions [20]. Accordingly, an association of PVL with streptococcal sepsis in preterm infants ([21]; see also Chap. 7) and a 9.4-fold greater risk of antenatal PVL for preterm neonates with purulent amniotic fluid [22] was found. Further, an overexpression of tumour necrosis factor-alpha and IL-6 could be demonstrated in neonatal brains with PVL [22].

Pontosubicular neuronal necrosis is observed between week 30 of gestation until 2 months postpartum occurring consecutively to hypoxia/ischaemia or hypoglycaemia. It presumably relates to an increased perinatal hypoxic vulnerability of pontine and subicular neurons. However, the pyramidal cells of the subiculum as well as in CA1 and CA2 also belong to the most vulnerable neurons concerning hypoxia/ischaemia in the adult. The affected neurons in pontosubicular necrosis show the typical picture of apoptosis including apoptotic bodies and DNA fragmentation. In addition, the Fas/Fas ligand system and caspase-3 were revealed to contribute to pontosubicular necrosis [23].

CP is not exclusively a disorder of the brain but also involves the neuronal circuitry of the spinal cord. Development of the corticospinal tract starts in the first trimester, but establishing effective connections between motor cortex and muscle takes until near term. Postnatally synaptic connectivity is refined until adolescence depending on activity of spinal neurons. In an early phase, which lasts until the age of 6–12 months, laterality of the initial bilateral spinal projections is determined by synaptic competition. In the second phase, which lasts until adolescence, the strength of synaptic connections is shaped (for *review* see [24]).

5.3 Animal Models

Animal models play an important role in CP research since they allow studying the pathophysiology of this heterogeneous disorder systematically in living organisms. However, the relevance of the results may—just as in vitro experiments—be of limited value to human pathology. Mammals with a gyrencephalic brain and a gestation time of several months like rabbits, sheep

and primates resemble the human situation better than small rodents such as mice and rats.

Gunn and Bennet [25] reviewed data from hypoxia in foetal sheep pointing out that the brain can fully adapt to a moderate reduced oxygen supply down to 10–12 mmHg as long as substrate delivery is assured and no hypotension occurs. In this situation vasoconstriction redirects blood flow to the heart and brain, oxygen extraction from the blood increases and the brain switches to lower EEG frequencies. Energy consumption of the cells may be reduced by reduction of nonobligatory energy consumption via inhibitory neuro-modulators like adenosine. To some extent anaerobic glycolysis can become a source of energy.

Asphyxia without hypotension is associated with only modest brain damage. Neuronal loss in foetal sheep was only seen if in addition to prolonged severe partial asphyxia (partial occlusion of the uterine artery), episodes of acute hypotension occurred. Therefore, acidosis resulting from asphyxia is by itself a clinical measure with only limited predictive value.

The predominant mechanism of brain injury is severe hypotension which after a short phase of compensative vasoconstriction leads to progressive deterioration of brain function. In the course of events, the blood flow is diverted from the cortex to the basal ganglia and brain stem. The initial vasoconstriction ceases and finally a profound systemic hypotension develops.

In transient (*peripartal*) hypotension (*successful resuscitation*), a short period of clinical recovery may be seen after normalisation of blood and oxygen supply, both in animal models and in newborn infants. Nevertheless, if the brain damage initiated a cascade of biochemical reactions leading to delayed cell death, a second phase of deterioration will follow 6–15 h after birth.

Due to redirection of blood flow to the brain stem and the basal ganglia in hypotension, these areas are often spared from injury. A single ischaemic insult of 30 min mainly resulted in neuronal loss in the parasagittal cortex (*watershed regions*) in near-term foetal sheep. However, after three 10-min episodes of hypotension at 1-h intervals, the striatal damage prevailed the cortical injury. Since the injury affected primarily inhibitory striatal neurons Gunn and Bennet [25] speculated that the damage might in part result from abnormal excitatory inputs to these neurons. Lastly, the authors underlined the neuro-protective effect of hypothermia which is disproportionate to the changes in metabolism associated with the temperature change. This correlation also applies to an increase in body temperature. *Hyperthermia* of 1–2 °C markedly worsens brain damage.

Inder et al. [26] presented an animal model of periventricular leukomalacia in the baboon which differed from other models in that there was no direct insult other than the standard neonatal intensive care situation. A white matter injury occurred in 50% of the animals and was mostly located in the parietal and occipital lobes. In addition, haemorrhages were seen in the subarachnoid space (38%), ventricles (5%), germinal matrix (9%), white matter (28%) and cerebellum (9%).

A model for peri- and intraventricular haemorrhage was presented by Chua et al. [27] using rabbit pups. The risk of spontaneous germinal matrix haemorrhage in premature rabbits could be increased from 10 to 80% by intraperitoneal administration of glycerol. This procedure resulted in dehydration and high osmolarity of the serum and arterial hypotension leading to haemorrhage. Posthaemorrhagically 70% of the pups survived for 14 days or longer developing ventriculomegaly, motor dysfunction with increased muscle tone or complete paralysis. Upon autopsy gliosis and reduced myelination of the white matter were noted. Hence, the model mimics many of the clinical and histopathological alterations found in germinal matrix haemorrhage in preterm infants. However, the authors also pointed out some limitations of the model. Since the pups were delivered by caesarean section and hand-fed, the model is somewhat laborious. Furthermore, glycerol may potentially open the blood-brain barrier which would lead to metabolic changes. Like Inder et al. [26] the work of Chua et al. [27] mainly focused on the reproduction of certain clinical and morphological aspects of perinatal brain injury; new data on the pathophysiology and biochemical signal cascades of the disorder was not presented.

A more recent study focused on the activation of the inflammatory cascade in chronic foetal hypoxia in the guinea pig [28]. The authors confirmed earlier data of alterations in mRNA levels of P53, Bax and Bcl-2 involved in proliferation and apoptosis. Further, a significant neuronal loss in the hippocampus was demonstrated as well as an upregulation of inflammation cytokine genes by means of quantitative RT-PCR. Three cohorts of six animals were held in chambers with normoxia or 12.5% and 10.5% oxygen, respectively. Of 22 cytokines that showed changes in expression levels under hypoxic conditions, TNF-α and IL-1β were upregulated under hypoxia in a dose-dependent manner.

5.4 Morphology of Brain Lesion Associated with Cerebral Palsy

5.4.1 Haemorrhage

Subependymal, intraventricular or leptomeningeal haemorrhages are the most common autoptic pathological finding in brains of premature asphyctic infants. Most haemorrhages were found between 5 and 35 h postpartum for gestational ages between 27 and 31 weeks [29]. In an autoptic study by Leech et al. [30] on 170 infants with respiratory distress syndrome, the most common sites of intracranial haemorrhage were found to be the subependymal tissue (60%), the ventricles (68%), the subarachnoid space (44%) and the dura (intradural 48%, subdural 3%).

Subependymal bleeding spreads within the germinal tissue and may disrupt the ependyma resulting in intraventricular haematoma. Massive haematomas may occlude the aqueduct and obstruct the flow of CSF. Cases in which the subependymal parenchyma is destructed may later suffer from cerebral palsy [31]. On autopsy fresh lesions are readily identified macroscopically and impress as masses of erythrocytes on histological examination (Fig. 5.1a). Haematomas are resolved by macrophages, some of which remain within the residual cystic defect as haemosiderophages.

Subarachnoid haemorrhage may result from spreading of an intraventricular bleeding to the brain surface but may also arise independently in asphyctic conditions in any location over the cerebral hemispheres, probably resulting from capillary diapedesis. Subsequently to subarachnoid haemorrhage, obstructive hydrocephalus may develop, either acute from haematomas clogging the basal cisterns or over a longer period of time due to fibrosis of the subarachnoid space. Furthermore, a superficial siderosis may develop as demonstrated by MR imaging of seven infants [32]. In adults the siderosis may lead to ataxia due to neuronal degeneration predominantly of Purkinje cells in the cerebellum.

Intradural haemorrhage into the falx and tentorium may frequently be observed in term and premature infants, is absorbed quickly without residua and has no clinical significance.

Subdural haematomas are most often related to head trauma at delivery. They result from a rupture of a bridging vein between dura and arachnoidea.

5.4.2 Prenatal Neuronal Death

Neuronal necrosis in premature infants typically is observed in the ventral pons and subiculum of the Ammon's horn [6]. In infants delivered before the 28th gestational week, karyorrhexis may also be observed in other brain regions such as the inferior olivary nucleus, the cerebellum, the basal ganglia, thalamus and cerebral cortex, implicating that neuronal maturation as one of the pathogenic factors for this type of neuronal necrosis [33]. The alterations are related to asphyxia at birth and are frequently associated with subependymal haemorrhage or infarcts [34].

Upon autopsy, there is no macroscopic alteration of the hippocampus and pons. Histological examination reveals scattered shrunken eosinophilic neurons with condensed and karyorrhectic basophilic nuclei in the subiculum of Ammon's horn and in the ventral pons in fresh lesions (Fig. 5.1b). The damage in the subiculum diminishes towards the hippocampal CA regions and towards the parahippocampal gyrus.

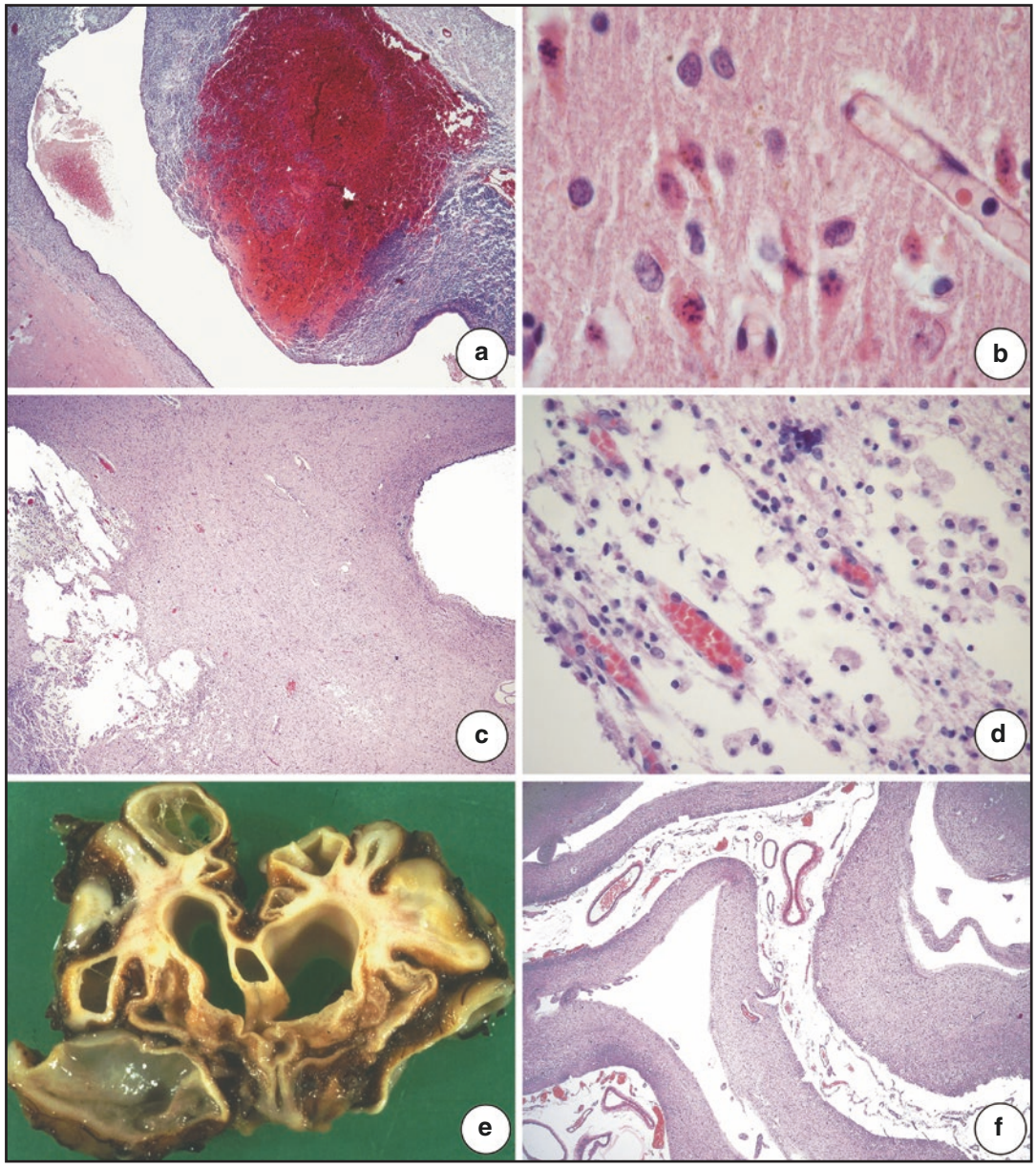

Fig. 5.1 Pathology of pre- and perinatal brain lesions. (**a**) Fresh haemorrhage in the germinal layer in a female foetus with a malformation of the heard, 25th gestational week (H&E, original magnification ×5); (**b**) fresh neuronal necrosis presenting as eosinophilic neurons with karyorrhectic nuclei in the subiculum of a male foetus, intrauterine death at the 38th gestational week (H&E, original magnification ×250); (**c**) old absorbed ischaemic periventricular leukomalacia in an asphyctic female infant suffering from a tumour of the heard, born at the 38th gestational week, survival 24 days (H&E, original magnification ×25); (**d**) same case as in **c**, numerous macrophages and foam cells are present at the borders of the lesion (H&E, original magnification ×100); (**e**) macroscopic findings in multicystic encephalopathy of a female full-term infant with perinatal asphyxia born by caesarian section; (**f**) same case as in **e**, histological overview showing gliotic remnants of the cortex (H&E, original magnification ×5); (**g**) immunohistochemical labelling of reactive astroglia at the border of the necrosis, same case as in **e** (GFAP, counterstain haemalum, original magnification ×100); (**h**) immunohistochemical labelling of residual axons and axonal swelling in the cortex of multicystic encephalopathy, same case as in **e** (neurofilament, counterstain haemalum, original magnification ×100)

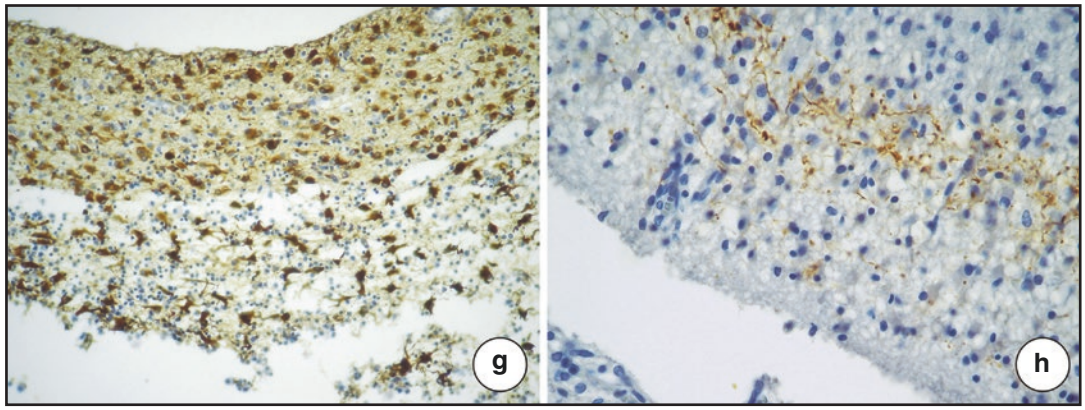

Fig. 5.1 (continued)

An astrocytic response to the injury develops after 3–5 days [6]. The neuronal necrosis is absorbed by macrophages and activated microglia within a few weeks; some of the affected neurons may mineralize. Since the glial elements persist, the lesion does not impress as a defect, but the parenchyma may focally show a spongy texture.

Karyorrhexis is a feature of programmed cell death, and accordingly previous studies have demonstrated fragmentation of DNA as indicator of apoptosis in pontosubicular necrosis [35] as well as expression of apoptosis-related protease caspase-3 and poly-ADP-ribosylated proteins [36].

5.4.3 Periventricular Leukomalacia

On autopsy, the necrotic lesions macroscopically impress as pale, yellowish or chalky, sharply demarcated areas measuring a few millimetres in diameter with a distance of 1–15 mm from the ependymal surface (see Chaps. 1 and 6). A perifocal oedema may present as softening of the adjacent tissue. In the course of absorption, the lesions become cystic cavities which contain cell debris and later clear extracellular fluid; finally a ventricular enlargement is seen. The defects are separated from the ventricles by glial tissue. Most frequently the infarcts are located anterior to the frontal horns, near the lateral corners of the lateral ventricles and lateral to the occipital horns. The size and weight of the brain may be normal, but a reduction in the volume of the brain is seen in the dissected brain with enlargement of the lateral ventricles and a thin corpus callosum. Since the upper part of the pyramidal radiation runs near the lateral corners of the lateral ventricles, periventricular leukomalacia frequently results in diplegia of the legs.

Histologically the earliest signs of necrosis consist of a sponginess of the tissue, cytoplasmic eosinophilia and nuclear pyknosis. The microglia is activated in the vicinity of the lesion, macrophages invade the necrosis from its borders and astrocytes proliferate (Fig. 5.1c, d). The absorption of necrotic tissue is completed by 3–4 weeks. Mineralisation of axons near the lesions may be observed. Most lesions are ischaemic; hence, no haemosiderin may be found in the lesion in contrast to periventricular haematomas. However, haemorrhages may occur subsequently to focal tissue necrosis which may be massive [37]. PVL may occur in association with status marmoratus of the basal ganglia [38] or cortical infarction [39]. In severe cases the entire white matter may be involved resulting in a spongy state formed by multiple cavities.

In the more diffuse form of PLV, typical alterations include an astrogliosis and temporary microglial activation, but total tissue necrosis with formation of cysts is not observed.

5.4.4 Cortical Infarction

Upon autopsy acute border zone infarctions (ulegyria) are rather indistinct lesions and may be missed on inspection. In the phase of absorption, the lesions are more easily identified as cortical defects or narrowing of the cortex at the bottom of the gyri.

Histologically acute lesions present as pale spongy oedematous tissue with neuronal chromatolysis, nuclear pyknosis and dissolution of neurons. Within a few weeks, a massive proliferation of glia and blood vessels and an abundance of macrophages are seen. The residual state of the *necrosis* is characterised by partial or total neuronal loss and a radial gliosis in the form of small gliotic scars extending from the bottom of the lesion towards the pia mater resulting in an irregular granular appearance of the cortical surface (granular atrophy). A possible explanation for the peculiar morphology of the lesions was given by Norman [40] who presented a case of ulegyria in which viable neurons were found along cortical arteries descending from the leptomeninges interspersed by stripes of neuronal necrosis. Hence, the radial scarring may represent microscopically small border zones between penetrating arteries in an immature cerebral vasculature. Ulegyria may also present as laminar necrosis mainly affecting the large neurons in the third cortical layer. Further, in minor lesions abnormally orientated myelinated fibres may be present (plaques fibromyeliniques) which are similar to status marmoratus of the basal ganglia. Depending on the damage of the grey matter, a rarefication and gliosis of the underlying white matter may be encountered. Although the cerebellar cortex is less vulnerable to hypoxic-ischaemic injury in newborn, some infants also suffer from border zone infarctions between the superior cerebellar artery and the posterior inferior cerebellar artery presenting as gliotic band along the edge between the convex basal surface and the flat upper cerebellar surface.

Territorial infarction due to complete thromboembolic occlusion of a cerebral artery is most frequently observed in the territory of the left middle cerebral artery which may be explained by haemodynamic differences due to a patent ductus arteriosus and by the shorter distance between heart and left carotid artery in comparison to the right side. The middle cerebral artery originates as direct continuation of the internal carotid artery and supplies the largest part of the premotor and motor cortex. The earliest morphological alteration consists of oedema presenting as spongy state around the necrosis. In the majority of cases, the thromboembolus undergoes lysis resulting in secondary haemorrhagic transformation of the lesion. Within a few weeks the necrotic tissue is absorbed by macrophages leaving a cystic cavity behind which is filled with cerebrospinal fluid and surrounded by a dense astrocytic gliosis. In haemorrhagic lesions haemosiderin may be detected.

5.4.5 Status Marmoratus

Marbled state of the basal ganglia was first described by Anton [41] and refers to abnormally myelinated scars in the basal ganglia frequently seen bilaterally. Additionally to the striatum and thalamus, the claustrum, the red nucleus and the subthalamic nucleus may be affected, whereas the substantia nigra, amygdala and mammillary bodies are usually spared. Clinically the children may show bilateral *choreoathetosis* from early infancy, mental retardation, motor deficits, spastic paraplegia and epilepsy. In a compilation of data from 42 well-documented cases given by Friede [6], an association with complicated delivery was observed in 70% of the cases. About half of the cases reported were full-term infants and less than 5% premature births; the rest was without data.

Early lesions in infants about half a year old are not associated with macroscopic changes but histologically present as randomly distributed myelinated fibres within glial scars of microinfarctions of the striatum [42]. Late lesions in contrast are visible with the naked eye and present as white spotty irregular areas. The affected nuclei may be of normal size or show different degrees of atrophy.

Microscopically late lesions are characterised by focal loss of neurons and a network of thin dispersed myelinated nerve fibres which are not grouped in bundles like in the normal striatum. The thin nerve fibres cross the gliotic area and continue in the normal parenchyma. Mineralised neurons may commonly be found in the affected areas.

In electron microscopic studies, abnormally thick myelin sheaths were found covering structures which were thought to represent astrocytic processes [43]. However, Friede and Schachenmayr [42] exclusively observed myelinated nerve fibres in marbled state. The findings of Friede and Schachenmayr [42] were later confirmed by immunohistochemical studies on 12 cases with marbled state which demonstrated that glial fibrillary acidic protein (GFAP)-expressing astrocytes showed no continuity with abnormally myelinated fibres [44]. Hence, the data suggests that status marmoratus is caused by microinfarcts developing perinatally or in early infancy which may be caused by repeated hypotensive episodes (see Sect. 5.3). Upon scarring a disorientation of fibres occurs which sprout through the lesion. The deviant fibres are abnormally myelinated, including myelination of normally unmyelinated fibres. Since myelination in the basal ganglia starts approximately in the sixth postnatal month, marbled state may not form later than within the first 6–9 months of life.

5.4.6 Lobal Hypoxic-Ischaemic Encephalopathy

Cerebral injury during early development results in deviant formation of cerebral structures. Depending on the severity of the insult, a necrosis may present as circumscribed hemispheric lesion termed porencephaly or as massive hemispheric necrosis termed hydranencephaly in which the residual parenchyma of the hemispheres forms thin-walled fluid-filled bubbles.

Porencephaly develops in utero before the adult features of the brain manifest [45]. The defects are commonly found in the insula and pre- and postcentral gyri and are in continuity with the ventricular walls. The frequent bilateral manifestation indicates a systemic hypotension as causative event. On the brain surface, the lesions are covered by a thin arachnoid membrane. The septum pellucidum is usually absent. The bordering cortex may either show polymicrogyria, which may be present in a patchy pattern over the hemisphere, even distant to the defect, or the gyri adjacent to the lesion may radiate towards the defect. There is no or little gliosis around the lesion. Frequently a loss of the laminar architecture of the cortex is observed with irregular, sometimes heterotopic masses of grey matter near the porus. Some pyramidal neurons may be transformed into local-circuit interneurons, and some of the interneurons may be enlarged [46]. On the basis of polymicrogyria, porencephaly may be dated to develop in the fifth month of gestation.

Infants presenting with hydranencephaly often die at delivery if the basal ganglia and the hypothalamus are affected; the other patients show neonatal automatisms, absence of motor development, spasticity and epileptic seizures. At birth the cranial size may be normal or microcephalic with an enlargement occurring in the following months, attributed to gliotic stenoses of the aqueduct or of the foramina of Monro. The defects in the hemispheres usually occur bilaterally and typically correspond to the territories of the carotid arteries. The temporal lobes and the basal occipital cortex are usually preserved. The cortical surface lacks the pattern of convolutions and presents as a fluid-filled sac with a smooth inner surface. The leptomeninx may be fibrotic and contains haemosiderophages. The remnants of the cortex consist of gliotic tissue with some residual and/or mineralised neurons. The basal ganglia and thalamus may be intact. The brain stem shows no abnormalities, except for the absence of the cerebral peduncles and medullary pyramids. The cerebellum may show some cystic defects and/or alterations on the microscopic level.

A hypoxic-ischaemic injury of the brain towards the end of gestation or in early infancy may lead to multicystic encephalopathy. In a study by Sie et al. [47], it was found that relatively mild episodes of hypoxia-ischaemia may

suffice for a consecutive development of multicystic encephalopathy. The alterations present as multiple bilateral cavities with varying distribution separated from each other through gliotic tissue (Fig. 5.1e–h). The basal ganglia and the structures supplied by the vertebrobasilar circulation are often spared [48]. Microscopically the lesions present as incomplete necrosis of brain tissue with neuronal loss, reactive gliosis and lipid-laden macrophages.

In contrast to multicystic encephalopathy, global hemispheric necrosis refers to large total necrosis of brain tissue. Clinically the disorder starts with sudden onset between the first days after delivery and up to 18 months of age. The infants present with loss of consciousness, coma, convulsions and bulging of the fontanel as signs of decerebration. Consecutively to the total necrosis of the brain tissue, neuronal and glial proteins appear in the cerebrospinal fluid, like GFAP which was found to be elevated fivefold in infants with perinatal asphyxia [49].

As an underlying cause for the infarction, meningitis [50] and systemic infections (see Chap. 1) have been reported. Furthermore, thromboembolic infarction and hyperviscosity of the blood due to polycythaemia may cause gross necrosis of brain tissue [51]. Ford et al. [52] reported on a case of a 63-year-old man with a history of birth asphyxia, cerebral palsy, seizures and mild mental retardation who presented with left cerebral hemispheric hemiatrophy associated with an extensive ulegyria involving all cerebral lobes on that side. The authors proposed that in addition to severe hypoxia-ischaemia and hypotension, the position of the head at the time of the injury may play a pivotal role in defining the brain regions that are damaged.

Because of the peri- or postnatal onset of multicystic encephalopathy and global hemispheric necrosis, there is no alteration in the development of the cerebral cortex. Global hemispheric necrosis resembles hydranencephaly with the difference that the cerebral convolutions are discernible and the ventricular wall persists.

The various types of hypoxic-ischaemic lesions and their date of origin are summarised in Table 5.2.

Table 5.2 Types of pre-, peri- and postnatal hypoxic-ischaemic brain injury in children and their date of origin

Type of lesion	Date of origin
Periventricular leukoencephalopathy	Perinatal in preterm births, declining prevalence with increasing gestational age
Germinal/ventricular haemorrhage	Perinatal, predominantly in preterm neonates
Por-/hydranencephaly	5th month of gestation
Pontosubicular necrosis	30th gestational week to 2nd postnatal month
Border zone infarction/ ulegyria	Mature neonate
Territorial infarction	Mature neonate to infancy
Marbled state	Perinatal period until an age of 6–9 months
Multicystic encephalopathy	Early infancy
Global hemispheric necrosis	Postnatally up to an age of 18 months

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Aetiological Factors

6

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Abstract

The aetiology of cerebral palsy (CP) is heterogeneous, multifactorial and only partially understood. The brain development begins with neurulation (3 weeks of gestation) and makes further important steps during the first 2 years of life, in particular in the first 12–15 months. CP can result from brain injury occurring during the prenatal, perinatal or postnatal periods. This chapter discusses the aetiological mechanisms that underpin the development of CP. For some, e.g. iodine, perinatal arterial ischaemic stroke (maternal, placental, fetal, neonatal), head injury, coagulation defects and haemorrhage, the relationship with the development of disability is clear. But for others, sometimes considered risk factors rather than aetiological factors, for example, premature birth, small for gestational age, and multiple pregnancies, despite strong evidence of an association, the aetiological mechanisms remain obscure. The potential mechanisms underlying the relationship between hypoxia and the role of neonatal encephalopathy in the development of CP are explored, and the role of genetic and familiar factors associated with CP is identified and discussed. In summary, the aetiological factors associated with CP are complex and diverse, and the precise causal mechanisms underpinning the development of CP for several of the associated risk factors are still unknown.

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6.1 Introduction

The aetiology of cerebral palsy (*CP)* is heterogeneous, multifactorial and only partially understood. When looking at aetiological risk factors [1], traditionally within the context of CP, they are considered by likely timing of exposure, i.e. prenatal, perinatal (i.e. around the time of birth, usually from 28th week of pregnancy until 7th day of life) or postnatal. But with greater use of imaging, and better understanding of brain development, it becomes apparent that the causal pathways to the development of CP are more complex. While CP may result from exposure to a single aetiological factor such as perinatal stroke, it may also follow serial exposure to multiple factors, interacting to produce irreversible brain injury [2] (for more, see Chap. 5). Perinatal asphyxia in the preterm neonate, for example, may be followed by circulatory failure and neonatal infection. Intrauterine infection, an important although relatively rare aetiological factor of CP, is discussed elsewhere (see also Chap. 7).

The resulting spectrum of cerebral damage is further influenced by the fact that different brain structures show different susceptibilities towards damage at different ages of gestation. Whereas brain malformation may result from noxae occurring during early pregnancy, later injury will cause structural brain damage (see also Chap. 5). Even with modern diagnostic techniques, a specific aetiological factor can be identified in no more than 50–75% of all CP cases. Krägeloh-Mann et al. [3] studied a group of 487 infants with CP. They failed to identify a specific aetiological factor in 44% of them. Table 6.1

Table 6.1 Risk factors and aetiology of cerebral palsy (adopted from [4])

	Prenatal	Perinatal	Postnatal
Maternal	Vascular (hypoxia, ischaemia, thrombosis), maternal epilepsy and mental retardation, cervical or third-trimester bleeding, maternal trauma and infection during pregnancy, antiphospholipid autoantibodies, fertilisation problems	Labour complications, especially infections	
Infections	Congenital infections of the neonate (herpes, toxoplasma, rubella, CMV, syphilis)	Bacterial and viral neonatal infections	Bacterial and viral CNS infections
Metabolic	Iodine deficiency, maternal hypothyroidism and hyperthyroidism	Hyperbilirubinaemia (kernicterus), hypoglycaemia, vitamin K deficiency	Hypoglycaemia
Prematurity associated		Prematurity, intracranial haemorrhage, periventricular leukomalacia	
Birth associated		Placental complications (abruption, premature rupture of membranes, chorionitis), hypoxia or anoxia, trauma during labour, meconium aspiration syndrome	
Teratogenic drugs	Teratogenic agents, maternal drug or alcohol abuse	High-dose steroids in preterm infants	
Genetic	Migrational disorders, chromosomal abnormalities, family history of CP or epilepsy	Thrombophilia, metabolic diseases	Thrombophilia, cytokine polymorphisms, metabolic and neurodegenerative diseases
Other	Intrauterine stroke, intrauterine hypoxia, placenta previa, multiple pregnancies, low birth weight, intrauterine death of a co-twin	Cerebral infarction, venous sinus thrombosis	Near drowning, suffocation, cardiac arrest, CNS injuries (head trauma), acquired thrombophilia, infarction, child abuse

summarises important risk factors. In a similar study, Panteliadis and Korinthenberg [4] reported a 42% rate of CP of unknown aetiology. The elucidation of the aetiology of CP is further complicated by the proportion of children with distinct risk factors in their history yet who do not develop CP [2]. Similarly the long-held view that a "difficult birth" is responsible for the origins of CP [5] is not supported by evidence; Odding et al. [6] suggested that among children with tetraplegic CP, a prenatal aetiology was likely to be responsible for 50–55% of the children, with a perinatal aetiology for 30% and a postnatal aetiology for 15–20% for the remainder. Thus, even known aetiological factors are neither necessary nor sufficient to cause CP.

Observational studies have identified many factors associated with the subsequent development of CP, although the aetiological role of these risk factors is less clear. There is clear evidence that low birth weight, usually associated with premature birth, is associated with increased risk of CP; Sellier et al. [7] reported prevalence rates of CP ranging from 1.13/1000 live births (LB) among infants of normal birthweight (>2500 g) to 52.1/1000 LB among children of birthweight of 1000–1500 g. Within each birthweight group, risk of CP is lowest in babies who are of above-average weight for gestation at birth but rises when weight is well above normal as well as when it is well below normal. Whether premature birth or deviant growth is the cause or a consequence of the disability remains to be determined [2, 6, 8].

6.2 Intrauterine Exposure to Toxic Agents

Iodine deficiency during pregnancy is associated with neurological endemic cretinism, a form of CP common in areas of severe iodine deficiency, with brain image findings in affected children very similar to those seen in children with non-iodine-related CP [9]. Furthermore, when at-risk mothers are treated with iodised oil supplements, the prevalence of CP declined [10]. However, whether other causes of maternal hypothyroidism contribute to the aetiology of CP is less clear [9]. There is some evidence that harmful maternal use of alcohol during pregnancy also has an aetiological role in CP, with a 2.5-fold increase risk of CP reported [11]. Other potential teratogenic agents associated with CP included methylmercury and toxicosis of CO, (*maternal*) malnutrition, some antiepileptic drugs and intrauterine infections (*TORCHS*). Some types of hyperaminoacidaemias may also increase the risk of CP; studies of premature and of term newborns have demonstrated that a transient hypertyrosinaemia (tyrosine values exceeding 14 mg/dl) is associated with *low* IQ and mild forms of CP [12]. Nutritional protein is of special significance in the synthesis of all known neurotransmitters [4].

6.3 Multiple Pregnancies

While there is strong observational evidence that children from a multiple pregnancy are at increased risk of CP, the aetiological understanding for this is much less clear (Table 6.1). Pluripara have a three- to fourfold higher incidence of CP (*mainly spastic diplegia*) [13–15], and children born after in vitro fertilisation (*IVF*) also have an increased risk of CP, probably due to the high frequency of twin pregnancies in this population [16]. However, although much of this excess is secondary to the increased risk of prematurity and low birth weight associated with twin birth, it is not entirely so. For example, the incidence of CP is higher in monozygous than in heterozygous twins, probably due to vascular anastomoses in the placenta in monozygotic twin pregnancies [14, 17, 18]. When one twin dies in utero, the survivor may be disrupted and injured by release of thromboplastic substances, by embolisation, haemodynamic shifts or other mechanisms. When this occurs early in gestation, before 16 weeks, microgyria and neuronal heterotopia in the surviving twin may result. The only clinical evidence that one twin has disappeared may be mild vaginal bleeding. Later in gestation, death of a twin can cause lesions in the brain, kidneys, gut, skin and other tissues of the survivor. Ultrasound evidence for fetal disappearance in the first trimester, the "vanishing twin" phenomenon, suggests that the contribution of

twinning to the aetiology of CP may be greater than that based on twinning at birth [19]. In contrast to these observations, Newton et al. [20] suggested that the vanishing twin syndrome was unlikely to account for a high proportion of cases of CP. Research evidence on the risk of CP among survivors of vanishing twin pregnancies is not available.

6.4 Preterm Labour and CP

The two major pathologies associated with CP and preterm labour are periventricular leukomalacia (*PVL*) and intraventricular haemorrhage (*IVH)* [21]. The major cause of *PVL* is an hypoxic-ischaemic event occurring in the medullary layer around the lateral ventricles, a brain region which is not supplied by a redundant arterial system but by end arteries. *PVL* especially affects premature infants of less than 32 weeks of gestational age, whose arteries also show immature vascular autoregulatory properties such that a decrease in arterial blood pressure is closely followed by a decrease in cerebral perfusion. The white matter in premature infants is poorly vascularised and contains oligodendrocyte progenitors (*pre-oligodendrocytes*) which are sensitive to the effects of ischaemia and infection [22–24]. The resulting hypoxic cellular injury may progress to necrosis (*white matter atrophy*), ventriculomegaly, focal cyst formation and connective tissue changes (gliosis). For more details, see Chap. 5.

There are no specific signs or symptoms for developing PVL. The diagnosis is commonly established during routine brain ultrasound studies and advanced neuroimaging techniques [25]. Diffuse *PVL,* which may be more frequent, is not readily accessible to ultrasound studies but is commonly diagnosed during MRI performed for evaluation of spasticity during later life [26]. *Prolonged* CO_2 reduction, e.g. within the context of a mechanical hyperventilation (excessive respiration causing reactive vascular constriction), favours *PVL* as do postnatal high-dose steroid therapy [27] and neonatal infectious diseases (for more, see Chap. 7) [28, 29].

IVH, the second major anatomical disruption of CP in preterm infants, arises from the sub-ependymal germinal matrix, a highly vascularised region. Three major mechanisms may account for *IVH*: the fragility of the vessels within the germinal matrix, alterations of the cerebral blood flow (*CBF*) and platelet or coagulation disorders (thrombocytopenia, *DIC*). Alterations of the *CBF* may derive from fluctuations of arterial perfusion (persistent ductus arteriosus, acidosis, airway suctioning), a high cerebral venous pressure (pneumothorax, high ventilation pressure), abnormal arterial blood pressure (hypotension, hypertension, septicaemia) and impaired cerebral autoregulation in extreme prematurity [30]. In *addition* to the mass effect of the blood clot within the ventricles or within the brain parenchyma, various secondary processes, such as inflammatory and oxidative stress reactions, may result from the extravasation of blood components, enhancing brain damage [31]. Moreover, bleeding into the stem cell layer may result in reduced cortical grey matter volume [32]. This intraventricular—parenchymatous—haemorrhage in the preterm child should be distinguished from subdural, subarachnoid and intraparenchymal haemorrhages in the term-born neonate (see below).

6.5 Hypoxia and Neonatal Encephalopathy

Intrauterine hypoxia of the fetal brain is a common *prenatal* risk factor associated with CP. Hypoxia can be classified as acute, subacute or chronic and may be due to insufficient blood supply in utero during the last weeks of pregnancy or secondary to other anomalies of the placenta and umbilical cord, premature placental separation or *EPH*—gestosis (pregnancy syndrome with oedema, renal proteinuria and hypertension) (Table 6.1). In the second and third trimester of pregnancy, the predisposing factors are mainly related to dysfunction of the placenta and to other problems that may cause chronic endometrial asphyxia.

The diagnosis of intrauterine hypoxia is problematic: commonly used diagnostic tools for recording/monitoring oxygen supply to the human fetus include the cardiotocography (*CTG),* recording fetal heart rate and contractions of the uterus, and the analysis of maternal blood hormones (*such as oestradiols*). Signs of fetal circulation deficit will include low heart rate and metabolic acidosis of the fetal blood. Both methods are sensitive but their specificity is low; a transiently abnormal *CTG* result can be observed in about 30% of all pregnancies. Fetal tachycardia or abnormal reactions of heart rate to exogenous stress like uterus contractions may be the only evidence of subacute or chronic hypoxia. Chronic hypoxia, that is, impaired cerebral supply of the fetus over an extended period of the pregnancy, is associated with adverse mental-cognitive development and may be manifested through inadequate head growth, as measured by head circumference. Chronic intrauterine hypoxia with onset after the 34th week of gestation is only rarely associated with *PVL* or sub-ependymal cerebral haemorrhage, and commonly hypoxic cerebral lesions in the border zone range between the supplied areas of the large cerebral arteries are observed (border zone infarction) in the cerebral cortex, in the basal ganglias or in the brainstem. A fetus can completely recuperate from transient under-oxygenation. Therefore, normal *Apgar* scores after delivery and absence of symptoms during the first days of life do not exclude a prenatal cerebral lesion [33].

During labour, the normal (*healthy*) fetus has many specific physiological mechanisms that protect it from repeated mild hypoxic episodes during labour, so only severe hypoxia or prolonged anoxia causes neurological deterioration. Examples of such events include premature detachment of the placenta, reduced uteroplacental blood flow, etc. [34] Cerebral lesions due to hypoxia or ischaemia have been described (Leijser et al. [35, 36, 37]) (see Chap. 5). Other signs of acute perinatal oxygen deficit include a prolonged low heart rate, discharge of meconium and an acidosis with capillary blood pH values <7.2–7.0.

Although perinatal difficulties were previously thought to be strongly associated with CP, the role of perinatal asphyxia as an aetiological factor is now debated. Ellenberg's and Nelson's [38] systematic review of the proportion of CP attributable to birth asphyxia found that estimates ranged from 3 to over 50%. The observed variation related to variations in the exposure "birth asphyxia" and the outcome (CP), i.e. whether "non-asphyxia aetiologies" were excluded. Other epidemiological studies report that 90% of cases of CP that were first supposed to be due to perinatal asphyxia were due to other causes, while about 10% had perinatal or prenatal causes. In most cases, the causes of CP *are* found in the history of pregnancy, e.g. endometrial infection, endometrial dystrophy, prematurity, multiple pregnancies, coagulopathies and chromosomal or congenital abnormalities [39, 40].

The American College of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy [41] has defined signs consistent with acute intrapartum or peripartum asphyxia as follows:

- APGAR score of <5 at 5 and 10 min
- Fetal umbilical artery acidosis, with pH <7.0 and/or base deficit of ≥12 mmol/L
- Multisystem organ failure consistent with a hypoxic-ischaemic event
- A sentinel hypoxic or ischaemic event occurring immediately before or during labour, with fetal heart rate patterns consistent with such an event
- Neuroimaging evidence of acute brain injury, with timings consistent with the observed sentinel event

The task force report suggests that only severe cerebral palsy, e.g. spastic quadriplegia or dyskinetic cerebral palsy, is associated with hypoxic-ischaemic encephalopathy. Neonatal encephalopathy affects term-born and late preterm newborns. The risk of perinatal problems, such as neurological morbidity, especially CP, is high [42].

6.6 Meconium and Asphyxia

Severe meconium aspiration syndrome is defined by meconium-stained amniotic fluid before delivery, presence of meconium below the vocal cords at the time of birth, evidence of respiratory distress and radiological evidence of aspiration pneumonitis. These critically ill children may develop persistent pulmonary hypertension, circulatory failure, hypoxia, need for aggressive artificial ventilation or even *ECMO*, pneumothorax and infectious complications. Among term-born children with severe meconium aspiration syndrome, 41% may develop mild neurological defects, 7% CP and 14% severe global developmental sequelae [43].

6.7 Perinatal Stroke

Perinatal stroke can be defined as a disruption to cerebral blood flow between 20th week of fetal life to 28th postnatal day, with the two most common types being arterial ischaemic stroke (*AIS*) and cerebral sinovenous thrombosis (*CSVT*) [44]. AIS comprises a group of arterial ischaemic injuries that can occur in the prenatal, perinatal and postnatal periods in term and preterm infants with different types of AIS, different clinical presentations and risk factors [45] (Table 6.1). According to Fluss et al. [46, 47], the aetiology of AIS remains speculative, e.g. thrombosis in the carotid artery and rarely by carotid occlusion through thromboembolic process in the placenta.

The middle cerebral artery is the most common site of *AIS*, with an excess of these occurring within the left hemisphere. Perinatal stroke has a prevalence of approximately 1 per 2300 live births, with CSVT much less common at 1–2 per 1,000,000 births; together they account for about 15% of the children with hemiplegic CP [48, 49]. Risk factors include maternal pre-eclampsia, a history of impaired maternal fertility, small and large for gestational age, traction on neck vessels during delivery, perinatal infections, dehydration and hypotension of the newborn, the use of intravascular catheters, placental thrombotic lesions and hereditary thrombophilia [2].

Otherwise, thrombotic material originating from a central venous catheter in a child with hereditary thrombophilia may cross a patent foramen ovale to finally occlude a cerebral vessel. In a similar fashion, congenital heart defects involving right to left shunts through septal defects or a patent ductus arteriosus may predispose to embolic stroke in neonates. Further prothrombotic constellations include bacterial meningitis with vascular inflammation or polycythaemia, for example, due to chronic intrauterine hypoxia or hereditary causes. In the majority of patients, however, no clear cause can be identified.

Although much less common, CSVT may occur anywhere in the cerebral venous system and leads to ischaemia and sometimes to infarction, usually haemorrhagic. Infection, traumatic labour, dehydration, polycythaemia, congenital heart disease and protein C deficiency have all been implicated as causes of cerebral venous thrombosis in neonates. However, no cause may be found in many affected children [50–52].

6.8 Subdural, Subarachnoid and Intraparenchymal Haemorrhage

Much less common than *IVH*, haemorrhages may also affect the subdural (*SDH)* and subarachnoid (*SAH*) space or present as isolated intraparenchymal (*IPH*) haemorrhage. While *SDH* occurs more commonly in the term infant, *SAH* is more common in premature infants.

SDH in neonates may primarily result from mechanical trauma, leading to shearing forces which create tears in the vein of *Galen* or in superficial cerebral veins. Tears at the junction of falx and tentorium may generate large subdural blood collections in the relatively small posterior fossa culminating in compression of the brainstem and cerebellar tonsillar herniation. Situations promoting the application of increased force upon the fetal head include cephalopelvic disproportion, rigidity of the bony pelvis, prolonged duration of labour, unusual presentations or the need for prolonged manipulation or forceps application [53–55].

Blood may reach the subarachnoid space by different ways: first, after haemorrhage in the cerebral parenchyma or in the periventricular region and, second, after disruption of superficial leptomeningeal arteries or of the fragile vessels bridging the subarachnoid space. Primary subarachnoid haemorrhage commonly occurs after hypoxic-ischaemic brain insults and after fetal head trauma. Often the distinct pathogenesis remains unclear.

IPH in the absence of intraventricular haemorrhage occurs most commonly in term infants, with haemorrhage into the parenchyma of the cerebral hemispheres due to head trauma, vascular malformation, coagulopathy, tumour or infarction. While *vitamin K*, a carboxylating and activating agent for the clotting factors II, VII, IX, and XI, is routinely administered to newborns, its deficiency should be considered in breast-fed full-term neonates who present with intracranial haemorrhage within the first weeks of life. In the absence of recognised coagulation or anatomic abnormalities, cerebral hemispheric IPH is usually is a manifestation of haemorrhagic infarction. In this circumstance, an embolic stroke precedes haemorrhage. When the embolic material occluding the cerebral vessel eventually fragments, partial or total perfusion through the previously occluded vessel is re-established. Haemorrhage ensues as blood escapes through the vascular walls which have been weakened by the embolus-induced ischaemia [55–57].

6.9 Postneonatal Risk Factors for CP

Postneonatal CP is much less common, with about 1.20–2.0 cases per 10,000 population [58–60]. It is usually defined as originating more than 28 days after birth, and with a variable upper age limit, although in most cases, the cause can be found during the first 12 months of life (Table 6.1). The most common causes are infections, usually originating in the CNS, and accidents, for example, head injury due to accidents or child abuse ([59, 61]; for more, see Chap. 7).

Other causes include heart failure or cardiac arrest leading to generalised anoxia with anoxic encephalopathy; cerebral infarcts, as a complication of meningitis and of septicaemia; diffuse intravascular coagulation; cortical vein thrombosis; vasculitis; cerebral cysts; venous sinus thrombosis; rupture of cerebral aneurysmatic vessels; arteriovenous malformations; hydrocephalus; or hypoglycaemia. The latter may occasionally manifest as a mild form of *CP,* but usually does not cause any permanent lesions.

Modern radiological techniques allow early detection of these lesions [4, 25, 62]. Prognosis and severity of disability are the same for acquired as for congenital CP.

6.10 Genetic Factors in CP

Familial predisposition towards CP referring to either a classical type of inheritance or to a multifactorial aetiology has long been suggested from different epidemiological studies (see Table 6.1). A report from Sweden suggested that 1.5% of CP cases might be inherited in a recessive pattern, while from Norway, a study has shown a ninefold increase in risk of a second child having CP, with smaller but increased risks associated with half siblings and for those with CP having an affected child [63]. Studies in small communities have shown that CP is more frequent in populations where marriages between relatives take place, and according to data of the European CP study [28], about 12% of children with CP may show normal *MRI* findings which also points to a genetic cause of CP in these cases. CP is also more frequent among children showing cerebral and non-cerebral congenital malformations, hydrocephalus or microcephaly ([2, 64]; see Chap. 7). In the beginning of the year 2017, the OMIM (Online Mendelian Inheritance in Man) database includes more than 100 monogenic diseases with cerebral palsy as major symptom. These conditions mirror the complete spectrum of mechanisms discussed in this chapter, including metabolic, neuromuscular, haematological and neurodegenerative diseases, diseases of the native immune system (Aicardi-Goutières) and

brain malformations. There are also an increasing number of genetic conditions which mirror intrauterine infections (pseudo-TORCH) and should therefore be considered in case of intracerebral calcifications [65].

In addition to these monogenic diseases, candidate genes that may influence various processes critical in the pathogenesis of lesional CP *in a polygenic fashion* are increasingly recognised. This includes genes increasing the risk of preterm birth, such as variants of the β2-adrenergic receptor gene, of inducible nitric oxide synthase or of thrombomodulin [66]. A genetic contribution to the aetiology of placental abruption, pre-eclampsia and chorioamnionitis has also been suggested [2]. In the neonate, this includes genes influencing metabolic processes (e.g. allelic variants of inducible NO synthase and of apolipoprotein E) or the inflammatory response (e.g. allelic variants of interleukin 8, *TNF*-α, IL-1β, IL-4, IL-10 and *LTA*) [67–69] or genes encoding for coagulation factors (see below). In this context, IL-1β and IL-4 polymorphisms may be related to the occurrence of intraventricular haemorrhage, and IL-1β and IL-10 polymorphisms may be related to the occurrence of periventricular leukomalacia.

Mutations in coagulation factors may contribute to CP in different ways. In preterm children, these may increase the risk to develop diplegia (*factor* V *Leiden* mutation, *MTHFR* C677T mutation) [2, 69]. In term children thrombophilic polymorphisms, especially *MTHFR C677T*, prothrombin gene mutation *G202101* and factor V *Leiden* mutation, are discussed to increase the risk of arterial stroke or venous thrombosis [70, 71].

With advances in exome sequencing, it has been suggested that up to 14% of cases of CP have single gene mutations and up to 31% have clinically relevant copy number variations, but whether these are causative requires further investigation [72].

6.11 Acquired Coagulation Defects and CP

During the past years, studies have shown an association of cerebral abnormalities with the presence of antiphospholipid autoantibodies in the mother's or the neonate's serum promoting both the occurrence of neonatal thrombotic disease and placental abnormalities, resulting in preterm birth or spontaneous abortions [2].

Moreover, there is a causal relationship between the presence of immune thrombocytopenia, vitamin K deficiency and secondary coagulation defects due to maternal drug intake (*anticonvulsants*) and neonatal cerebral haemorrhage.

6.12 Maternal and Familial Factors Contributing to CP

Delay or disorders of menses and low fertility are related to the increased incidence of CP (see Table 6.1). Also, an immaturity of the endometrial environment and undiagnosed chromosomal abnormalities may increase the danger of CP.

There may also be an association of CP with maternal mental retardation, motor disabilities of a sibling, maternal epilepsy and a history of two or more fetal deaths in the family.

6.13 Summary

The aetiological factors associated with cerebral palsy are complex and diverse and yet are pathognomonic in only a minority of cases, as the precise aetiology of most cases of cerebral palsy remains obscure.

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Intrauterine Infection and Cerebral Palsy

7

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Abstract

Intrauterine infection is an underappreciated but vital cause of cerebral palsy (CP). While the origin of cerebral palsy is multifactorial, we explore the evidence linking infection in pregnancy and development of cerebral palsy. In this chapter, we begin with a review of embryologic brain development in humans to understand the etiology of cerebral palsy on a structural level. We will then describe the role of cytokines in inflammation and their effect on brain development in a broad sense before introducing the fetal inflammatory response syndrome to describe intrauterine inflammation. We conclude the chapter by discussing the quintessential link between intrauterine infection and cerebral palsy, both in humans and animal models.

7.1 Introduction

The development and maturation of the human brain in utero occur throughout the fetal period and are orchestrated by a set of complex interactions among various receptors, genetic factors, epigenetic factors as well as environmental influences. The principal stages of development during the gestational period and their relative time of development are subcategorized as follows (depending on how gestational age and intrauterine infections affect different steps of development):

Primary neurulation (3–4 weeks of gestation)
Prosencephalic development (2–3 months of gestation)
Neuronal proliferation (3–4 months of gestation)
Neuronal migration (3–5 months of gestation)
Neuronal organization (5 months of postnatal period)

Myelination follows the coordination of these steps en route to formation of the human brain beginning in the second trimester in utero and continuing postnatally into adulthood (see also Chap. 5). The fastest rate of growth occurs in the immediate neonatal period. Anomalous development in any of the aforementioned stages constitutes cerebral

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pathology and maldevelopment. The timing and type of insult are critical in determining how that developmental aberration will be manifested. As examples, abnormalities in primary neurulation can lead to neural tube defects, while abnormalities of neuronal organization can lead to mental retardation or trisomy 21 [1]. Therefore, not only the localization but also the timing of the insult has an important role in proper cerebral function. The effects of these insults engender cognitive, behavioral, and psychiatric disorders. It is in this spirit that we look at intrauterine inflammation and related infection resulting in alteration of brain function and cerebral palsy.

7.2 Etiology of Cerebral Palsy

Cerebral palsy (CP) is a constellation of clinical syndromes of varying severity including aberrations in muscle tone, posture, and gross movement having a prevalence of 2 per 1000 live births. The well-established paradigm that the developing brain exposed to various insults at specific time points in gestation is the underlying cause of CP (for more, see Chaps. 2, 3, and 6). The drawback is that while risk factors have been associated with the development of CP, causal relationships have not been established. Early gestational age and low birth weight at delivery are important risk factors [2], but intrauterine infection comprises nearly one-third in over 200 children diagnosed with CP in an Australian cohort [3], suggesting that our antenatal preventative measures need to focus on the multifactorial etiology of CP not only in preterm but also in term infants (see Chap. 6).

7.3 Infection and the Effect on Fetal Brain Development

Infections activate downstream inflammatory pathways causing the release of various inflammatory biomarkers such as cytokines, interleukins, and other molecules. This inflammatory response can be gauged in the setting of pregnancy through physiologic behavioral responses, histologic evaluation of specific brain regions, or molecular upregulation. All of these indicators of an inflammatory process have been associated with adverse neurologic outcomes such as autism spectrum disorders, schizophrenia, and neurodevelopmental sequelae. Such literature gives further evidence for the theory that maternal infection during pregnancy can cause fetal brain damage and therefore alter cognitive and psychological function later in life.

Cytokines are molecules produced by cells involved in the inflammatory pathway. They act to modulate the immune response by binding to receptors and causing downstream effects. They are defined by their primary cellular origin:

- T-helper type 1 (Th1), functioning in cell-mediated immunity against intracellular pathogens
- T-helper type 2 (Th2), functioning to promote humoral immunity against extracellular pathogens
- T-helper 17 (Th17) involved in the mediation of septic shock
- T-regulatory (Treg) cytokines, involved in dampening and shutting off of the inflammatory response

Generally speaking, the various cytokines within the inflammatory pathway are grouped molecularly by their primary cellular lineage. The Th1 axis includes IL-2, TNF-β, and INF-γ, while the Th2 axis includes IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. Additionally, the Treg axis includes IL-1 antagonist and TGF-β, and the Th17 axis includes IL-1β and IL-17 [4–6].

Maternal cytokines dictate the type and severity of the immune response, which can portend brain pathology and subsequent function. Gomez and colleagues measured plasma IL-6 levels in fetuses with preterm labor or preterm premature rupture of membranes. The group showed that neonates with exposure to elevated IL-6 during development (14.0 pg/mL vs. 5.2 pg/mL) suffered severe neonatal morbidity including the presence of periventricular leukomalacia (PVL), a known precursor of CP [7]. Subsequently, IL-6 is involved in the survival of various neuronal subcategories including acetylcholinesterase-positive, catecholaminergic, cholinergic, and dopaminergic neurons. In *addition*, Yoon and his colleagues [8]

showed that elevated levels of IL-6 and IL-8 and the presence of histologic funisitis (inflammation of the umbilical cord) were independently correlated with increased odds of developing cerebral palsy at 3 years of age [8]. These studies suggest that maternal infection in pregnancy is inextricably linked to fetal outcome and prevalence of CP.

7.4 Fetal Inflammatory Response Syndrome

In humans, studies of preterm birth have coined the term fetal inflammatory response syndrome (FIRS), a condition characterized by systemic activation of the fetal innate immune system. It was originally defined in fetuses with preterm labor or premature rupture of membranes as an elevation in the concentration of interleukin-6 (IL-6) in fetal plasma [7]. Histopathologic hallmarks of FIRS include funisitis and chorionic vasculitis. Fetuses with FIRS are known to have an elevated risk of preterm labor in the setting of preterm rupture of membranes, regardless of the presence or absence of intra-amniotic infection. It has been proposed that ascending intrauterine infection (IUI) results in local inflammation and the release of various pro-inflammatory cytokines and can also cross membranes to affect the fetus and initiate the FIRS [9]. The FIRS is also associated with elevations in IL-6, IL-8, and TNF-α. The intrauterine inflammation which is associated with infectious causes of preterm birth can lead to a fetal inflammatory response syndrome characterized by elevated pro-inflammatory cytokine levels. This same pathway is associated with the development of periventricular leukomalacia (PVL) [10, 11].

7.5 Preclinical Models of Infection and Their Association with Cerebral Palsy

Some of the ways in which cytokine responses have been measured in response to infection are through animal models. Smith and his colleagues postulated the maternal immune activation (MIA) as a mechanism by which maternal inflammation explains abnormal fetal brain development. By injecting IL-6 in utero on day 12.5 gestational age in pregnant mice, they were able to elicit behavioral, histological, and differential gene expression, leading to downstream neurologic sequelae consistent with schizophrenia and autism. The MIA model showed that anti-IL-6 antibodies and IL-6 knockout mice do not show the same amount of behavioral aberrations as the wild-type group. The study corroborates MIA as a possible mechanism of fetal cerebral pathology without describing a specific mechanism [12]. The mechanism has now been more recently uncovered as microglial priming, a process by which developing microglia respond to inflammatory stimuli, implicated in development of epilepsy and CP [13].

Another more modern method of mimicking infection in animal models is through the exposure of modified proteins, which result in a strong innate immune response in the absence of infection. Specifically, lipopolysaccharide (*LPS*) is a component of gram-negative bacteria which mimics bacterial infections in pregnant mice and causes preterm birth. Lipopolysaccharide exposure induces the production of IL-6, TNF-α, IL-1β, and stress hormones, including corticosterone (*COR*) [14]. Similarly, polyinosinic-polycytidylic acid (poly I:C) is a synthetic double-stranded RNA which mimics viral infection in pregnant mice [15].

Multiple experimental models have exposed pregnant rats to either LPS or poly I:C at a specific gestational age so as to pinpoint molecular changes involved with maternal infection heralding the development of CP. Models of preterm birth by Burd et al. [16] had demonstrated that inflammation-induced preterm birth by lipopolysaccharide, in which preterm birth is induced by intrauterine inflammation, is associated with fetal neuroinflammation [16, 17]. Rousset and her colleagues injected LPS intraperitoneally in pregnant rats and observed fetal brain astrogliosis and global hypomyelination consistent with significant white matter injury, an underlying pathophysiologic mechanism of CP [18]. The findings are congruent with the work of Saadani-Makki and colleagues, showing that intrauterine

endotoxin administration leads to white matter injury and motor deficits in a rabbit model of CP [19]. In a similar fashion, administration of maternal poly I:C has been shown to increase the fetal inflammatory response and white matter damage and inhibit the regeneration of microglia, exacerbating the cerebral hypoxia-ischemia, a known precursor of CP [20].

7.6 Clinical Evidence Linking Intrauterine Inflammation and Cerebral Palsy

The literature has focused on characterizing CP in preterm neonates given their high preponderance of complications of prematurity (see Chap. 6). In fact, the very low birth weight (<1500 gm) cohort sees higher rates of CP ranging from 5 to 15% secondary to periventricular PVL, intraventricular hemorrhage (IVH), and bronchopulmonary dysplasia (BPD) [21]. The combination of preterm birth, IVH, and inflammation associated with hypoxia-ischemia has been proposed to be the etiology of white matter injury underlying the development of CP [22].

Maternal intrauterine infection, including chorioamnionitis, is linked with an increased risk of CP in infants [23]. Chorioamnionitis is the process of active infection within the amniotic cavity that can also induce a fetal inflammatory response and affects up to 10% of pregnancies. The inflammatory process underlying maternal intrauterine infection is the mechanism of a significant portion of perinatal brain injury and a leading risk factor for neonatal sepsis (see Chap. 6). Despite its perinatal predisposition, chorioamnionitis can result in not only short-term but long-term neurodevelopmental disabilities. Long-term outcomes include an increased neonatal death rate, respiratory distress syndrome, periventricular leukomalacia, and cerebral palsy. The unifying hypothesis is the overwhelming fetal production of cytokines that leads to, among other effects, brain cell damage [22]. Studies investigating the pathogenesis of the sepsis cascade have unveiled IL-1β as the biomarker mediating brain injury in utero [24]. Macrophages, monocytes, and activated platelets can all release IL-1β, which works in two predominant pathways. IL-1β has both paracrine and endocrine effects. The former elicit the coagulation cascade, recruitment of other interleukins, and activation of T cells. The latter can decrease blood pressure and induce fever by releasing prostaglandins.

A meta-analysis from 2000 revealed a relative risk (RR) of CP of 1.9 for both clinical and histologic chorioamnionitis [25]. Subsequent case-control studies have unveiled a strong association between maternal chorioamnionitis, maternal infection, and neonatal infection with CP [26, 27]. Clinical evidence of chorioamnionitis has been significantly associated with both cerebral palsy and cystic periventricular leukomalacia (cPVL), while histologic chorioamnionitis has been similarly associated significantly with cPVL (Wu et al. 2000). To buttress these studies, in vivo fetal quantitative MRI has shown promise to unveil the organizational and remodeling process of the fetal brain affected by CP so as to propose an architectural template to characterize neonates affected by the disease [28].

While the emergence of CP in preterm infants has decreased in the past three decades, the rate in term infants has plateaued in that same time frame (see Chap. 2). The statistics indicate that while preterm neonates are the most vulnerable population to acquire CP, this is not a comprehensive model to explain all cases of CP, and further characterization is required. Pregnancy and embryologic development are a natural starting point, and both basic science and clinical research add value to the origin of this disease.

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8 Magnesium Sulfate for the Prevention of Cerebral Palsy

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Abstract

Three large, randomized placebo-controlled trials of antenatal $MgSO_4$ for fetal neuroprotection have been conducted; separately and together, they demonstrate that $MgSO_4$ diminishes the risk of cerebral palsy among the survivors of early preterm birth. A meta-analysis of these three trials, and a fourth, smaller one, shows that not only does the maternal administration of magnesium sulfate for fetal neuroprotection lower the subsequent risk of childhood cerebral palsy but also the combined risk of cerebral palsy or death. The use of magnesium sulfate on clinical grounds for the prevention of cerebral palsy has become widespread. The Netherlands, Australia, New Zealand, the United Kingdom, and Canada have promulgated national guidelines for the use of magnesium sulfate to prevent cerebral palsy.

8.1 Introduction

Drs. Karin Nelson and Judy Grether were the first to make the observation that magnesium sulfate ($MgSO_4$) administered to mothers delivering prematurely might prevent cerebral palsy in their offspring. In their case-control study [1], children with cerebral palsy were significantly less likely to have been exposed to $MgSO_4$ than controls (odds ratio 0.14, 95% confidence interval 0.05–0.51). Even after controlling for confounders, this protective association persisted. Moreover, it has biologic plausibility: magnesium can reduce vascular instability, prevent hypoxic damage, and ameliorate cytokine or excitatory amino acid damage [2].

8.2 Clinical Administration

Since the report of Nelson and Grether, three large, randomized placebo-controlled trials of antenatal $MgSO_4$ for fetal neuroprotection have been completed, and their results are available.

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Separately and together, they demonstrate that $MgSO_4$ diminishes the risk of cerebral palsy among the survivors of early preterm birth.

The first trial reported was by Crowther and colleagues [3]. They studied 1062 women at imminent risk of delivery before 30 weeks' gestation [4]. They administered $MgSO_4$ as a 4-gm intravenous bolus and then a constant infusion of 1 gm/h for up to 24 h. The combined outcome of stillbirth or death before age of 2 was less frequent among the offspring of women randomized to $MgSO_4$ than among those randomized to placebo, 13.8% vs. 17.1% (relative risk [RR] 0.83, 95% confidence interval [CI] 0.64–1.09). Substantial gross motor dysfunction (inability to walk unaided by the age of 2) was significantly less frequent among children in the $MgSO_4$ group, 3.4% vs. 6.6% (RR 0.51, 95% CI 0.29–0.91).

The second major trial to be reported was the "BEAM" trial in which 2241 women deemed to be at imminent risk of delivery between 24 and 31 weeks' gestation were enrolled [4]. In this study, $MgSO_4$ was administered as a 6-gm loading dose and then a constant infusion of 2 gm/h for up to 12 h. The primary study outcome was a composite: fetal/infant death or moderate or severe cerebral palsy (inability to walk unaided by the age of two). Although $MgSO_4$ had no significant effect on this composite outcome, 11.3% in the $MgSO_4$ group vs. 11.7% in the placebo group (RR 0.97, 95% CI 0.77–1.2), children born to mothers in the $MgSO_4$ group had a significantly reduced risk of the prespecified secondary outcome of moderate or severe cerebral palsy, 1.9% vs. 3.5% (RR 0.55, 95% CI 0.32–0.95). Without adjustment for major congenital malformations, $MgSO_4$ was associated with a small, nonsignificant increase in the risk of fetal or infant death, 9.5% vs. 8.5% (RR 1.1, 95% CI 0.85–1.5). But when infants with major congenital malformations were excluded, there was no difference in the rate of death between groups, 8.3% vs. 8.1% (RR 1.0, 95% CI 0.77–1.4). Among the children of those women randomized prior to 28 weeks, $MgSO_4$ was associated with a greater reduction in the absolute risk of moderate or severe cerebral palsy, 2.7% vs. 6.1% (RR 0.45, 95% CI 0.23–0.87).

The third major trial was that of Marret et al. [5]. They randomized 573 mothers to either $MgSO_4$ or placebo. The $MgSO_4$ was administered as a 4 gm bolus only. The mortality rate of the children of women randomized to $MgSO_4$ was lower, 9.7% vs. 11.3% (RR 0.85, 95% CI 0.55–1.3), as was the rate of cerebral palsy, 7.0% vs. 10.2% (RR 0.69, 95% CI 0.41–1.2).

The above three trials and two more form the basis for a Cochrane Systematic Review [6]. The two additional trials include a small, four-armed study of 150 women and a subgroup analysis of a large trial whose purpose was to evaluate the use of $MgSO_4$ to prevent eclamptic convulsions. The systematic review included a total of 6145 children. In the overall analysis, $MgSO_4$ significantly reduced the rate of cerebral palsy (RR 0.68, 95% CI 0.54–0.87) and had no effect on fetal or infant mortality (RR 1.04, 95% CI 0.92–1.17). In the analyses confined to the four trials (4446 children) in which neuroprotection was the specific outcome, $MgSO_4$ was associated with a reduction not only in the rate of cerebral palsy but also with a reduced rate of the composite outcome of fetal/infant death or cerebral palsy (RR 0.85, 95% CI 0.74–0.98) [6].

Secondary analysis of the BEAM trial provides reassurance as to the neonatal safety of magnesium sulfate when used for fetal neuroprotection. Johnson et al. [7] evaluated the association of cord blood magnesium concentration and the need for neonatal resuscitation in 1507 infants from the BEAM trial and found no association between the two, in either the need for any form of resuscitation or for specific levels of resuscitation. That is, the range of fetal concentrations of magnesium achieved with the use for neuroprotection was not associated with neonatal depression.

Since the publication and dissemination of the results of the BEAM trial and the Cochrane meta-analysis, the use of magnesium sulfate on clinical grounds for the prevention of cerebral palsy has become widespread. The Netherlands, Australia,

New Zealand, the United Kingdom, and Canada have promulgated national guidelines for the use of magnesium sulfate to prevent cerebral palsy. In their joint Obstetric Care Consensus on Periviable Birth [8], the American College of Obstetricians and Gynecologists (ACOG) and the Society of Maternal Fetal Medicine recommend that magnesium sulfate be administered when delivery is threatened and imminent at or beyond 24 weeks of gestation (and that it be considered as early as 23 weeks). ACOG recommends that the upper gestational age limit for the use of magnesium sulfate for neuroprotection be 31 weeks and 6 days, and it has developed a Patient Safety Checklist for the use of neuroprotective magnesium sulfate [9].

Gibbins et al. [10] assessed the use of magnesium sulfate in their large women's hospital in the 4-year period subsequent to the publication of the BEAM trial. They reported an increase in the use of magnesium sulfate in women delivering before 32 weeks, from 20% in the first year to 94% in the fourth. The therapy was fairly efficiently delivered: the majority of women (84%) who received magnesium sulfate delivered before 32 weeks, and the medium number of treatment courses was one. No serious adverse events, either maternal or perinatal, were attributed to magnesium sulfate. Bouet et al. reported their similar experience [11].

Even though $MgSO_4$ has a high margin of safety, it needs to be used with care. Maternal deep tendon reflexes should be closely monitored (neuromuscular depression occurs at Mg^{++} concentrations of 10 mEq/L and above) as should urine output (Mg^{++} is renally excreted). With renal dysfunction, Mg^{++} toxicity is much more likely. In the event of respiratory depression or cardiopulmonary arrest, 1 gm of intravenous calcium gluconate should be administered and the $MgSO_4$ discontinued [12].

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Early Markers for Cerebral Palsy

9

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Abstract

Among the most reliable markers for cerebral palsy are abnormal general movements. Two specific patterns of abnormal general movements predict cerebral palsy: (a) cramped-synchronised general movements at preterm and term age; they lack the usual smoothness and fluent character; limbs and trunk muscles contract almost simultaneously and thereafter relax almost simultaneously; and (b) the absence of fidgety movements at 3–5 months post-term age; fidgety movements are small movements of the neck, trunk and limbs in all directions and of variable acceleration. Besides high predictive values (sensitivity >94%; specificity >81%), the assessment of general movements is non-intrusive, easy to acquire and cost-effective.

9.1 General

One of the most challenging tasks for paediatric health-care professionals is to predict in early infancy what sort of development might cause severe impairment in the future. The parents, on their part, are all the more anxious to learn about the developmental prospects of their infant, especially if the infant has an adverse perinatal history. At the same time, one should consider that overt clinical symptoms of cerebral palsy (CP) do not usually emerge before the child is 6 months old.

In 1997, Heinz Prechtl and his colleagues proved the *assessment of spontaneous general movements (GMs)*—particularly during the third month of age—to be a reliable and valid tool for distinguishing between infants who are at significant risk of developing neurological deficits and infants who are not. The findings were based on a longitudinal study in 130 infants who represented the whole spectrum of perinatal brain ultrasound diagnoses [1]. Central to the study were the age-specific *fidgety movements*—small movements of the neck, trunk and limbs in all directions and of variable acceleration [2, 3]. They are the predominant motor pattern in awake infants aged 3–5 months [2, 4]. Infants develop normally if

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such fidgety GMs are present and normal, even if their brain ultrasound findings indicate a disposition to later neurological deficits. Conversely, if fidgety movements are absent, infants develop neurological deficits even if their ultrasound does not indicate a significant risk [5].

9.2 The Absence of Fidgety Movements at the Age of 3–5 Months Marks Cerebral Palsy

Various work groups have emphasised the significance of *fidgety movements* for an early prediction of the neurological outcome at a post-term age of 24 months or older. Taking as a basis the data on more than 2000 infants, they reported a specificity of 82–99%, a sensitivity of 95–100%, a negative likelihood ratio of <0.05 and a positive likelihood ratio of >51 (e.g., [4, 6–10]). An intra-scorer agreement of 85%, an inter-scorer agreement of 89–93% and an average kappa of 0.88 obtained in more than 15 studies document the high objectivity of the GM assessment [4]. Such high values can be achieved after a mere 3–4 days of extensive training [11]. Kappa values from 0.90 to 0.96 demonstrate the high interindividual consistency [12].

A Trondheim work group has recently developed a software called General Movement Toolbox that provides assistance in identifying absent fidgety GMs in infants [13]. With this computer-based analysis of video recordings, the identification rate of infants who later developed CP has been significantly high (sensitivity = 85%; specificity = 88%), which suggests that it is actually possible to detect the characteristic features of fidgety GMs with the help of special tools [14].

However, the mere absence of a particular motor pattern cannot predict the subtype or the severity of CP, although it has recently been shown that a more detailed analysis of the whole motor repertoire of 3- to 5-month-old infants can provide deeper insight. The following markers are associated with a lowered level of self-mobility at school age (assessed by means of the Gross Motor Function Classification System):

- Cramped-synchronised movement character [15–18]
- Lower motor optimality score [18]
- Repetitive opening and closing of the mouth [18]
- Abnormal finger postures [18]
- Monotonous kicking [15]
- Absence of fidgety movements [15, 16, 18]

Interestingly enough, fidgety movements are absent or only sporadically present [19] in all eventual subtypes of CP (Table 9.1), which indicates that it takes intact cortico-spinal fibres and normal outputs from the basal ganglia to generate normal fidgety movements [20]. Fidgety movements are also absent in infants with genetic disorders, for example, Rett Syndrome, whereby the infants with the most severe phenotypes show no

Table 9.1 Developmental trajectories with a high predictive power for normal development and the development of CP

GMs during the preterm period	Writhing GMs (term age)	Fidgety GMs (3–5 months post term)	Neurological outcome
Poor repertoire or normal GMs	Poor repertoire or normal GMs	Normal	Normal
Poor repertoire and/or cramped-synchronised GMs	Cramped-synchronised GMs	Absence of fidgety movements; abnormal findings in the neurological examination	Bilateral spastic CP
Poor repertoire GMs	Poor repertoire and/or cramped-synchronised GMs	Absence of fidgety movements; asymmetrical segmental movements; often normal findings in the neurological examination	Unilateral spastic CP
Poor repertoire GMs	Poor repertoire GMs	Absence of fidgety movements; circular arm movements and finger spreading	Dyskinetic CP

fidgety movements when aged 3–5 months, while otherwise their development is found to be more or less normal [21].

After discovering fidgety movements as an age-specific, distinct form of GMs, Prechtl [22] speculated about the potential biological function of this transient movement pattern. One might conjecture that one of the ontogenetic adaptive functions of these small movements is the optimal calibration of the proprioceptive system. This hypothesis is supported by the fact that fidgety movements emerge during the transformation of neural functions at 3 months of age [23] and therefore precede visual hand regard, the onset of intentional reaching and visually controlled manipulation of objects [22]. Since in many respects adaptation to the extrauterine condition is not completed before the third month post term, the proprioceptive system is still matched to the intrauterine environment. A recalibration of this sensory system is required in order for future fine motor skills to develop properly. As a matter of fact, it becomes apparent that adolescents with a dysfunction of fine manipulation show poorly expressed or even abnormal fidgety movements during infancy [24]. Infants with a total loss of sight due to retinopathy of prematurity but with no brain lesion show fidgety-like movements with a very high amplitude and a pace too slow. Lasting much longer than normally, namely, until the age of 8–10 months, such movements might represent an attempt to compensate for the poor integration of vision and proprioception [25].

9.3 Consistently Present Cramped-Synchronised General Movements: A Predictor of Spastic Cerebral Palsy at Preterm Age

In the late 1980s, Prechtl and his group demonstrated that foetuses and preterm infants moved differently if their nervous system were impaired [26, 27]. It is the *lack of variability, complexity and fluency* of movements in particular that marks an impaired nervous system at such an early stage. Normally, GMs of foetuses, preterm infants and full-term neonates comprise the entire body and manifest themselves in a variable sequence of arm, leg, neck and trunk movements. They appear and cease gradually, varying in intensity and speed. Rotations and frequent slight variations of the direction of motion make them look complex but smooth [4]. They are among the first movements that the embryo develops: at 8 weeks' gestation, the whole body moves, albeit slowly and within a limited range [28]. No more than a week later, the speed, amplitude and direction start to vary a little. Thereafter (i.e. from 9 weeks and 3 days' gestation onwards), most GMs show a substantial degree of variation not only in speed, amplitude and direction but also in the sequence of body parts [29]. No matter how variable the movements, they always appear graceful and fluent in character.

While referring to *foetal* or "preterm GMs" before term, we call them "writhing movements" from term until about 6–9 weeks post-term age [3]. The latter are characterised by a slower pace and a moderate amplitude [4]. As the writhing GMs gradually disappear by the end of the second month, the fidgety GMs gradually emerge.

Foetal, preterm and writhing GMs display various patterns of abnormality, including the so-called cramped-synchronised GMs. These abnormal GMs appear rigid as they lack the usual smoothness and fluent character. All limb and trunk muscles contract and/or relax almost simultaneously [26]. Observing this pattern consistently over several weeks can be highly predictive (98%) of the eventual development of spastic CP (Table 9.1). The sooner the cramped-synchronised GMs evolve and the longer they last, the more severe the future functional impairment will be [16].

9.4 How Can We Identify a High Risk for Unilateral Cerebral Palsy by Means of Observation?

Infants with a future unilateral spastic CP show abnormal (usually cramped-synchronised) GMs during term age; moreover, they lack fidgety movements at 3–5 months post-term age [30].

This circumstance refutes the hypothesis of a silent period of unilateral CP. At about the age of 2–4 months, the first asymmetries can be observed: contralateral to the side of the lesion and regardless of the position of the head, the so-called segmental movements (isolated finger and toe movements) are reduced or even absent [31, 32]. At this age, neurological examination (e.g. the Hammersmith Infant Neurological Examination, HINE) may still yield normal results, but combining it with the assessment of GMs facilitates early identification of unilateral CP [33]. In the largest longitudinal study to date, 13 children out of more than 900 preterm infants were eventually diagnosed with unilateral CP. Eleven of them had shown no fidgety GMs. This finding is especially remarkable since nine of the infants had a persistent flare on the brain ultrasound with no signs of unilateral damage, meaning that their brain ultrasound had not predicted unilateral or indeed any other form of CP. Surprisingly, the HINE scores of all but one infant were within the normal range [33]. These results clearly lead to the conclusion that a 3- to 4-month-old infant with a *normal neurological score* but *missing fidgety GMs* and *asymmetrical segmental movements* is at a high risk of developing unilateral CP [34].

9.5 A Lack of Fidgety Movements Coinciding with Abnormal Arm Movements Is a Marker for Dyskinetic Cerebral Palsy

Until the second month post term, infants who later become dyskinetic display a so-called poor repertoire of GMs [35]: the sequence of movement components is monotonous, and the movements of the various body parts do not appear in the complex way seen in normal GMs [26]. Apart from the poor repertoire GM, the infant moves his/her arms "in circles", spreading the fingers. Characteristically, these abnormal *circular arm movements* are present at least until the age of 5 months post term. They are uni- or bilateral, monotonous, slow forward rotations originating in the shoulder (see also Chap. 18). The monotony in speed and amplitude is the most characteristic quality of such abnormal arm movements. From the age of 3 months onwards, *absent fidgety movements* and a lack of movements towards the midline (particularly foot-to-foot contact) are another marker for future dyskinetic CP [35].

Conclusion

The methodological breakthrough of the GM assessment lies in its predictive value of the development of neurological deficits, in particular of CP, at a very early age. In addition, the assessment of GMs is non-intrusive, easy to acquire and cost-effective. A number of studies have shown that combining the GM assessment with neuroimaging—especially MRI—and/or a neurological assessment is even more effective in predicting the neurological outcome than the GM assessment alone (e.g. [17, 36, 37]).

The great advantage of detecting an increased risk of CP at such an early stage consists in the *possibility of intervention* long before the emergence of pathological features. The consistent presence of cramped-synchronised GMs—and even more so the absence of fidgety movements—puts an infant at such a high risk of CP that physiotherapeutic intervention is justified. Even though intervention is most unlikely to prevent CP, it may have a positive effect on the child's functional abilities in the future [38, 39]. Psychological support for parents and the maximal functional deployment and early adaptation of the impaired child are crucial.

It is no less important to identify infants who, in spite of an increased risk due to their clinical history, have normal GMs and can thus be expected to have a normal neurological outcome.

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Clinical Characteristics

10

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Abstract

Cerebral palsy (CP) is the most frequent motor disability in childhood, occurring in about 2 per 1000 live births. The motor impairment may be accompanied by disturbance of other functions, such as cognition, communication, perception, behaviour and epilepsy.

The evaluation of the child includes:

- Differentiating CP from progressive causes of neuromotor disability and spinal lesions, to define the musculoskeletal impairment and decide on ways of treatment and to identify, evaluate and address accompanying impairments.
- Assessment of muscle tone, strength and selective motor control of specific muscle groups, contractures, posture, balance and equilibrium responses as well as severity of motor impairment.
- Classification according to predominant motor disorder into spastic, dyskinetic or ataxic CP. Spastic CP is the most common type, classified as uni- or bilateral spastic CP. Dyskinetic CP is classified as choreoathetotic or dystonic CP. Special forms of ataxic CP, the least common type, are dysequilibrium syndrome and ataxic diplegia.

More than half of the patients also have additional clinical problems, affecting activity and participation. The occurrence of accompanying impairments increases with gross motor severity, while some impairments are specific for the type of lesion and clinical CP type.

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10.1 Introduction

Cerebral palsy (CP) is the most frequent motor disability in childhood, occurring in about 2 per 1000 live births. The motor disorders of cerebral palsy are often accompanied by disturbance of sensation, cognition, communication, perception, behaviour and/or by a seizure disorder [1] and may be highly complex; they tend to become even more complicated in severely affected patients. The primary deficits include muscle tone abnormalities, influenced by position, posture and movement, impairment of balance and coordination and decreased strength and loss of selective motor control. Secondary musculoskeletal problems are added progressively with time in response to the primary deficits and produce further motor dysfunction; these are muscle contractures and bone deformities.

10.2 Clinical Evaluation

The clinical evaluation of the child with CP should take the form of a standardized stepwise assessment that has three specific goals:

- To differentiate CP from progressive causes of neuromotor disability and spinal lesions
- To define the musculoskeletal impairment and decide on ways of treatment
- To identify, evaluate and address accompanying impairments

This requires a detailed history (mother, pregnancy, delivery and child), recording of the developmental milestones and a paediatric and neurological examination, with particular attention to growth charts and head circumference; search for malformations and abnormalities of the skin should be included in addition to examination for hepatosplenomegaly and other signs of neurometabolic diseases (see also Chaps. 9 and 11).

The neurological examination of an infant or a young child depends on the careful observation of the child's behaviour, the way he/she plays, moves, observes and communicates with the environment [2]. A standardized neurological examination should be performed. Special developmental tests and testing of cognitive functions are also helpful in the evaluation of the child with CP. Finally, upon completion of the clinical evaluation, neuroimaging, preferably magnetic resonance imaging (MRI), is important for further diagnosis. All children with CP should have a routine MRI scan to provide information on the timing and extent of the lesion [3, 4]. A recommended age for MRI is 2 years or more (see also Chap. 13).

A careful definition of the accompanying impairments is of great importance. For children with an established diagnosis of CP, review of the physiotherapy regimen, medication history and review of previous surgery are also necessary. The American Academy of Neurology and the Practice Committee of the Child Neurology Society have developed practice parameters as strategies for patient management based on analysis of evidence [5].

An examination that is specific for the patient with CP includes the following:

- Assessment of muscle tone
- Determination of strength
- Examination of selective motor control of specific muscle groups
- Estimation of static deformity and/or muscle contracture at each joint
- Evaluation of posture, balance and equilibrium responses in standing position

10.2.1 Assessment of Muscle Tone

Muscle tone is the resistance to passive stretch while a person is attempting to maintain a relaxed state of muscle activity. Hypertonia is an abnormally increased resistance to an externally imposed movement about a joint. Hypertonia may be caused by spasticity, dystonia, rigidity or combination of these. Spastic hypertonia manifests with an increase in the resistance at higher speeds of the movement (*spastic catch*). It may be measured by several methods. The most widely used technique is the modified *Ashworth scale* [6, 7]. This is an ordinal scale of tone

intensity; patient and test condition variability contribute to unreliability. This scale was tested in children with CP and was not found as effective in quantifying a change in spasticity as the *Tardieu scale*. The *Tardieu* scale may be more useful in quantifying the neural and peripheral components of spasticity. It has been validated for detection of the changes in spasticity resulting from botulinum toxin A treatment in a double-blind, randomized, controlled trial [8]. Dystonic hypertonia manifests with an increase in muscle activity when at rest, has the tendency to return to a fixed position, increases with movement of the contralateral limb and will be affected with any change in the mood or the posture of the child. Dystonia needs to be differentiated from spasticity. Dystonia is not velocity-dependent and is not mediated by hyperactive proprioceptive stretch reflexes. It is defined by Sanger as a movement disorder in which involuntary sustained or intermittent muscle contraction cause twisting and repetitive movements, abnormal postures or both [9, 10]. It is efferent mediated, arising from continuous supraspinal drive to the spinal motor neurons and is altered by postural changes.

In rigid hypertonia, contrary to spasticity, the resistance is almost the same regardless of the range or velocity of movement, like bending a lead pipe. Sanger et al. [9] have more specifically defined rigidity as hypertonia characterized by resistance to externally imposed joint movement at very low speeds of movement that does not depend on imposed speed and that does not exhibit a speed or angle threshold. Additionally, in rigidity, simultaneous co-contraction of agonists and antagonists may occur, and this is reflected in an immediate resistance to a reversal of the direction of movement about a joint; there are no fixed postures, and voluntary activity in distant muscle groups does not lead to involuntary movements about the rigid joints, although rigidity may worsen (see also Chap. 15).

Determination of strength is extremely important in the child with CP and is considered an integral part of the evaluation for optimal clinical outcome. It is carried out by manual muscle testing using the 5-point Kendall scale or a handheld dynamometer [6] for isometric strength measurement. This is a valid and reliable tool; validity depends on appropriate positioning, stabilization of the child and experience of the examiner. Normal values for young children exist as well as data for CP.

10.2.2 Examination of Selective Motor Control of Specific Muscle Groups

Children with CP have impaired ability to isolate movements upon request, appropriate timing and maximal voluntary contraction as well as to control them without overflow movement from other muscle groups. This contributes to their functional motor deficits and impaired ambulatory capacity [11]. It is important to include a selective motor control measurement in the evaluation of the child with CP. This is usually carried out together with strength measurement and typically has three levels:

0: No ability to isolate movement
1: Partial ability to isolate movement
2: Complete ability to isolate movement

10.2.3 Estimation of Static Deformity and/or Muscle Contracture at Each Joint

Examination of range of movement (ROM) will give some information on the type of the contracture—dynamic versus static—at each joint. Measurement of the slow passive range of movement gives an indication of the muscle length at rest (static muscle length). It is different from the dynamic muscle length which is identified by measuring the point of resistance to a rapid velocity stretch-catch. Differentiation between dynamic and static deformity is best carried out under anaesthesia; the dynamic contracture completely disappears, and what remains is static contracture. The joint range of motion (ROM) is measured by goniometry. There are a number of clinical tests that are performed in the spasticity clinic and aim to differentiate between static and dynamic deformity [12]:

Silfverskiold test: this test differentiates tightness of gastrocnemius and soleus muscles by assessing the degree of passive dorsiflexion of the foot and the mechanical tightness of the gastrosoleus complex and the Achilles tendon. If there is greater degree of dorsiflexion with the knee flexed than with the knee extended, then the gastrocnemius contributes more to the contracture than the soleus.

Duncan-Ely test: this test demonstrates spasticity of rectus femoris and hidden flexion contracture of the hip. It is done with the patient prone on the bed; the tested leg is flexed at the knee, while the other leg is extended on the bench, and the examiner keeps the hand on the lumbar spine of the patient. If there is no spasticity of the rectus femoris, the hip stays on the bed; if spasticity of the muscle exists, the hip lifts off the bed.

Thomas test: this test assesses shortening and increase of muscle tone of the iliopsoas. With the patient supine, start with both legs extended. Then maintain passive hip and knee flexion of the untested side until the lumbar spine is flattened on the bench. Keep one hand under the lumbar spine to ensure that lumbar lordosis is compensated; if the hip lifts off the bench, then there is hip flexion contracture.

Popliteal angle measurement: it measures knee flexion contracture. The test may be done with the opposite leg extended and then flexed, and from the difference in popliteal angle measurements, conclusions may be derived on the degree of tightness of the hamstrings as well as on the hip flexion contracture.

Adductor tightness: this test measures the hip abduction range with knees flexed and knees extended.

10.2.4 Evaluation of Posture, Balance and Equilibrium Responses in Standing Position

Posture of the trunk, pelvis and lower extremities needs to be examined during sitting, standing and walking, preferably both in sagittal and coronal planes. Balance and equilibrium responses are particularly important for children with ambulatory potential. The standing child may be pushed gently from the front, back and side, in order to evaluate his ability to regain balance. Many children with CP have delayed or deficient posterior equilibrium responses.

For ambulatory patients, gait may be evaluated by observation. During the clinical assessment, it is best to use a systematic method for the evaluation of gait parameters. Two validated instruments are recommended especially if outcome measurement is important: the observational gait scale [13] and the Edinburgh visual gait score [14]. Yet, a simple, careful videotaping of the patient's walking will provide the examiner with the opportunity for repeated careful observation of the gait patterns for further diagnosis and decision making and this cannot be underestimated. Computerized gait analyses with or without force plates and EMG give a more objective description of the gait, useful for evaluation of interventions [15].

10.2.5 Optimal Age for the Diagnosis of CP

The optimal age for diagnosis may be very different for the clinician and for the epidemiologist or other researcher. Initially some studies in Europe reported CP prevalence rates for children as young as 3 years of age; later, the Surveillance of Cerebral Palsy in Europe network of 14 centres decided, after harmonization of the data, to include cases of CP who were 5 years of age at diagnosis [16]. The child who is eventually diagnosed with CP shows a slow neuromotor development in infancy, and in many of these infants, the clinical picture is more or less established early. It is usually characterized by the persistence of primitive reflex movements that are typical of the neonatal period and the delay in the appearance of the advanced postural reactions that would normally appear in infancy [17]. These advanced postural reactions form the basis for the control of movements and balance as the infant grows up and is expected to progress from the primitive and reflex movement patterns of the neonate to the voluntary and controlled movements of the older child. Motor

findings suggestive of CP can improve or disappear at later age; thus, it can be expected that some children given a CP diagnosis at an early age will not fulfil the criteria later.

In *summary*, the evaluation of a child with CP should address the following:

- The phenomenology of the motor impairment syndrome, i.e. the type of CP, with comments on distribution, severity and accompanying impairments
- The localisation of the brain lesion that is responsible for the above
- The exclusion of a progressive lesion or spinal lesion

10.2.6 Severity of Gross Motor Function

The severity of gross motor involvement of the patient with CP can be classified with the Gross Motor Function Classification System [18]. GMFCS classifies gross motor function into five levels, from Level I (the most independent motor function) to Level V (the most restricted voluntary control of movement and ability to maintain antigravity head and trunk postures). The gross motor function at different ages (*age bands*) is described for the five levels. Developmental curves have been produced for each of the GMFCS levels [19], which are helpful when informing parents about prognosis of motor function.

10.3 Types of Cerebral Palsy

CP is clinically categorized into spastic, dyskinetic and ataxic types based on the predominant motor disorder. Terminology varies between classifications throughout the world. The description of CP type by limb distribution does not indicate severity level and very often does not offer prognostic utility [20]. Furthermore, there is great interrater variability when terms are not defined using functional scores for the upper and lower limbs. For these reasons, the new CP classification system introduced by the SCPE network in 2000 [21] with description of the distribution into bilateral and unilateral with further characterization of type by dominant neurological sign and severity by GMFCS level is favoured.

The need for harmonization was most needed in bilateral spastic CP (BSCP), where different terms coexist and cut-off limits between similar terms differ between countries.

10.3.1 Spastic CP

Spastic CP is characterized by muscle hypertonia of the pyramidal type, increased deep tendon reflexes, clonus, Babinski sign, co-contraction of agonists and antagonists and a tendency for permanent deformities, e.g. femoral anteversion resulting in scissoring, pes equinus, wrist flexion deformity, etc. This is the commonest type of CP, comprising 85–90% of the total group. Depending on the topographical distribution, bilateral and unilateral spastic CP is described. The clinical signs in spastic CP are related to a lesion of the upper motor neuron. The manifestations of an upper motor neuron lesion are best divided into positive and negative ones. The positive signs are spasticity, clonus and released flexor responses [22]. The negative signs include loss of finger dexterity, weakness and loss of selective control of muscles and limb segments, resulting in slow and difficult volitional mobility. It is often the negative features that determine the level of disability and long-term prognosis in CP rather than the positive signs of the upper motor neuron lesion. It is therefore important to document the relative contribution of all the elements of the upper motor neuron lesion, albeit difficult.

10.3.2 Bilateral Spastic CP

Overall, bilateral spastic CP (BSCP) constitutes about 50% of all CP, and the prevalence is decreasing [23]. Periventricular white matter lesion is the most common finding, especially in the preterm [22]. These lesions are detected early with the use of ultrasound and MRI. Neuroimaging findings may be different in the full-term and the preterm with BSCP [24, 25].

In ambulating children with BSCP, the upper limb is less involved. The involvement is bilateral but may be asymmetrical.

Rodda et al. [26] described five gait patterns recognized in the ambulant child with bilateral spastic CP in the sagittal plane that were of great importance for treatment decisions. These are the following:

- True equinus
- Jump gait
- Apparent equinus with knee and hip flexion
- Crouch gait
- Asymmetric gait with a combination of features, for example, apparent equinus and jump gait

True *equinus* refers to the position of the ankle in plantar flexion throughout stance; hips and knees remain extended. It indicates calf spasticity. Other musculoskeletal problems at the ankle are the valgus foot deformity and rarely the varus.

Crouch gait represents the common evolution from toe walking of the young child, i.e. from gastrocnemius dominant spasticity, to a pattern of increasing hip and knee flexion and eventually to "crouch" with ankle dorsiflexion. This is due to hamstring and psoas spasticity and excessive ankle dorsiflexion.

Jump gait is a very common gait pattern observed in the young child in the sagittal plane, characterized by excessive hip flexion, knee flexion and equinus in stance. This is due to spasticity of the flexors of the lower extremities. As a result the hips and the knees are in flexion and the ankles are in plantar flexion as well.

Stiff-knee gait is a gait pattern that has to do with rectus femoris spasticity or to the unopposed action of the rectus femoris after hamstring lengthening. It is characterized by limited motion of the knee joint especially a lack of flexion in the swing phase, observed in the sagittal plane.

Adductor spasticity and/or medial hamstring spasticity results in a scissoring posture. It may contribute to early hip displacement.

In severe bilateral spastic CP, all four limbs are involved, and there may be signs of dystonia (Fig. 10.1). This may lead to difficulties in classifying the dominant symptom. It is found in neonates after a prolonged and difficult labour and generally in infants born after severe perinatal complications [27]. Spastic tetraplegia with involvement mostly of the lower extremities is usually seen in preterm infants. Primitive reflexes remain longer than normal; there is difficulty in feeding, while later scissoring appears as well as flexion posture of the upper limbs. It is common to find hyperextension and opisthotonus in the supine position and flexion in the prone [22, 28]. The child is at great risk of not being able to sit without support. Contractures are common later in life. The most frequent

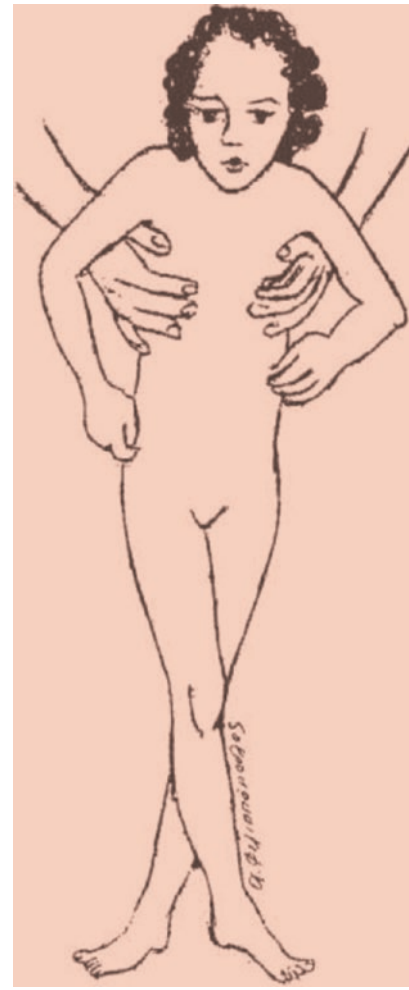


Fig. 10.1 Bilateral spastic cerebral palsy (tetraplegia) with scissoring

secondary musculoskeletal deformities in the non-ambulatory bilateral spastic patient that requires orthopaedic intervention are dislocation of the hip and spinal deformity (scoliosis). Musculoskeletal problems at the knee and at the ankle similar to those of the child with milder bilateral spastic CP are encountered and are handled in similar ways. The upper extremities are also affected. The end result is wrist flexion contractures and deformities.

Spasticity, dystonia, loss of selective motor control and sensory deficit contribute in various degrees to decreased utilization of the upper limbs; this in combination to the visual and/or intellectual impairments that usually accompany this type of CP contributes further to the problem. Some children with moderately severe BSCP may achieve independent walking at the age of 7–8 years, an age where the peak motor performance occurs in children with CP, while some children will lose their walking ability as they grow.

In ambulatory children with BSCP, occurrence of accompanying impairments is lower than in severe cases. Intellectual impairment, learning and memory [29], epilepsy, visual impairment and pseudobulbar palsy (paresis of facial, lingual and pharyngeal muscles) resulting in drooling, feeding and speech difficulties [30] are common in severe BSCP. Recurrent infections of the respiratory tract are also common. In the total group of bilateral spastic CP, 56% had intellectual impairment, 46% had epilepsy, and 22% had severe visual impairment in a Swedish study [31], while intellectual impairment in 39–74% and epilepsy in 14–53% was reported from Australia [32]. Visual impairment may include visual field impairment, oculomotor dysfunction and reduced visual attention [33].

10.3.3 Unilateral Spastic CP

Unilateral spastic CP (USCP) constitutes about 35% of all CP and is increasing in prevalence [23]. The aetiology is heterogeneous, mostly pre- and perinatal (70–90%), while in 30% the cause is unknown. In premature infants the commonest causes are white matter lesions. In full-term infants the most frequent aetiologies are cerebral malformations, cerebral infarction or haemorrhage [28, 34]. The pathogenetic mechanism of the vascular lesions may involve thrombosis, embolism, infarction or haemorrhage in the distribution of the middle cerebral artery or in the territory of a major cerebral vessel [3, 28, 35].

The diagnosis of USCP is rarely possible immediately after birth even though some evidence may be found after a detailed examination in arm movement immediately after birth. Asymmetry may also be due to brachial plexus palsy. Later, asymmetries in the Moro reflex, in the walking reflex, in the ATNR as well as a permanent grasping position of the hand may lead to an early diagnosis of unilateral involvement. Later, there is asymmetry in the parachute reflex, while even later difference in the movement patterns and in the use of the involved limbs becomes obvious. Muscle tone is initially reduced and later increased with emerging spasticity, increased reflexes, ankle clonus and Babinski sign. There is weakness mainly in the antagonist muscles and inability to perform fine movements. The elbow is in a flexed posture, the foot usually assumes an equinovarus position, although valgus deformity may also be seen. Later, atrophy appears in the affected side and flexion contractures appear in the elbow, wrist and knee joint [34, 36]. The affected side may be shorter depending on the severity of the involvement. In the older child, the clinical presentation is characteristic. The upper extremity is in adduction at the shoulder and internal rotation; the elbow is flexed and pronated; the wrist and the fingers are flexed, and the thumb is in the palm (Fig. 10.2). Spontaneous movement of the upper extremity is reduced and abnormal. Fine movements are clumsy or impossible to be performed. In more severe cases, scoliosis may also develop. It is rare for the child with unilateral spastic CP to start walking during the first year of life; independent ambulation usually begins around the 18th to 20th month of life and in severe cases even later.

Fig. 10.2 Unilateral spastic cerebral palsy (hemiplegia) on the right side

The posture and the gait pattern are fairly typical. The classic gait cycle of the unilateral spastic gait pattern includes:

- Toe strike
- Flexion of the hip and knee or knee recurvatum
- Retraction and elevation of the pelvis
- Posturing of the ipsilateral arm
- Greater knee flexion of the contralateral side

Based on gait analysis, Rodda and Graham described in 2001 [37] a comprehensive classification system with four hemiplegic gait patterns that is very relevant to the clinician when treatment decisions are made.

Epilepsy is a common accompanying clinical problem of USCP occurring in 25–40%. Impaired growth of the affected upper and lower limb may be noted as well. Most children with USCP have no intellectual or speech impairment [32]. An ipsilateral visual field impairment may be present, as well as strabismus [33].

Wu et al. [24, 25] reported the MRI findings in a retrospective study of 96 children with unilateral spastic CP; 30% of them had perinatal arterial infarcts. In the same study, the most frequent finding in children born preterm was periventricular white matter lesion.

10.3.4 Dyskinetic CP

Dyskinetic CP is characterized by involuntary movements, distorted voluntary movements and abnormal postures due to sustained muscle contractions [38]. Dyskinesia includes choreiform, athetoid and dystonic abnormal involuntary movements. Choreiform movements are fast, irregular, pathological and involuntary contractions of individual muscles or small muscle groups; these most often involve the face and bulbar muscles, proximal limb muscles resulting in "chorea" (χορός = Greek for dance), as well as toes and fingers. Athetosis refers to slow writhing movements (Fig. 10.3) mainly of the distal muscles that result in the inability of the child to maintain a position [39]. Dystonia, chorea and athetosis frequently co-occur in the child with dyskinetic CP [40].

Dyskinetic CP is classified into dystonic and choreo-athetotic subtypes based on the dominant neurological sign; the dystonic group constitutes 80%. Overall, dyskinetic CP accounts for about 6–15% of all cases of CP, and its prevalence appears to be stable in children with a normal birth weight in Europe [41]. Muscle tone is variable but more commonly on the hypotonic side during infancy. Involuntary postures and movements are induced or exacerbated by emotional factors or movement.

Dystonic CP is the more severe and more common type of dyskinetic CP. It has a different

Fig. 10.3 Athetotic type of dyskinetic cerebral palsy, typical position

presentation and a different evolution; it results to a lesser extent in contractures. It would respond well to therapies modifying motor nerve or muscle activity, such as botulinum toxin. Dystonia may vary from day to day and from hour to hour. It is influenced by intrinsic (patient) and extrinsic (environment) factors. Occasionally, status dystonicus can occur, characterized by prolonged or increasingly frequent generalized dystonia, requiring early detection and urgent management. High correlation was found between dystonia and level of gross motor function and manual ability [40].

Dyskinetic CP is related to lesions in the basal ganglia and in the thalamus. Around 70% have lesions in the basal ganglia and/or thalamus on MRI, but other brain lesions also occur and a few have normal scans. Its commonest causes are hypoxia. In the past decades, kernicterus was common, leading to athetotic CP, frequently with high tone deafness. With successful treatment of hyperbilirubinaemia and prophylactic actions against foetal haemolysis in Rh-negative mothers, the incidence of kernicterus has greatly decreased in the Western world. In a Swedish study, it was found that children with dyskinetic CP were mainly full-term babies with a history of perinatal problems and particularly asphyxia [42].

In a study of 578 children with dyskinetic CP, 70% of whom were born at term between 1976 and 1996 with a birth weight of >2500 g, it appeared that these children had more severe motor impairment than children with other types of CP and that the percentage with intellectual impairment, epilepsy and visual and hearing impairments increased with the severity of the motor impairment. Almost 60% used a wheelchair for ambulation, which was significantly more common than in children with bilateral spastic CP. More than half had accompanying impairments, such as severe intellectual impairment and epilepsy [41]. In a Belgian study, 47% individuals with dyskinetic CP were able to communicate (sending and receiving messages, regardless of method) with unfamiliar partners [40]. Augmentative and alternative communication is often needed.

10.3.5 Ataxic CP

Ataxic CP is characterized by a disturbance of balance, coordination and control of fine movements (Fig. 10.4). The motor pattern is characterized by movements that are performed with abnormal force and rhythm and that deviate in accuracy. Intention tremor and dysmetria are common neurological signs as well as low muscle tone; there is gait ataxia. Ataxic CP accounted for a little over 4% of CP cases in the SCPE database, had a prevalence of 0.09 per 1000 live births in a Swedish study [43] and comprised 2.4% of the total number of children with CP in an American study [44]. A neuroanatomical correlate, such that is found in other CP types, is rarely found in children with ataxic CP. Children are usually hypotonic in the first few years of life,

Fig. 10.4 Ataxic cerebral palsy with wide gait and tendency to fall

and ataxia becomes evident after the second year of life. Ataxia may improve with time. Specific ataxic forms are ataxic diplegia and simple ataxia including disequilibrium syndrome. Recognizing ataxic diplegia and disequilibrium syndrome as special subtypes within the ataxia group is helpful in the clinical setting [43]. It is important to rule out a neurodegenerative disorder. Minor congenital anomalies were more frequent in those with ataxic CP than in control subjects [45]. These anomalies may be markers of early prenatal factors. There are cases of ataxic cerebral palsy that are inherited as an autosomal recessive trait, and specific genetic loci are sometimes found [46]. Only a few children have congenital hypoplasia of the cerebellum.

A Canadian study [47] has demonstrated that 44% of the children with ataxic CP were nonverbal, 44% had seizures in the last 12 months, 33% had severe auditory impairment, and 11% had cortical blindness.

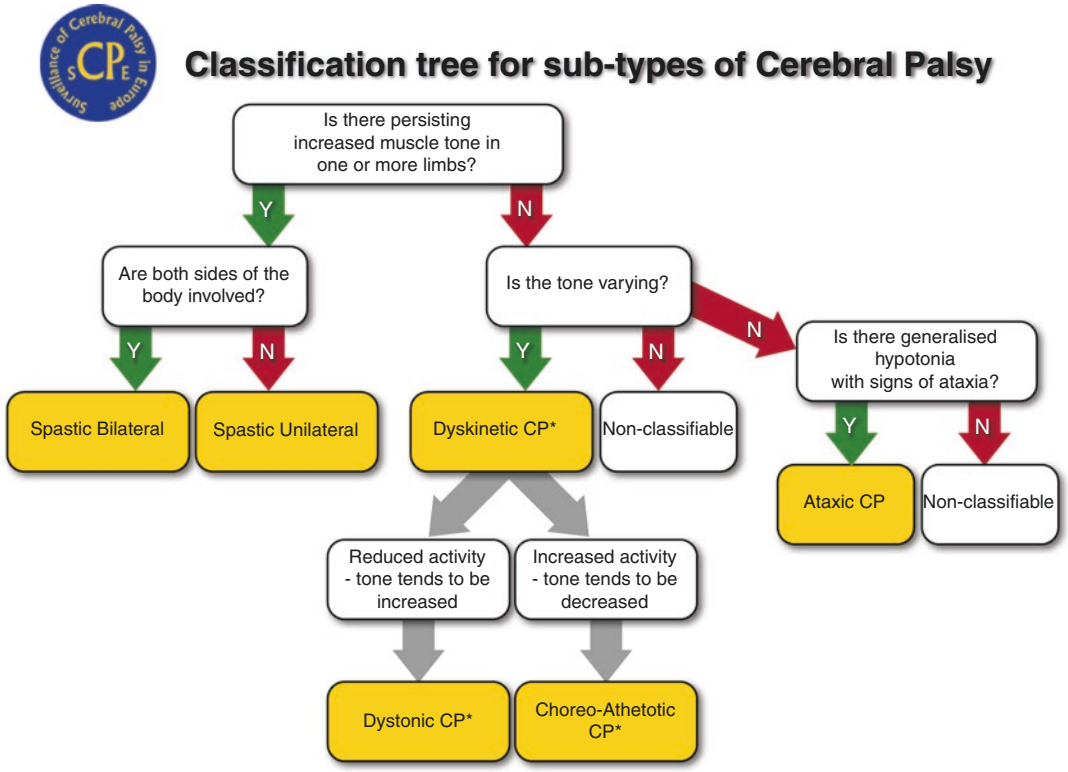
10.4 Additional Comments

10.4.1 Mixed Types of Cerebral Palsy

As previously mentioned, more than one neurological sign may be present in the child with CP. It is recommended to diagnose the subtype based upon the dominant symptom. The classification tree suggested by the SCPE is helpful in this respect. It is found on the SCPE website, in the Reference and Training Manual section [www.scpenetwork.eu/en/my-scpe/rtm/cp-and-cp-subtypes/] (Fig. 10.5).

10.4.2 Accompanying Impairments

Cerebral palsy may present only as a motor impairment. However, more than half of the patients also have additional clinical problems. The occurrence of accompanying impairments increases with gross motor severity. Some impairments are specific for the type of lesion and clinical CP type. The accompanying impairments may be affection activity and participation more than the motor impairment in CP. Emerging knowledge about communication, visual impairment, neuropsychiatric disorders and feeding increases the spectrum of functions to assess (for more details, see Chap. 27).



SCPE Collaborative Group. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Developmental Medicine and Child Neurology*. 2000;42:816-24.

Fig. 10.5 Classification tree for cerebral palsy subtypes (Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol 2000; 42: 816–824)

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Early Diagnosis and Differential Diagnosis of Cerebral Palsy

11

Rudolf Korinthenberg and Christos P. Panteliadis

Abstract

Cerebral palsy (CP) is a multi-aetiological term, including residua of early brain damage as well as certain nonprogressive genetic conditions. However, progressive diseases such as brain tumours, neurometabolic and neurodegenerative disorders have to be excluded. When the perinatal history is severe and acquired brain damage has been documented, the early diagnosis of cerebral palsy is easy. On the other hand, with an unsuspicious history, the diagnosis of CP usually requires prolonged observation based on adequate developmental tests and neurological examinations.

An early diagnosis and treatment of CP are usually believed to lead to an improved outcome; however for several reasons, this has never been proven with adequate research methods. This chapter gives a short overview on the most important conditions and syndromes that have to be differentiated from CP including some references for further reading.

11.1 Introduction

The diagnosis of cerebral palsy (CP) is not an aetiological but a phenomenological one and based on clinical assessment. CP is an "umbrella term" covering various clinical pictures with predominantly motor symptoms originating in the pre-, peri- or early postnatal period. It is a nonprogressive disorder, although the symptoms change with the child's growth and development (see also Chap. 2). It is necessary to differentiate CP from other neurological diseases with progressive deterioration over time, such as brain tumours, degenerative and neuromuscular diseases and inborn metabolic disorders. One must also differentiate CP from spinal cord diseases and disorders

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revealing purely intellectual dysfunction (*mental retardation*). However, depending on the degree of the severity of cerebral palsy, cognitive impairment, disorders of sensory perception and epilepsy frequently coexist.

Concerning *aetiology*, many authors use the term CP to describe only cases with acquired early brain damage secondary to infections, hypoxic-ischaemic, cerebrovascular or traumatic events (see also Chap. 6). Such a definition can be useful mainly for genetic counselling. However, the consequences of *early* prenatal brain damage can often not be discerned from primary brain malformations, and several genetic syndromes have a clinical picture similar to that of cerebral palsy. It is therefore quite sensible to use the purely phenomenological definition and defining the aetiology on a separate level.

11.2 Early Diagnosis

Early diagnosis of CP together with early treatment is expected both to improve the parents coping with their child's disability and to improve treatment effects making use of the higher plasticity and regenerative capacity of the brain in early infancy. However, recent reviews and meta-analyses stressed that such a superior treatment effect could never be confirmed in adequately designed clinical trials. Besides a true lack of effect, a variable definition of "*early*" treatment, variable interventions and variable disease severity could be causative for these negative results. Scandinavian authors recently concluded that there is still a large unmet need of research in the field of early intervention in cerebral palsy [1].

In infants with severe complications of neonatal intensive care a probable diagnosis of CP can frequently be made early. However, without such apparently brain damaging events due to the evolving character of symptoms an early clinical diagnosis during the first 12–18 months of life may be difficult if not impossible. Nevertheless, such an early diagnosis is desirable for the child and its family. In the Danish study by 1291 children, born between 1995 and 2003, the overall median corrected diagnostic age of CP to be 11 months [2]. The first symptoms are disturbances of muscle tone (either hypotonic or hypertonic), persistence of primitive reflexes (e.g. Moro, ATNR), abnormal postures and movements and delayed motor milestones, presence of epilepsy and abnormalities in the cerebral neuroimaging and ultrasonography (see also Chap. 9). However, these symptoms are not CP specific. They may be observed in all disturbances of brain development including pure mental retardation and autism but also as a transient phenomenon of unknown aetiology with a benign outcome. During the third and fourth trimesters of life, more specific signs appear, such as a spastic hemiplegic pattern or hypertonic patterns in the arms and legs with scissoring and increased deep tendon reflexes.

11.3 Diagnostic Work-Up

The *first* and most *important* question is whether an observed delay in developmental milestones (retention of primitive reflexes, muscular weakness) or a postural abnormality is severe enough to suspect *CNS* pathology. For example, does the infant not yet sitting or the toddler not yet walking independently have a neurological problem, or do they just demonstrate borderline development? To answer this question, one must consider the variability of normal development in all developmental fields (motor, adaptation, perception, hearing, vision and social contact), ideally relying on standardised developmental tests. Not only should the *quantity* of motor development be considered but also the quality of those movements. A neurodevelopmental examination will exclude or identify the signs that are pathognomonic of cerebral damage such as increased tone, abnormal reflexes and later (possible) cognitive dysfunction [3].

A number of infant developmental tests have been developed and validated to objectively investigate neurological function and predict outcome in young infants. The Hammersmith Infant Neurologic Examination (*HINE*) has been validated for neonates, infants and low- and high-risk premature from term gestation onwards [4, 5]. Its predictive value for cerebral palsy has been

shown to be high throughout the first year of life. The most predictive items are those assessing movement quality and quantity [6]. The Infant Motor Profile (*IMP*) is applicable in children from 3 to 18 months. It has been shown to differentiate between infants with normal neurological condition, simple and complex minor neurological dysfunction and abnormal neurological conditions [7]. The general movement assessment is based on the Gestalt perception of spontaneous movements in young infants. Its predictive value for normal or abnormal development is very high in infants with various developmental risk situations and underlying diseases (see also Chap. 9).

Prechtl [8] proved the quality of spontaneous general movements (*GMs*)—particularly during the third month of corrected (postmenstrual) age—to be a reliable and valid tool for distinguishing *between* infants who are at significant risk of developing neurological deficits and infants who are not.

However, despite these investigations the initial diagnosis is often only one of suspicion. In these cases, the patient must be re-evaluated at regular time intervals.

When the *presence* of a pathological condition is confirmed, it is imperative to take a detailed history and perform a complete paediatric and neurological investigation. Neuroradiological studies are generally recommended, and sophisticated laboratory tests are sometimes necessary.

The presence of similar symptoms in other *family members*, as well as the parent's consanguinity is clues diagnosing a genetic disease. The full family history has to include at least three generations.

In many patients, *prenatal* or *perinatal* factors can be identified that are known to be associated with an increased risk of brain damage and cerebral palsy [9]. However, identifying such possible risk factors and differentiating CP from genetic diseases is often problematic. Although an infant with perinatal asphyxia may present with CP later in life, most do not. On the other hand, the absence of risk factors for CP cannot exclude it from the differential diagnosis (25–35% cases of CP do not have risk factors (see also Chap. 6)) but should lead to more thorough investigation for other possible causes. Therefore, when taking the perinatal history, a critical approach is necessary. To establish asphyxia as the cause of CP, one must identify clear signs of an acute neonatal hypoxic-ischaemic encephalopathy (somnolence or coma, newborn multifocal seizures, abnormal muscle tone). In addition, a 5-min Apgar score <5, a distinctly abnormal umbilical cord pH and an indication of multiorgan failure (such as necrotising enterocolitis, renal insufficiency, respiratory and haematological complications) are indications of asphyxia sufficiently severe to give rise to long-term disability [10]. However, we must not forget that prenatal neurological diseases and genetic syndromes can cause prematurity and asphyxia.

In infants with severe perinatal conditions, in addition to the clinical neurological findings of cranial ultrasound, the *EEG* and *MRI* investigations of the brain are helpful to predict the risk of cerebral palsy. In a cohort of 102 preterm babies born at <32 weeks of gestation or with a birth weight of <1500 g, 76.5% showed a suboptimal *HINE* score at term as compared with only 13.7% in a group of low-risk preterm infants. However, the predictive value for an abnormal *HINE* score at 12 months of age was much lower than that of cranial ultrasound investigations performed in parallel [11]. In a group of 1053 *NICU* patients with regular ultrasound examinations in the neonatal period and prospective neurological evaluations at 2 years of age, 44% of the children with ventriculomegaly and 52% with abnormal echolucencies developed cerebral palsy. However, 43% of children with cerebral palsy had shown normal ultrasounds in the neonatal period [12]. In neonates with hypoxic-ischaemic encephalopathy, an abnormal EEG background pattern was highly predictive of an abnormal neurological outcome (positive predictive value=0.88) which was even more increased by an abnormal ultrasound or MRI finding (PPV 1.0). An abnormal signal in the posterior limb of the internal capsule and diffuse cortical grey matter damage were the most predictive MRI findings [13]. Recent MRI techniques such as diffusion tensor imaging and fibre tracking can predict the severity of periventricular leukomalacia and neurological impairment [14, 15].

The diagnosis of a *progressive* neurological deficit in infants and children is frequently much more difficult than expected. Most diseases of the *CNS* in children delay brain growth and development. As the child grows older, the difference between the patient's abilities and those of a healthy child of the same age becomes greater and more obvious to the parents and health professionals; although no real loss of function has occurred. To obtain a reliable indication towards the diagnosis of a progressive disease, one has to look for an apparent loss of function and skills acquired earlier or at least for developmental stagnation. The coexistence of secondary nutritional and respiratory problems, orthopaedic complications and epileptic encephalopathy in children with CP can also lead to the mistaken impression of a progressive disease.

At the **clinical investigation**, the presence of certain clinical signs suggests the presence of genetic, neurometabolic, space-occupying or neuromuscular disorders, rather than CP (Table 11.1). Kuban et al. [16] developed an algorithm with three assumptions for the evaluation of the child with cerebral palsy in a cohort of 2-year-old children: *microcephaly* (head circumference <3rd percentile) already apparent at birth (e.g. familiar, genetic/primary hereditary, intrauterine infection or dystrophy, foetal alcohol abuse syndrome, perinatal/postnatal injures, etc.). *Macrocephaly* (>97 percentile) and an increasing head circumference either indicate a space-occupying lesion (hydrocephalus, tumour, hygroma, craniofacial dysplasia, leukodystrophies, some neurocutaneous disorders, etc.) or a neurometabolic disorder (glutaric aciduria *Type* 1, accumulation of abnormal lipids). *Specific* and *unspecific* major or minor malformations are indicative of a genetic aetiology especially when multiple. Epidemiological studies have shown that genetically abnormal neurological development associated with multiple, unspecific stigmata occurs much more frequently than specific genetic syndromes.

Table 11.1 Clinical findings suggestive of a disease other than CP

• Primary microcephaly
• Macrocephaly and/or rapidly increasing size of skull
• Specific or unspecific malformations and stigmata
• Psychomotor regression
• Corneal clouding, cataract, atrophy of the optical nerve and retinopathy
• Skin lesions such as depigmentation or hyperpigmentation
• Hepatomegaly and splenomegaly
• Cardiomegaly and cardiomyopathy
• Severe muscle weakness, absent tendon reflexes
• Blindness, deafness, other sensory deficits

The *clinical* investigation must also contribute to the differentiation whether the neurological abnormality is due to a central nervous system disorder (upper motor neuron) or to a disease of the peripheral neuromuscular system (lower motor neuron and muscle fibres). The presence of profound muscular weakness, severe hypotonia and diminished or absent tendon reflexes supports the latter diagnosis, while normal strength, hypertonus and increased reflexes support the former [17].

Modern *neuroradiological* methods such as *MRI*, *CCT* and cranial ultrasound can be extremely helpful in the diagnosis and differential diagnosis of CP in early life [18]. Typical CP patterns have been defined reflecting both the topography of damage and its timing during brain development. On the other hand, malformations, brain tumours and patterns specific for defined metabolic syndromes can be discerned. In more than 80% of CP cases, the examination will reveal pathological findings and contribute to the diagnosis [18, 19]. Damage to the brain during the first trimester of pregnancy gives rise to dysplastic findings such as agenesis of the corpus callosum, migrational disorders such as pachygyria, cortical heterotopia and schizencephaly. Later, polymicrogyria, periventricular leukomalacia and the residua of intraventricular haemorrhage are hallmarks. From the 37th week onwards, typical findings include selective neuronal necrosis with brain atrophy and ulegyria, parasagittal watershed infarctions, multicystic encephalopathy and localised infarctions giving rise to porencephaly. Subependymal and parenchymal calcifications are indicative of prenatal infections (cytomegalovirus, toxoplasmosis) and

some neurodegenerative disorders (Cockayne syndrome, Aicardi-Goutieres syndrome).

Further investigations must be performed regarding individual indications. An electroencephalogram during waking and sleep is necessary when epileptic seizures or developmental regression/stagnation due to subclinical continuous epileptic activity is suspected. Acoustic and visual evoked potentials are indicated at the suspicion of a sensory deficit. Nerve conduction studies, electromyography and a muscle biopsy are carried out to prove or exclude the presence of a peripheral neuromuscular disease or peripheral involvement in a multisystem disorder. Metabolic and genetic tests can be performed at a low degree of suspicion on a screening basis (amino acids, organic acids, chromosomes), but they should usually be done selectively on the basis of a clinically founded diagnostic hypothesis.

11.4 Differential Diagnosis

In most cases, the diagnosis of cerebral palsy can be confirmed by history (e.g. pregnancy, birth), clinical findings and perhaps additional neuroradiological investigations after an adequate observation period. However, the diagnosis of CP remains a diagnosis of exclusion in some cases (Table 11.2).

The main characteristics of CP are the static character of the underlying brain damage and motor disability secondary to cerebral dysfunction (see also Chap. 10; [15]). Cerebral palsy must be differentiated from several other neurological disorders with progressive course or different topography, such as neuromuscular, neurodegenerative and neurometabolic disorders, brain tumours, damage to the spinal cord and isolated cognitive dysfunction [20, 21].

Table 11.2 Groups of diseases to be differentiated from CP

• Nonprogressive genetic syndromes
• Progressive neurodegenerative diseases
• Dyskinetic syndromes and disorders of monoamine metabolism
• Neurometabolic diseases
• Neoplasias
• Hydrocephalus
• Spinal cord damage (developmental or traumatic)
• Neuromuscular disorders

11.4.1 Neuromuscular Disorders

This is a broad group of diseases affecting the lower motor neurons, nerves or muscle cells not usually affecting the brain. The diseases most frequently found in infancy are spinal muscular atrophy Types I and II, congenital myotonic dystrophy and the congenital muscular dystrophies. The so-called congenital structural myopathies and the congenital myasthenic syndromes are more rare diseases. The differential diagnosis can be difficult particularly during the first months of life when CP is still in its hypotonic phase [17, 22]. Not typical for children with a brain lesion, severely hypotonic and weak infants are mentally alert with absent deep tendon reflexes. Excessive muscle weakness can cause respiratory and swallowing difficulties. The congenital muscular dystrophies frequently present with early contractures (Figs. 11.1 and 11.2). The presence of mental retardation is usually indicative of a central nervous system lesion; however, one must remember that some of the classical neuromuscular disorders also show CNS involvement (myotonic dystrophy, the congenital muscular dystrophies with CNS alterations including Walker-Warburg syndrome, mitochondrial cytopathy).

The diagnosis of neuromuscular disorders requires a full work-up with testing of serum CK, electroneuromyography and muscular biopsy. In many of these diseases today, direct molecular genetic diagnosis is available and should be performed on a clinical suspicion (e.g. spinal muscular atrophy, congenital myotonic dystrophy).

11.4.2 Severe Psycho-Intellectual Delay

Primary mental retardation is more frequently the cause of a delay in infant motor development than in CP. The problem of differentiating these

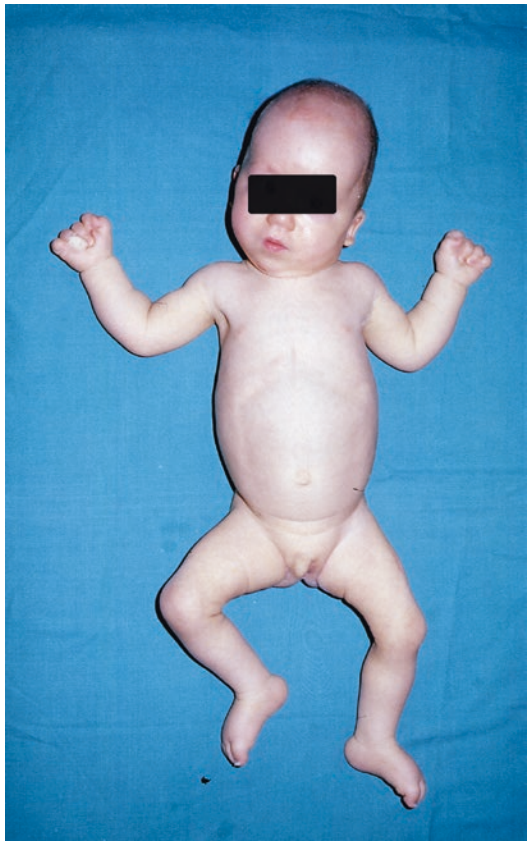

Fig. 11.1 Young infant with congenital muscular dystrophy showing both hypotonia and contractures

two conditions is obvious when one considers that CP is frequently associated with mental retardation. In pure intellectual delay, the motor retardation is usually mild or moderate, improving towards the end of the first year of life, whereas the learning difficulties (including speech problems) become more obvious. At the same time, the child with CP will develop the typical signs of spasticity. Thus, often there is a need of follow-up to differentiate the two conditions. Modern molecular-genetic diagnostic methods can contribute substantially to the aetiological understanding of these diseases [23].

11.4.3 Diseases of the Spinal Cord

Depending on the neurological level and degree of the damage, these patients present with partial or complete spastic paraplegia or less frequently tetraplegia associated with sensory loss with a sharp upper margin and bladder dysfunction. Brain function is normal. Tumours of the spine and spinal cord, traumatic perinatal damage (usually at the junction of the cervical and thoracic spine following breech delivery) or transverse myelitis must be considered as possible causes. Due to the

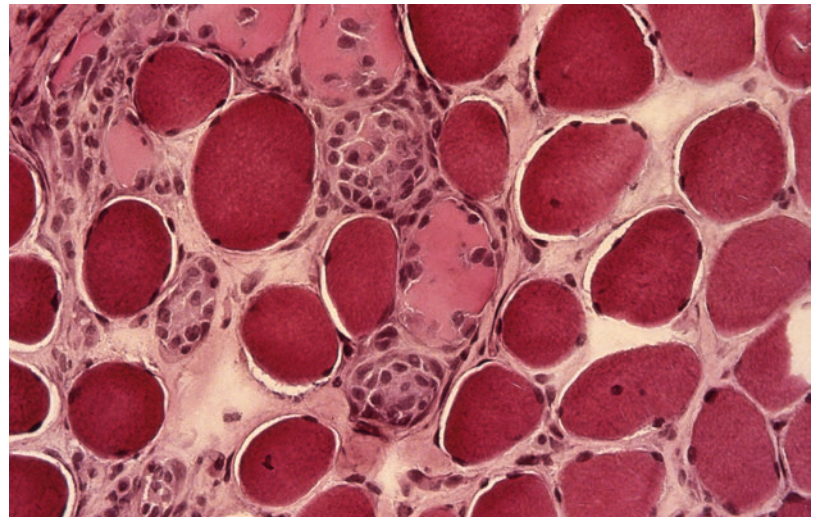

Fig. 11.2 Muscle biopsy in congenital muscular dystrophy, HE stain showing variable fibre size, centralised nuclei, necrotic fibres infiltrated by mononuclear cells and increased interstitial connective tissue

different therapeutic approach and rehabilitation schedules for these conditions, early differential diagnosis from CP is mandatory.

11.4.4 Brain Tumours

Brain tumours are the second most common neoplasm of childhood. They present with progressive neurological and visual symptoms and often with increased intracranial pressure. Appearance during the first 2 years of life is not infrequent. Symptoms are rather unspecific at this very early age, and a false diagnosis of CP is possible over a long period.

11.4.5 Dystonic Syndromes and Disorders of Monoamine Metabolism

Acquired damage to the basal ganglia can lead to dyskinetic CP with dystonia and choreoathetosis usually combined with spasticity and intellectual damage [24].

However, there are several rare genetic neurodegenerative diseases, the group of torsion dystonias that frequently begin in childhood and lead to progressive disability (Fig. 11.3). Their symptoms can be purely dystonic, but also combinations with spasticity and other neurological and sensory symptoms exist. An increasing number of these diseases can be diagnosed by genetic testing [25, 26]. Especially in pure dystonia with DYT1-mutation, deep brain stimulation has been proven to be of high therapeutic value in an increasing number of patients.

Of greatest importance is Segawa's syndrome. This is a hereditary disorder affecting the metabolism of dopamine due to an autosomal-dominant mutation in the GTP-cyclohydrolase gene. The symptoms can be fully controlled by lifelong administration of L-*DOPA* in a small dosage. In early publications, symptoms were reported as progressive, generalised dystonia with diurnal fluctuations: symptoms clearly improved after sleep, deteriorating during the course of the day. However, it has been well documented that the diurnal variation is not a prerequisite for the diagnosis. Many patients with the proven genetic defect and responding equally well to L-*DOPA* did not show fluctuations; some presented not with dystonia but with spasticity and increased reflexes or even with equinovarus alone. Cognitive function and MRI findings are normal [27]. Thus, for each child with suspected CP and

Fig. 11.3 Dystonic posture in a school-aged boy with primary torsion dystonia

normal MRI findings and an unknown aetiology, treatment with L-DOPA + carbidopa (starting with 25 mg/day and increasing up to 200–300 mg/day) should be attempted.

Some of the dystonias have been shown to be due to a metabolic defect. These include panthotenate kinase-associated neurodegeneration (PKAN, formerly Hallervorden-Spatz disease) (Fig. 11.4). The onset is usually in childhood, but earlier occurrence is possible and can erroneously lead to diagnosis of dyskinetic CP. Vigabatrin and high doses of panthetonate have anecdotally been reported to be of benefit. Glutaric aciduria Type 1 is primarily characterised by an abnormally increasing head circumference and unspecific developmental delay but following an acute metabolic crisis, static severe dystonia dominates the clinical picture. A controlled-lysine diet and supplementation with riboflavin and carnitine have been shown to prevent the metabolic crises.

Other metabolic defects include deficiency of tyrosine-hydroxylase or other disturbances of neurotransmitter metabolism. As opposed to Segawa's disease, these children cannot usually be cured, but their symptoms and quality of life can be significantly improved with special diets and treatment with neurotransmitter precursors [28].

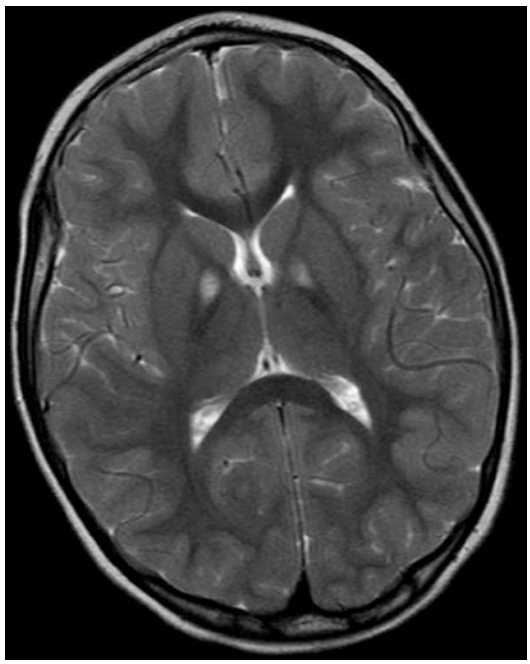

Fig. 11.4 Eye-of-tiger sign in T2-MRI in PKAN: gliosis and increased iron content in pallidum

11.4.6 Familial Spastic Paraplegia

The familial spastic paraplegias (FSPs) are a group of genetically and clinically heterogeneous diseases. Different gene locations have been reported, 70% of cases belong to the autosomal dominant type (gene location 2p). Other locations shown by chromosomal analyses are 15q, 14q, 8q and 12q. Autosomal recessive and x-linked inheritance are also on record [29].

Clinically these diseases are characterised by progressive spasticity of the lower limbs. The absence of additional neurological signs characterises noncomplicated or simple FSP (Strumpell-Lorrain type). Disease onset varies from early childhood to adulthood, as does the rate of progression and eventual prognosis. Cases with additional neurological symptoms, dementia, ataxia, ichthyosis, optical nerve atrophy, deafness or axonal neuropathy are classified as "complicated" forms of the disease. In 10–20% of patients, onset occurs before the end of infancy, making the differential diagnosis from CP a difficult one [30].

11.4.7 Ataxia

Nonprogressive ataxia is frequently called "*ataxic CP*" [15]. When making this diagnosis, one must be aware that exogenic, non-genetic damage to the cerebellum in early life is very infrequent and that most of these cases are due to developmental anomalies often of hereditary origin. Intellectual development is also abnormal in many cases. Recently, mutations of the reelin and VLDL-receptor genes have been shown to be causative in a few affected families [31]. This type of CP is *characterised* by significant heterogeneity both for its aetiology and for the clinical appearance.

The most frequent cause of ataxia in childhood is acute postinfectious ataxia bearing a good prognosis. Progressive ataxia, however, is due to cerebellar or brainstem tumours or to neurodegenerative syndromes. In children, the autosomal recessive ataxias (Friedreich's ataxia, ataxia telangiectasia, ataxia with vitamin E deficiency, ataxia-oculomotor apraxia 1 and 2) occur more frequently than the later-manifesting autosomal-dominant ataxias (spinocerebellar ataxias Type 1–18) [32, 33]. *Progressive* or *fluctuating* ataxia is also a symptom of several neurometabolic disorders that require a thorough diagnostic work-up [34].

11.4.8 Neurometabolic Diseases

Neurometabolic diseases are hereditary disorders of metabolism with primarily neurological symptoms [35, 36]. They can give rise to various progressive neurological signs including loss of vision, dementia, epilepsy, spasticity, dystonia and ataxia. It is of great clinical importance that these hereditary diseases be diagnosed. Otherwise, the opportunity of genetic counselling and prenatal diagnosis in future pregnancies is lost. Emerging treatment options include enzyme replacement therapy, substrate inhibition (*miglustat*) or bone marrow transplantation, but for most of these diseases, no cure is yet available.

The subgroups of leukodystrophies and mitochondrial cytopathies in particular (metachromatic leukodystrophy, Alexander disease (Fig. 11.5), Krabbe's disease, Canavan disease, Leigh's disease) presenting in infancy or early childhood with spasticity and ataxia can initially be mistaken for CP. However, developmental regression after earlier normal development, followed by a severely progressive course, makes the correct diagnosis possible in most cases [37, 38].

Due to its much slower clinical course, the diagnosis of Pelizaeus-Merzbacher disease (PMD) is usually much more difficult. PMD is due to a lack of myelination of the CNS caused by mutations of the proteolipid protein gene (PLP) located on Xq21.2-q22. A similar phenotype may also be transmitted in an autosomal pattern [39]. In the classic type of the disease, the first symptoms appear in early infancy with nystagmus, hypotonia and weakness. Later on, spasticity, dystonia and cerebellar symptoms develop. Cognitive functions are not significantly impaired [40]. The MRI of the brain shows a characteristic finding with an absence of myelin detectable from the age of 1 year. The diseases barely discernable progression during the first years of life frequently results in a mistaken diagnosis of CP, unless earlier cases have already been diagnosed in the same family.

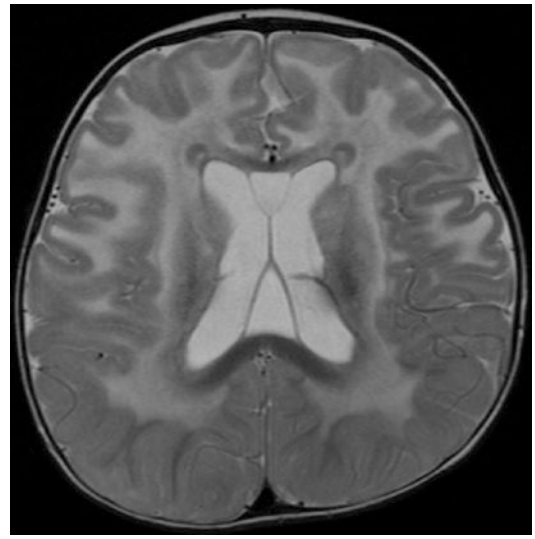

Fig. 11.5 T2-MRI: frontally accentuated leukodystrophy and macrocephaly in GFAP-mutated Alexander disease

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Cranial Ultrasound in Cerebral Palsy

12

Summer Kaplan and Ammie M. White

Abstract

Neurological injury underlying cerebral palsy (CP) typically occurs in the first month of life. At this age, cranial ultrasound is an ideal method for neurological imaging. Ultrasound is portable, can be performed at the bedside, and involves no radiation or sedation. Because it is usually readily available, it allows for multiple longitudinal assessments. Infants with neurological damage may have difficulty traveling for magnetic resonance (MR), and ultrasound may provide the only opportunity to visualize the acute abnormality, which may be less apparent over time on a later MR. Premature infants are at the highest risk for neurological injury leading to CP. The most common injury is intracranial hemorrhage of prematurity, typically centered in the subependymal layer at the germinal matrix. A four-stage grading system is typically used, with the more severe grades III and IV being associated with CP. Ischemic injury of prematurity can also lead to CP. In premature infants, global cerebral anoxia results in a characteristic pattern of injury known as periventricular leukomalacia. Global hypoxic-ischemic injury in term infants has a different pattern, affecting predominantly basal ganglia, corpus callosum, and watershed territories of the cerebral arteries. Hemorrhage in the term infant most commonly involves the choroid plexus, distinct from the germinal matrix hemorrhage seen in premature infants. Less commonly, CP may follow a perinatal infection or congenital developmental abnormality in either term or preterm infants. These findings are more subtle by ultrasound, but detection can be improved with training. Ultrasound is a valuable tool in assessment of the neonatal injuries that frequently underlie CP.

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12.1 Introduction

The neurologic damage underlying cerebral palsy (CP) most commonly occurs during the first month of life, most often in premature

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infants. Vascular insults, including *hemorrhage* and *infarct*, account for the majority of identified causes of CP, while infection and developmental anomalies contribute a smaller share [1, 2]. In the infant, ultrasound (US) and magnetic resonance (MR) imaging are the imaging modalities of choice to evaluate intracranial abnormalities. US is an ideal method for neonates as it uses no radiation, requires no sedation, and is portable and noninvasive. MR has superior field of view and contrast resolution, but many neonates are too fragile for transport to MR, and MR availability may be limited. For many infants, US provides the only opportunity for intracranial imaging, and it is the only modality that enables daily monitoring. The American Academy of Neurology and the Child Neurology Society recommend that all infants of gestational age ≤30 weeks be evaluated with cranial US between 7–14 days of age and again at 36–40 weeks postmenstrual age [3]. *Abnormalities* underlying CP may be less visible with age, and US imaging in infancy may offer the greatest insight into the etiology in some cases.

Techniques for US imaging are age dependent and individually variable, as the size and closure rate of the cranial fontanels differs. Evaluation is most comprehensive in the neonate, whose large, patent fontanels are ideal sonographic windows. Supratentorial brain is best evaluated through the anterior fontanel. Full evaluation becomes limited by 3–6 months post-term age as ossification of the calvarium progresses, but focused evaluation of midline structures may still be attempted. The parieto-occipital region can be evaluated through the posterior fontanel, temporal structures through the anterior lateral (*squamosal*) fontanel, and infratentorial structures through the posterior lateral (mastoid) fontanel. These three fontanels close within the first month of life after full-term gestation, but they may be accessible for several months in preterm infants. The brain stem can be best visualized from a posterior approach through the foramen magnum, but support devices and fragile infant state often preclude positioning for trans-foramen imaging. Both high-frequency linear array and low-frequency curved array transducers are used for brain ultrasound. High-frequency linear transducers ranging from 9–15 MHz may be used at the anterior and posterior fontanels. Low-frequency curved transducers ranging from 5–8 MHz are used at all access windows.

Doppler US and other advanced techniques may supplement grayscale US. *Color Doppler* is routinely used to document sagittal sinus flow. Circle of Willis flow may be evaluated with both color and spectral Doppler through the supratentorial fontanels (anterior, posterior, squamosal), with resistive index <0.5–0.6 predictive of poor outcome [3, 4] due to loss of cerebrovascular autoregulation. The use of other advanced US imaging techniques is limited. Three-dimensional ultrasound has been explored but is not yet part of routine clinical evaluation [5]. Both contrast-enhanced US [6] and US elastography [7] show potential in research models and are used clinically elsewhere in the body but have not been validated for cranial application.

12.2 Hemorrhagic and Ischemic Pathologies

12.2.1 Preterm Infant

Premature infants have characteristic patterns of hemorrhage and ischemia that differ from term infants. Premature infants are at higher risk for both intracranial vascular insults and CP [8]. Neurodevelopment requires a rich vascular supply to the subependymal germinal matrix (GM), where developing neurons begin migrating toward the cerebral parenchyma. GM hemorrhage is a common complication of prematurity. Patterns of intracranial hemorrhage characteristic of preterm infants have been described in four grades [9].

Grade I: Subependymal GM hemorrhage only. In the sagittal plane, GM hemorrhage appears as swelling and increased echogenicity in the caudothalamic groove, extending anteriorly. As it regresses, the hematoma may form a subependymal cyst. Grade I hemorrhage is associated with CP in 8% of cases [1, 10] but does not increase risk above baseline for prematurity [11].

Grade II: Intraventricular hemorrhage without ventricular dilation. Echogenic material fills part or all of a non-dilated ventricle, which may be difficult to diagnose by US. A scan through the posterior fontanel can aid diagnosis. Grade II hemorrhage is associated with CP in 11–12% of cases [1, 10] but also does not increase risk above baseline [11].

Grade III: Intraventricular hemorrhage with ventricular dilation (Fig. 12.1). Echogenic material fills part or all of the dilated ventricle. Chemical ventriculitis typically occurs due to the irritant properties of blood products. The trigones and occipital horns may dilate proportionally more than the frontal horns. About 15% of infants with intraventricular hemorrhage develop hydrocephalus requiring shunting [12]. Grade III hemorrhage is associated with CP in 19–28% of cases [1, 10].

Grade IV: Intracranial bleed including parenchymal hemorrhage (Fig. 12.2). The periventricular, fan-shaped echogenicity characteristic of grade IV hemorrhage was originally thought to be an extension of GM hemorrhage. However, it is now understood to arise from parenchymal venous infarction of the deep medullary veins with secondary hemorrhage [13]. Encephalomalacia develops over 2–3 months and may appear as cysts or porencephaly. Due to the predominance of venous infarction, some now regard grade IV as a separate entity. Grade IV parenchymal hemorrhage is one of the predictors most highly associated with CP, which occurs in 50–60% of infants with grade IV hemorrhage [1, 10]. *Parenchymal hemorrhage* in the parietal white matter adjacent to the ventricular trigone is most likely to be associated with CP [14].

Ischemia in the preterm infant typically distributes over different areas than in the term infant. During a global hypoxic-ischemic insult such as cardiac arrest or asphyxia, highly metabolic areas and watershed territories are most affected. In the preterm infant, these regions lie in the deep periventricular white matter at the level of the optic radiations and adjacent to the frontal horns at the foramen of *Monro*. Following global ischemia, these susceptible areas develop roughly symmetric echogenic areas of periventricular leukomalacia (PVL) (Fig. 12.3). The echogenicity will resolve in the majority of infants, but approximately 15% evolve to cystic encephalomalacia or irregular-appearing ventriculomegaly

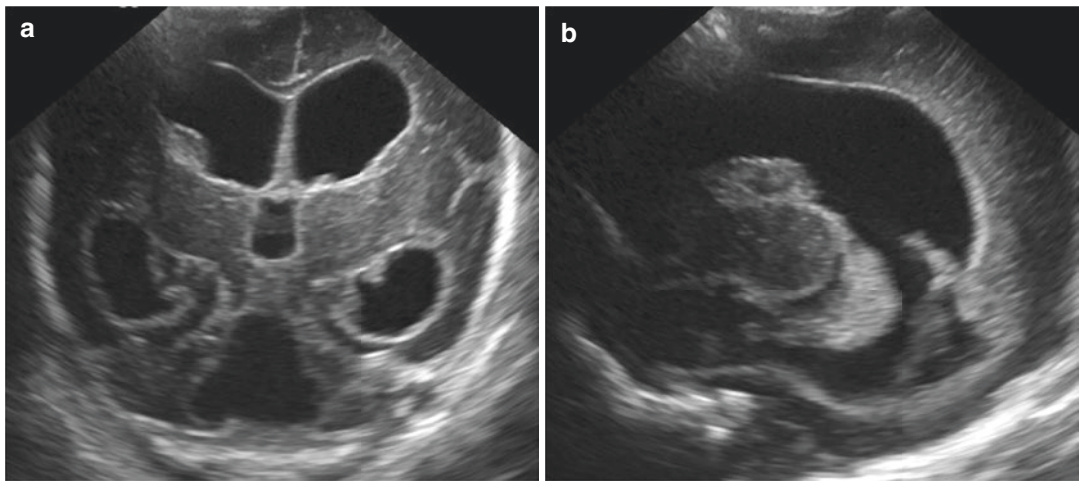


Fig. 12.1 A 26-week gestation male presents at 14 days with subacute grade III right germinal matrix (GM) hemorrhage. The GM hemorrhage is seen as echogenic swelling in the caudothalamic groove anterior to the choroid plexus in the coronal (**a**) and sagittal (**b**) planes. Echogenic thrombus layers in the dependent occipital horn on the sagittal view. Bilateral ventriculomegaly and thick echogenic ependyma follow chemical ventriculitis that occurs with hemorrhage. Though the bleeding occurred in the right lateral ventricle, free movement of blood products through ventricular system results in enlargement and ventriculitis also in the left lateral, third, and fourth ventricles

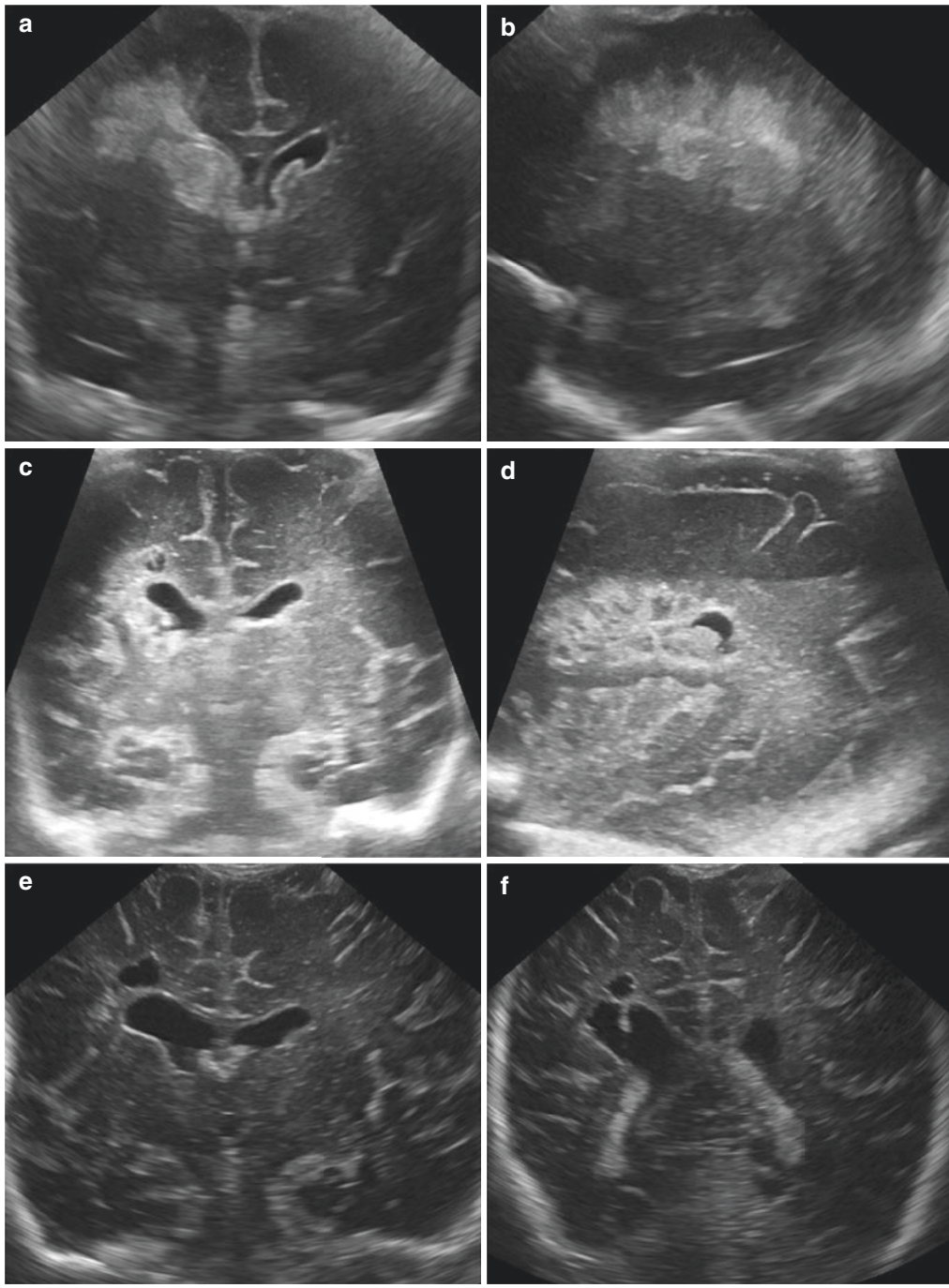
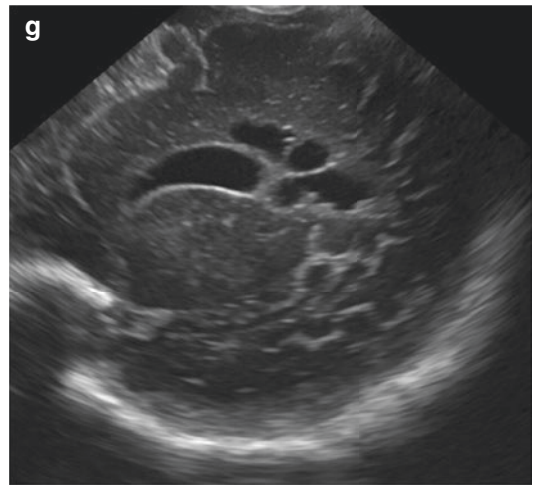


Fig. 12.2 A 29-week gestation male who required neonatal resuscitation presents at 6 days with a right grade IV germinal matrix (GM) hemorrhage. Early appearance of the grade IV hemorrhage shows echogenic swelling at the germinal matrix in the coronal plane (**a**). Ipsilateral fan-shaped periventricular echogenicity (**a**, coronal and **b**, sagittal) represents hemorrhagic venous infarction related to occlusion of the deep medullary veins. At 6 weeks (**c**, coronal and **d**, sagittal), the GM hemorrhage has retracted and the periventricular echogenicity is more defined, with cystic changes. At 10 weeks (**e**, coronal and **f**, sagittal), periventricular echogenicity has resolved, and ipsilateral ex vacuo ventriculomegaly is present. The periventricular cysts are now well formed. Some cysts have merged with the ventricle, creating areas of focal porencephaly (**g**, coronal)

Fig. 12.2 (continued)



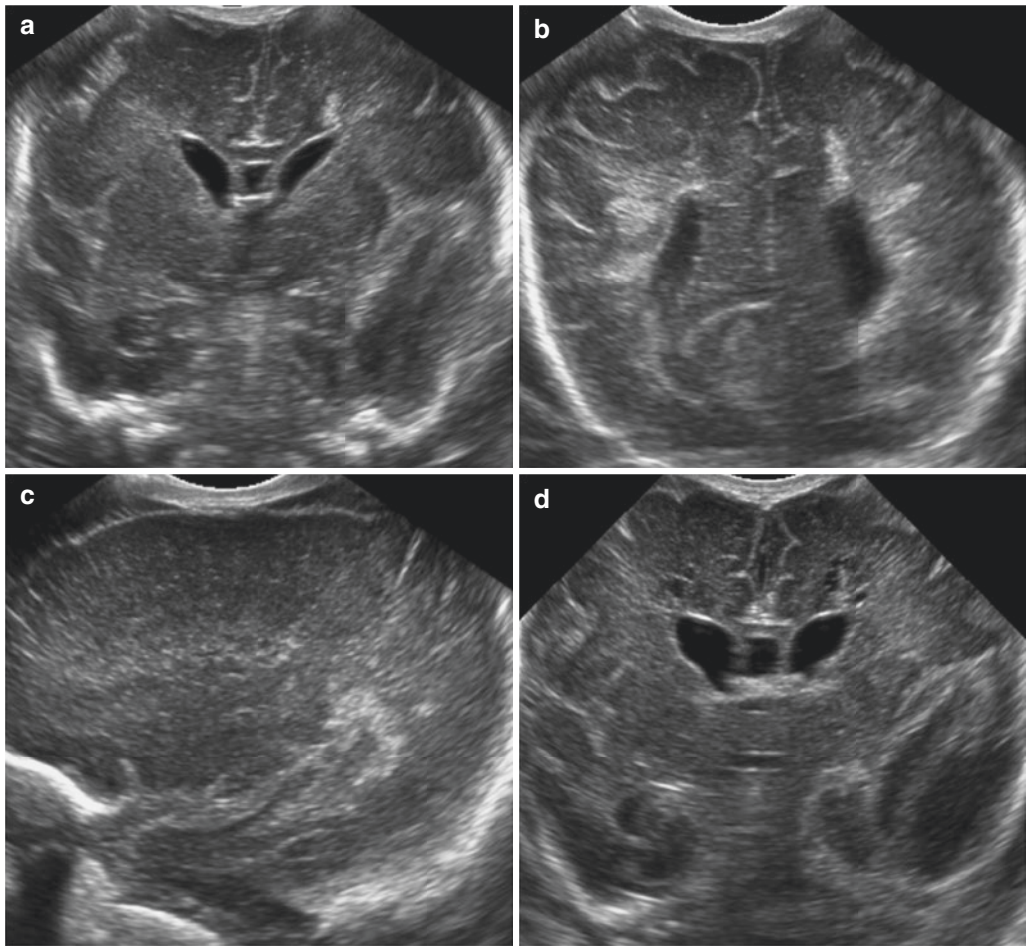


Fig. 12.3 A 29-week gestation male presents at 28 days with patchy areas of periventricular echogenicity (**a**, coronal frontal; **b**, coronal parieto-occipital; and **c**, sagittal). Compared with the grade IV hemorrhage in Fig. 12.2, these echogenic areas are bilateral and patchy, and there is no associated germinal matrix hemorrhage. At 34 days (**d**, coronal and **e**, sagittal), echogenicity has diminished and cystic change is occurring. At 57 days (**f**, coronal and **g**, sagittal), bilateral cystic PVL and ex vacuo dilation of the lateral ventricles are evident

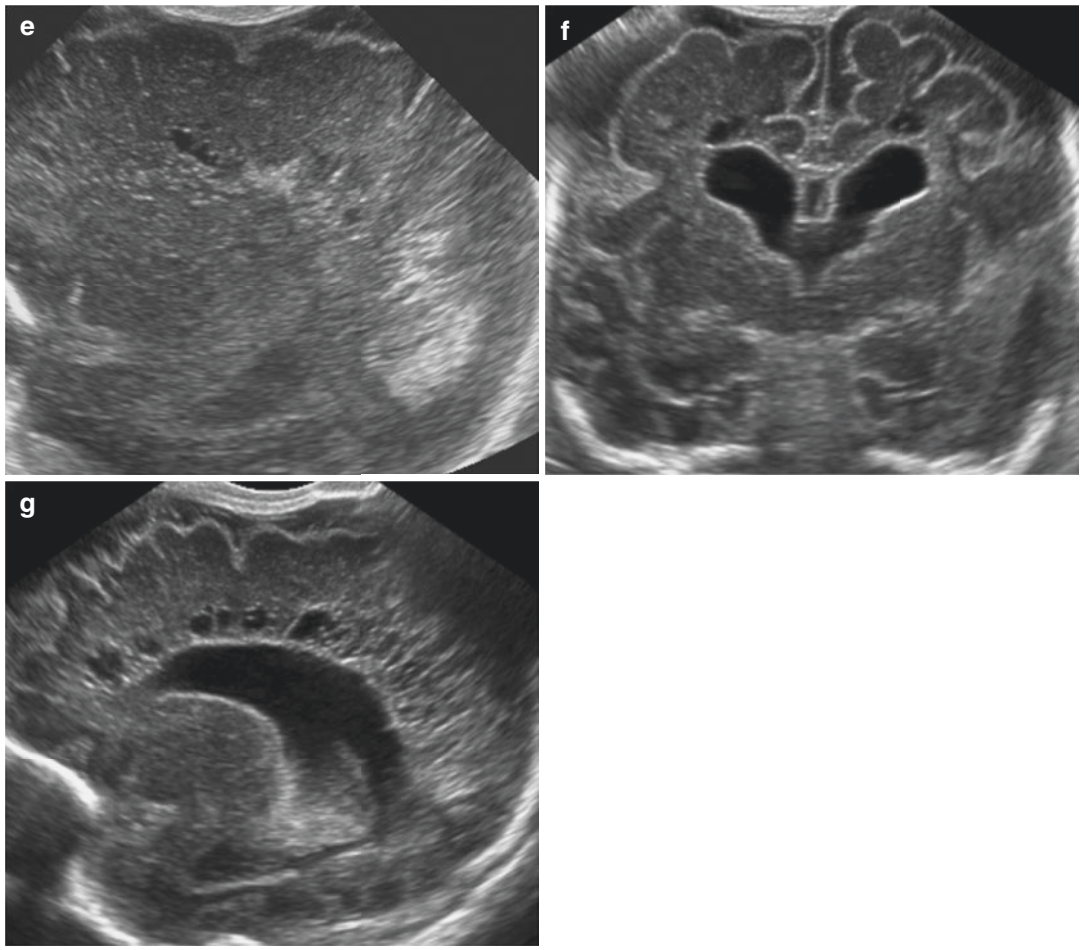


Fig. 12.3 (continued)

(Fig. 12.4). Grading systems for PVL have been used [15], but there is poor interobserver agreement for lower grades [16], and only cystic PVL is predictive of neurodevelopmental outcome [1, 2]. Among infants with cystic PVL, 57–61% develop CP. When cystic PVL is bilateral, 74–80% of these children develop CP [1, 10]. Appearance of cysts occurs later in the course of PVL and may not be detected before the infant is discharged from the hospital, leading to difficulty in predicting outcome [2]. PVL can appear similar to the periventricular cystic encephalomalacia accompanying a grade IV GM hemorrhage. However, abnormalities associated with a grade IV bleed are more commonly unilateral [14]. Both PVL and grade IV hemorrhage are highly associated with CP.

12.2.2 Term Infant

Intracranial hemorrhage in the term infant does not involve the germinal matrix but may occur in any compartment of the brain or extra-axial space. *Hemorrhage* most commonly occurs in the extra-axial space, associated with birth trauma or other accidental or non-accidental trauma. Extra-axial hemorrhage alone is not linked to the development of CP. However, with high impact or shearing injury, coexisting parenchymal injuries that are sonographically occult may lead to CP [17]. In these cases, MR is necessary for full diagnosis. *Intraventricular* blood in the term infant may appear similar to a grade III hemorrhage in a premature infant, with intraventricular thrombus, ependymitis, and ventriculo-

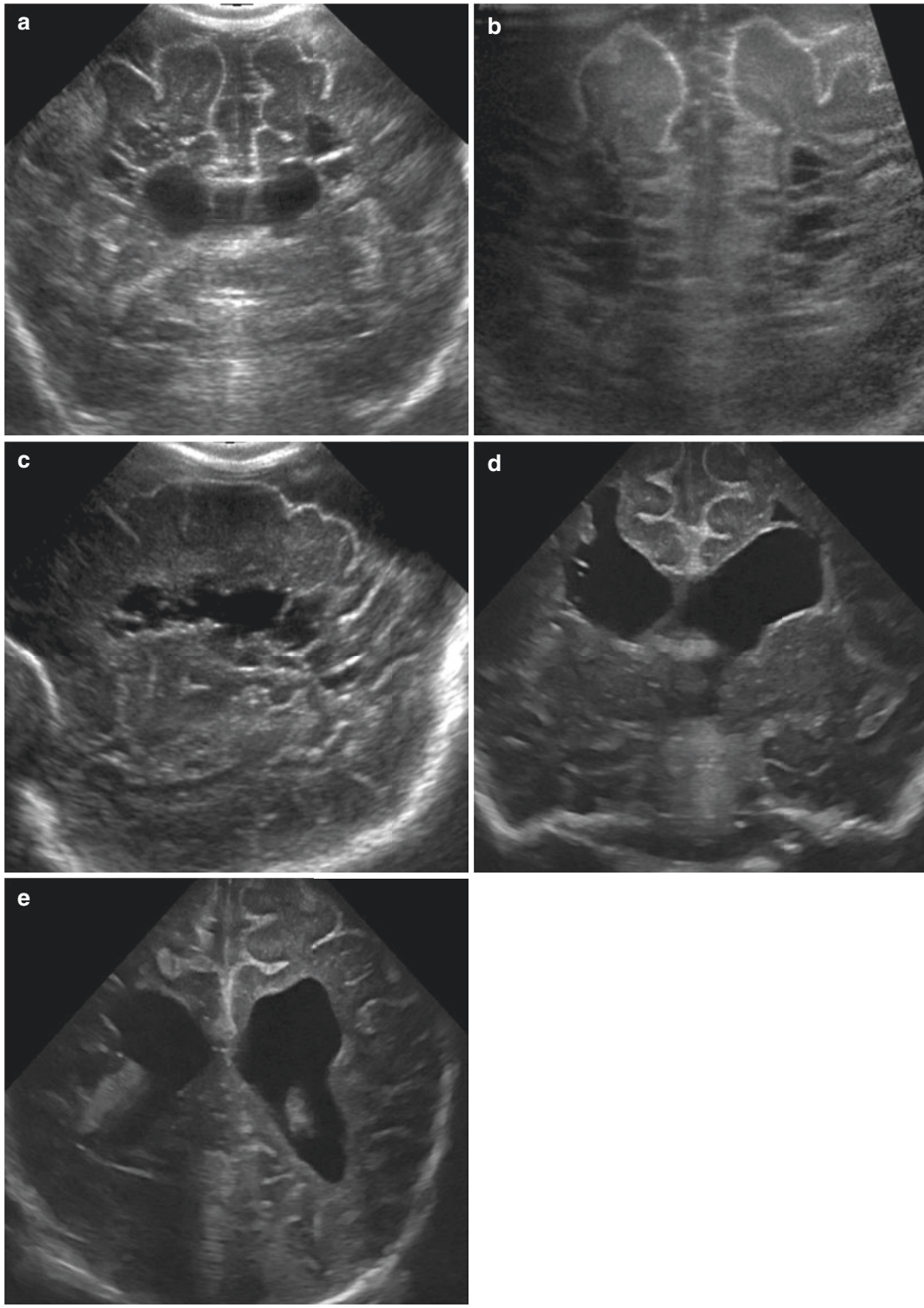


Fig. 12.4 A 24-week gestation male with history of prior cardiac surgery presents at 4 months with chronic cystic periventricular leukomalacia (**a**, anterior coronal; **b**, posterior coronal; **c**, sagittal). Extensive bilateral periventricular cysts are present. A 24-week gestation male twin with history of surgery presents at 4 months with enlarged, irregular ventricles (**d**, coronal anterior and **e**, coronal posterior). A right frontal porencephalic cyst is present where the periventricular cysts have merged with the ventricles (**d**)

megaly. This appearance in the term infant is most common with choroid plexus hemorrhage and does not involve the GM (Fig. 12.5). Parenchymal hemorrhage can occur anywhere, though infratentorial hemorrhage is less common in the term infant. Parenchymal hemorrhage may also arise from rupture of a friable vascular neoplasm or malformation.

Ischemic injury in the term infant follows the pattern typical of older children, with injury in the metabolically active deep gray nuclei, corpus callosum, and the parasagittal watershed territories. The appearance of hypoxic-ischemic encephalopathy in a term infant depends on the degree of cerebral edema (Fig. 12.6) [18]. In more severe cases, the sulci may be echogenic and blurred, cerebrospinal fluid (CSF) spaces effaced, and color Doppler may show compromised flow in the superior sagittal sinus and pericallosal arteries. In more subtle cases, the grayscale and color Doppler appearance may be unremarkable. Though less common, CP can also arise from arterial infarcts in term or preterm infants. These findings are also subtle and correspond

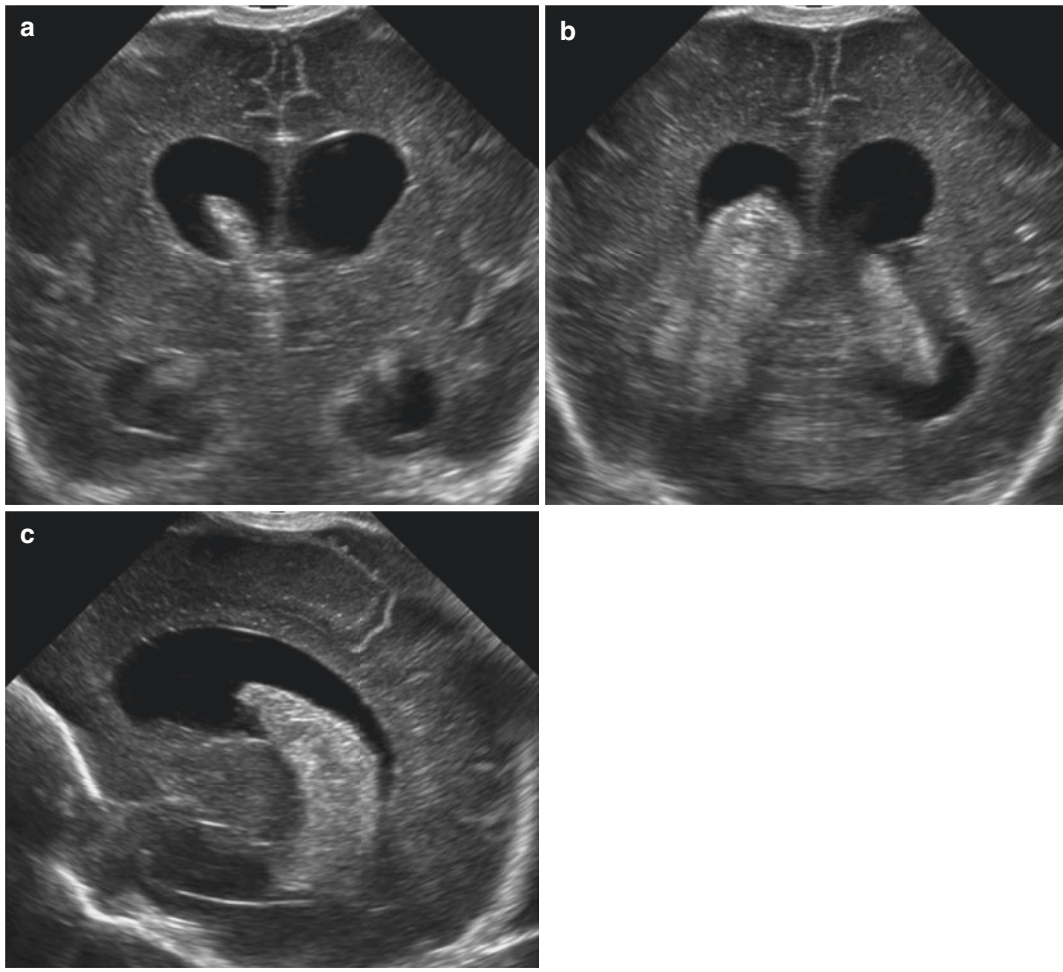


Fig. 12.5 A 36-week gestation female presents at 2 days with ventriculomegaly and right choroid plexus hemorrhage (**a**, anterior coronal; **b**, posterior coronal; **c**, sagittal). The right choroid plexus is bulky and heterogeneously hyperechoic. Ventriculomegaly is present bilaterally due to free movement of blood products through the ventricular system. In contrast to the grade III hemorrhage, there is no germinal matrix hemorrhage, and this patient is born at term

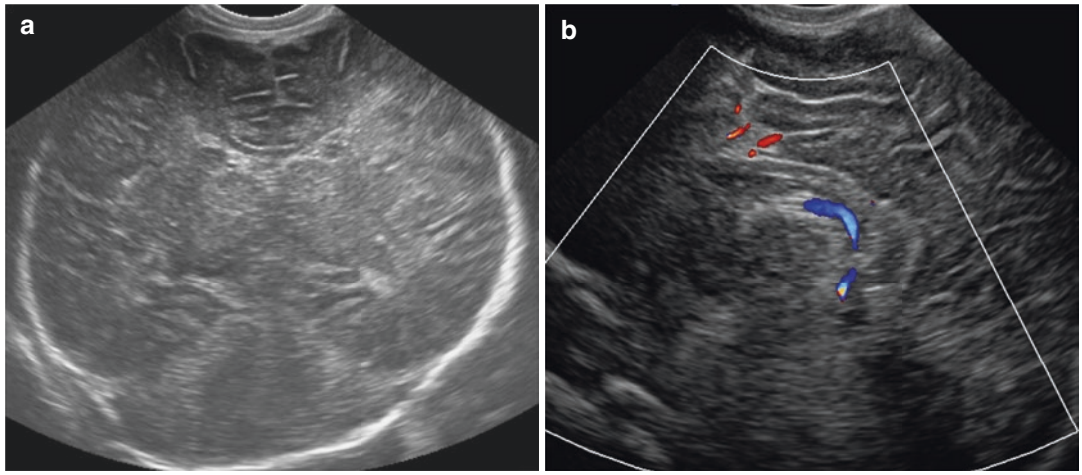


Fig. 12.6 A 39-week gestation female presents on day of birth with meconium aspiration and sonographic signs of acute hypoxic-ischemic injury (**a**, coronal and **b**, sagittal). The ventricular system and extra-axial spaces are completely effaced. There is bilateral diffusely increased parenchymal echogenicity, with more focal increased echogenicity in the thalami, as well as accentuation of gray-white differentiation. Minimal flow in the pericallosal arteries is secondary to increased intracranial pressure due to cerebral edema

to the underlying amount of cerebral edema. Venous infarcts with hemorrhagic conversion can also happen in both term and preterm infants. Hemorrhagic infarcts are typically more devastating in premature brain with its underdeveloped cerebrovascular regulation.

12.3 Infectious and Congenital Pathologies

Prenatal and neonatal infections have been linked to the development of CP in both preterm and term infants [19, 20]. Most infections are sonographically occult, but cytomegalovirus (CMV) is a common perinatal neurotropic virus associated with CP [21] that has a characteristic imaging appearance of periventricular and subcortical dystrophic calcifications. The calcifications are best visualized with CT but may also be identified with ultrasound (Fig. 12.7). Postnatal meningitis, encephalitis, and septic emboli may also lead to neurologic injury resulting in CP.

A wide array of *congenital anomalies* may be associated with CP, including anatomic developmental abnormalities and metabolic deficiencies. These anomalies require confirmation with MR, but may be detected on US, helping form a clinical management plan. While abnormalities such as holoprosencephaly and open-lip schizencephaly may be visualized, MR is necessary for more detailed and prognostic evaluation. More common abnormalities like cortical dysplasia and sulcation anomalies are typically sonographically occult. Subependymal heterotopic gray matter can be identified with US as isoechoic or slightly hyperechoic rounded nodules protruding from the ependymal surface (Fig. 12.8).

US has high diagnostic sensitivity for common perinatal causes of CP, such as high-grade intracranial hemorrhage, ventriculomegaly, and cystic PVL [2]. Sensitivity for other ischemic injuries is lower but may be improved with training [16]. More unusual causes of CP such as infection and congenital anomalies may also be first diagnosed with US in the neonatal period, allowing earlier intervention and planning. US is an essential tool in evaluating neonates, who often are not stable enough to undergo MRI. While MR remains the gold standard in diagnosing many of the etiologies underlying CP, US provides opportunity for on-going evaluation at a critical time and may reveal abnormalities that are less apparent on later MRI.

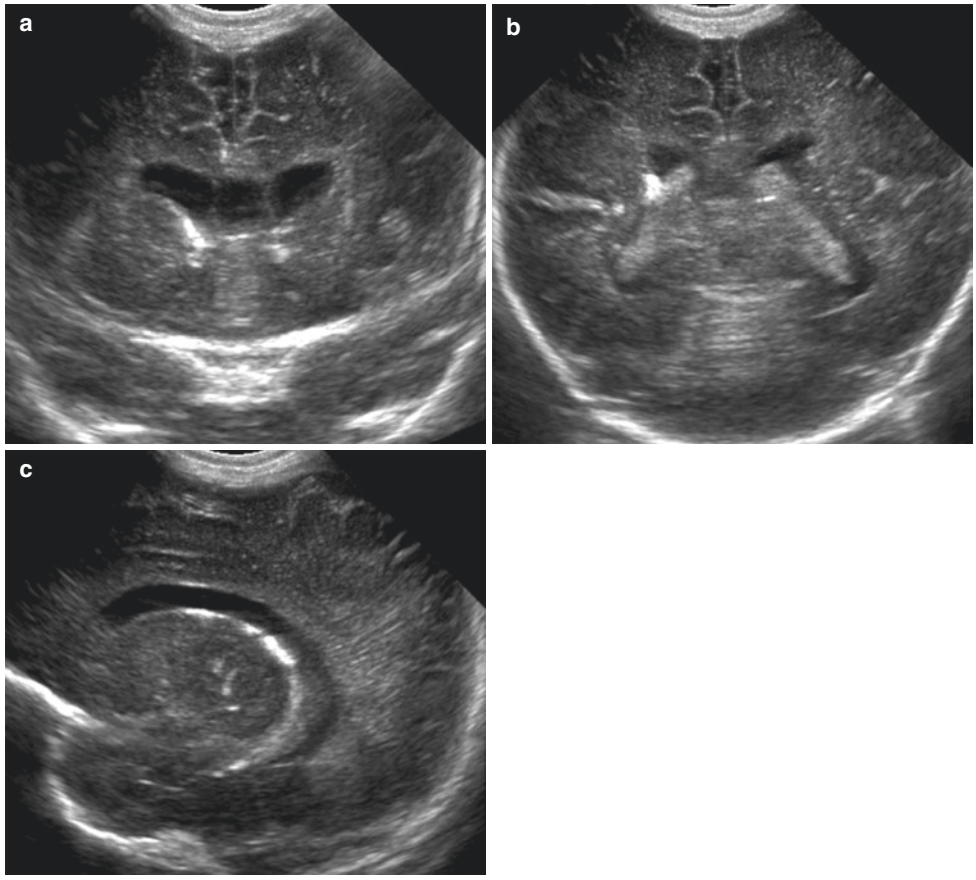


Fig. 12.7 A 36-week gestation male presents at 10 days for evaluation of known prenatal exposure to cytomegalovirus (CMV). Dystrophic periventricular calcifications are apparent as bilateral irregular echogenicities (**a**, anterior coronal; **b**, posterior coronal; **c**, sagittal). Lenticulostriate vasculopathy is apparent as linear echogenicities in the thalamus (**c**), a finding that has been described in association with prenatal infection, among other etiologies

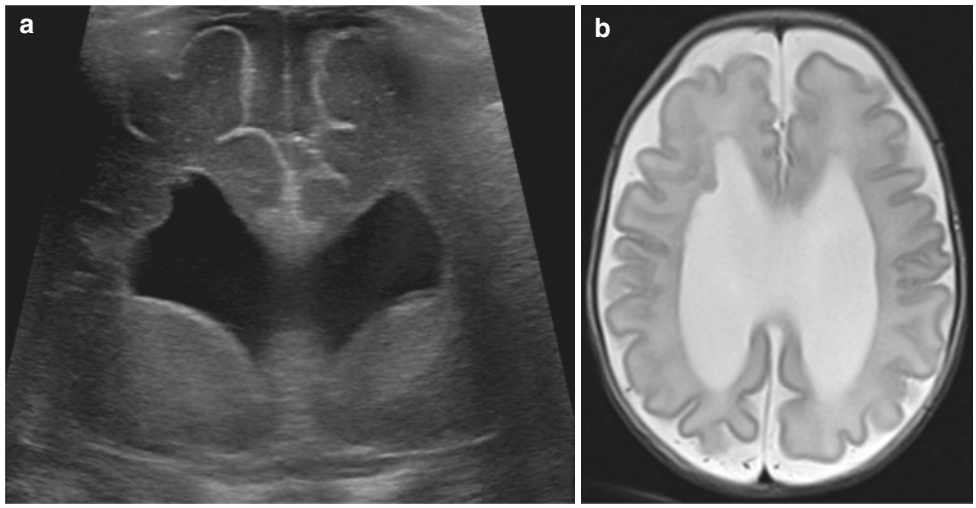


Fig. 12.8 A 29-week gestation female with fetal repair of myeloschisis presents at 55 days with subependymal heterotopic gray matter in the frontal horn of the right lateral ventricle (**a**, coronal). Confirmation is provided by T2-weighted magnetic resonance imaging (**b**, axial)

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13 Brain Imaging: Magnetic Resonance Imaging

Arastoo Vossough

Abstract

Imaging plays an important role in elucidating many of the aetiologies of cerebral palsy in children. Magnetic resonance imaging is a particularly powerful tool in the evaluation of the causes of cerebral palsy, both in the acute and chronic phases. We will review the role of MRI in assessment of various aetiologies contributing to cerebral palsies. These categories include congenital malformations, intracranial haemorrhage, hypoxic-ischaemic injury, periventricular leukomalacia and white matter injury of prematurity, perinatal ischaemic stroke and a number of other neonatal encephalopathies. In this chapter, we will review the utility of MRI in the evaluation of cerebral palsy in the young child.

13.1 Introduction

The American Academy of Neurology and the Child Neurology Society have recommended that neuroimaging of the central nervous system be a part of the diagnostic process for all patients with cerebral palsy [1]. While not all experts may agree with this recommendation, there is no doubt that neuroimaging can shed light into the possible aetiologies, extent of brain involvement, potentially better timing of responsible lesions and the complexity of the motor spectrum of disability [2, 3].

Imaging can be important in differentiating various disorders underlying cerebral palsy (CP), with further implications for treatment and prognosis. Most (83%) children with CP have abnormal neuroradiological findings [4]. In the early postnatal period, it may provide diagnosis of the specific brain injury or anomaly. Imaging in this phase of the newborn at risk may be of importance, as some lesions, particularly those of mild-to-moderate degree, may not be visible at a later date when the full-blown clinical picture of CP is apparent. Furthermore, prognostic assessments can be made with regard to the risk of neurodevelopmental disability. Imaging at the time the diagnosis of CP has been made provides information on the type and extent of the end-stage brain damage. The specification of a

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subtype of CP may also be possible on detection of characteristic neuroimaging findings. These can help in providing adjunct data in planning early interventions and treatments tailored to the specific needs of the child.

Hypoxic-ischaemic insults to the brain, neonatal encephalopathies, intracerebral haemorrhage, congenital malformations and congenital infections of the central nervous system are considered among a long list of possible aetiologies to be the leading causes of cerebral palsy (see Chap. 5) [4–6]. The precise aetiologic factor may not be recognised in many cases, but a common risk factor is prematurity [7]. In recent years, substantial improvement in the survival rates of very-low-birth-weight (VLBW) infants has been associated with an increase in the rates of CP [8]. The combination of increasing number of cases and advancements in various neuroimaging modalities has further facilitated the diagnostic imaging studies in CP. These comprise primarily of ultrasonography (US) and magnetic resonance imaging (MRI). The prospective comparison of state-of-the-art brain US with MRI for neonatal encephalopathy has brought to light the real value of US contrary to the relatively poor review of older retrospective studies [9]. In this study the head US and MRI were performed within 2 h in 76 consecutive patients. The comparison of these two modalities with MRI as the reference method revealed the following results for cranial US: sensitivity 100% (CI: 94.1–100), specificity 33.3% (CI: 7.5–70), positive predictive value (PPV) 91% (CI 81.5–96.6), negative predictive value (NPV) 100% (CI: 29.2–100) and accuracy 95.7%. The authors also noted that the parenchymal abnormalities depicted on US are not as florid or conspicuous as on MR, and fewer focal lesions may be detected. Consequently, US might underestimate the degree of injury and just reveal the tip of the iceberg. In light of these findings and particularly of the very high negative predictive value, US remains an excellent screening method, and MRI retains its position as the method of choice to obtain more detailed and accurate information [9, 10].

13.2 Magnetic Resonance Imaging (MRI) for Evaluation of Cerebral Palsy

The advantages of MRI in the imaging assessment of cerebral palsy include the ability to obtain high-resolution imaging in multiple planes, excellent tissue contrast between various structures in the brain and lack of radiation exposure. The disadvantages of MRI include less availability, high cost, long imaging times, sensitivity to patient motion, selective need for sedation, transport of very young or labile patients and problems with MR compatibility of monitoring or indwelling devices. Newer MRI techniques, such as diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), functional MRI (fMRI), perfusion MRI and magnetic resonance spectroscopy (MRS), have enhanced our capabilities to demonstrate injuries to the brain earlier, distinguish different patterns of brain injury and shed further light into the pathophysiologic mechanisms behind the neurological substrates of CP.

Similar to ultrasound, MRI can also provide prognostic information (see Chap. 12). For example, in analysis of several studies, 50–94% of the infants with changes in the basal ganglia on MRI had developed cerebral palsy, mental retardation and seizures at 1–2 years of age [11]. In a retrospective analysis of MR findings in 40 patients with cerebral palsy [12] found in the prematurely born patients signs of periventricular white matter damage. In those who had been born at term, three major patterns emerged: (1) gyral anomalies, suggestive of polymicrogyria, (2) isolated periventricular leukomalacia and (3) watershed cortical or deep grey nuclear damage.

Furthermore, MRI supports the categorisation of characteristic findings to a specific subtype of cerebral palsy [13]. In some patients with extrapyramidal cerebral palsy, focal high intensity in the posterior putamen and the anterior or posterior thalamus were detected [14]. PVL and posthaemorrhagic porencephaly have been categorised as preterm-type brain injury because

they are often based on immaturity of vascular system. *Border-zone* infarct, bilateral basal ganglia-thalamic lesion, subcortical leukomalacia and multicystic encephalomalacia are seen as more commonly term-type of brain injury due to the fact that these lesions have been more typically seen in asphyxiated term infants.

Okumura et al. [15] found that 84% of those with diplegia were born prematurely and in 88% showed MRI findings compatible with preterm-type brain injury. In the group with quadriplegia, only 33% were preterm-type, and 49% had term-type pathologic findings with 22% having various other brain anomalies. Patients with only hemiplegia had in 65% unilateral findings, and 42% were preterm-type lesions [16].

13.3 Congenital Malformations

A large variety of congenital malformations of the brain can cause CP and present with various functional impairments. These include microcephaly, holoprosencephaly, hemimegalencephaly, lissencephaly, heterotopias, schizencephaly, pachygyria, polymicrogyria, cortical dysplasia and infratentorial malformations, among others. In two large studies, approximately 8% of children with cerebral palsy had a congenital anomaly of the brain [17, 18]. The prevalence of cerebral anomaly was highest in children with ataxic CP (41.7%) and lowest in those with dyskinetic CP (2.1%). Conventional MRI is often crucial in the diagnosis of these entities and shows the severity of brain abnormality. The location and type of brain anomaly affects the incidence and type of cerebral palsy. For example, the location and extent of schizencephaly (Fig. 13.1), type of schizencephalic cleft (open vs. closed) and unilaterality vs. bilaterality of the disease will determine the extent of clinical symptomatology and motor deficit [19]. The use of higher-resolution and volumetric MRI imaging facilitates the detection of subtler cortical and subcortical abnormalities. For example, subtle cases of polymicrogyria may remain undiagnosed on routine

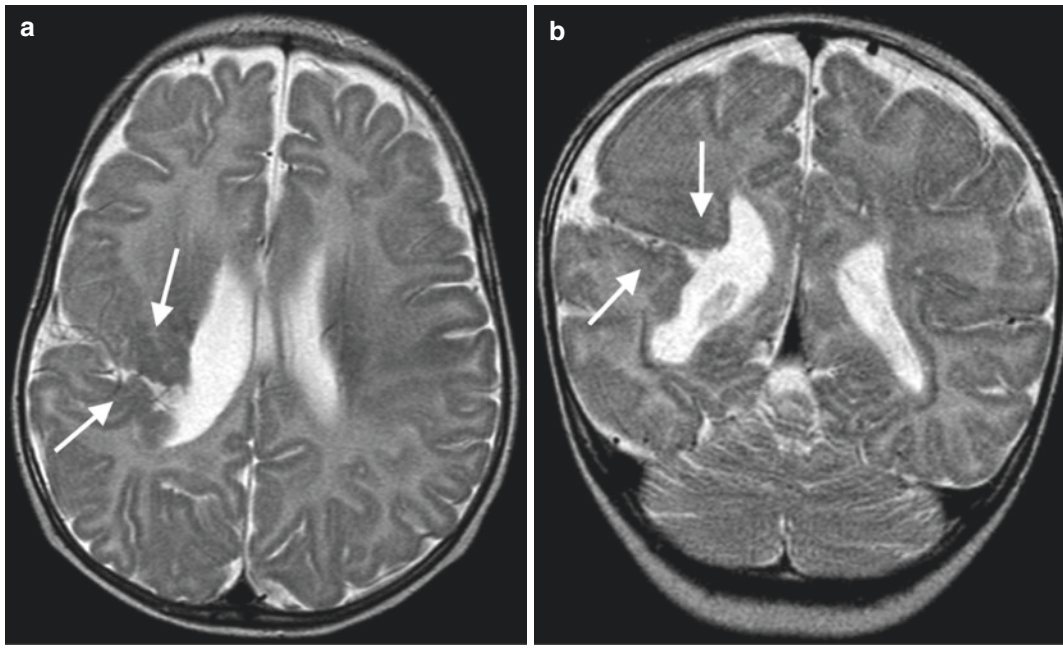

Fig. 13.1 Right-sided schizencephaly shown on axial (**a**) and coronal (**b**) imaging. The margins of the schizencephalic cleft are lined by grey matter (*arrows*)

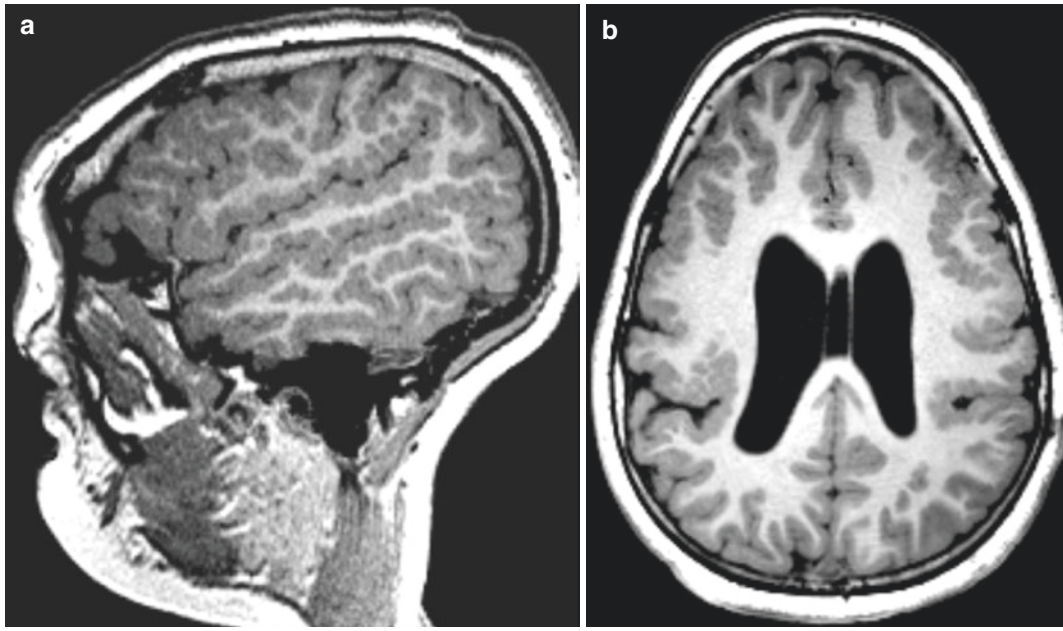

Fig. 13.2 Extensive bilateral perisylvian, frontal and temporal polymicrogyria as demonstrated on high-resolution sagittal (**a**) and axial (**b**) T1-weighted imaging at 3 T. Note the small serrated appearance of the grey-white matter junction due to polymicrogyria compared to a smoother junction in areas of normal cortex in the occipital and frontal poles

MRI exams, whereas higher-resolution scans increase the diagnosis rate. More extensive patterns of polymicrogyria are more easily detected by MRI (Fig. 13.2). Recent advances and more widespread use of foetal MRI result in more accurate diagnosis and characterisation of brain anomalies suspected on prenatal ultrasound; see also Chap. 12 [20].

13.4 Intracranial Haemorrhage

Intracranial haemorrhage is a common cause for cerebral palsy. Neonatal intraparenchymal haematomas are often iso- to slightly hypointense on T1-weighted images and markedly hypointense on T2-weighted images in the acute stage (sometimes up to first 3 days). They gradually turn bright on T1-weighted images while remaining dark on T2-weighted images over the next 3–7 days (Fig. 13.3). Between 7 and 14 days, the haematoma gradually turns bright on T2-weighted images and remains so while slowly turning isointense to CSF on T1-weighted images over the next several months [21]. Note that these timeframes are approximate and typically apply to intraparenchymal bleeds. The use of gradient echo T2* (Fig. 13.3b) or susceptibility-weighted imaging (SWI) sequences shows hypointensity in areas of haemorrhage. These sequences can sometimes increase the conspicuity and sensitivity of detecting small haemorrhages within the brain and may reveal signs of remote prior haemorrhage by demonstrating haemosiderin staining of the margins of the ventricles, cystic areas in the brain or brain surfaces.

The most common clinically important form of intracranial haemorrhage in neonates is intraventricular haemorrhage. The MRI signal of haemorrhage obviously depends on the stage of haemoglobin degradation, but IVH is most commonly seen as T2. T2* sequences can be very helpful for detection of subtle degrees of IVH, both in the acute stage and chronic phase (haemosiderin staining). The severity of neonatal intraventricular and germinal matrix haemor-

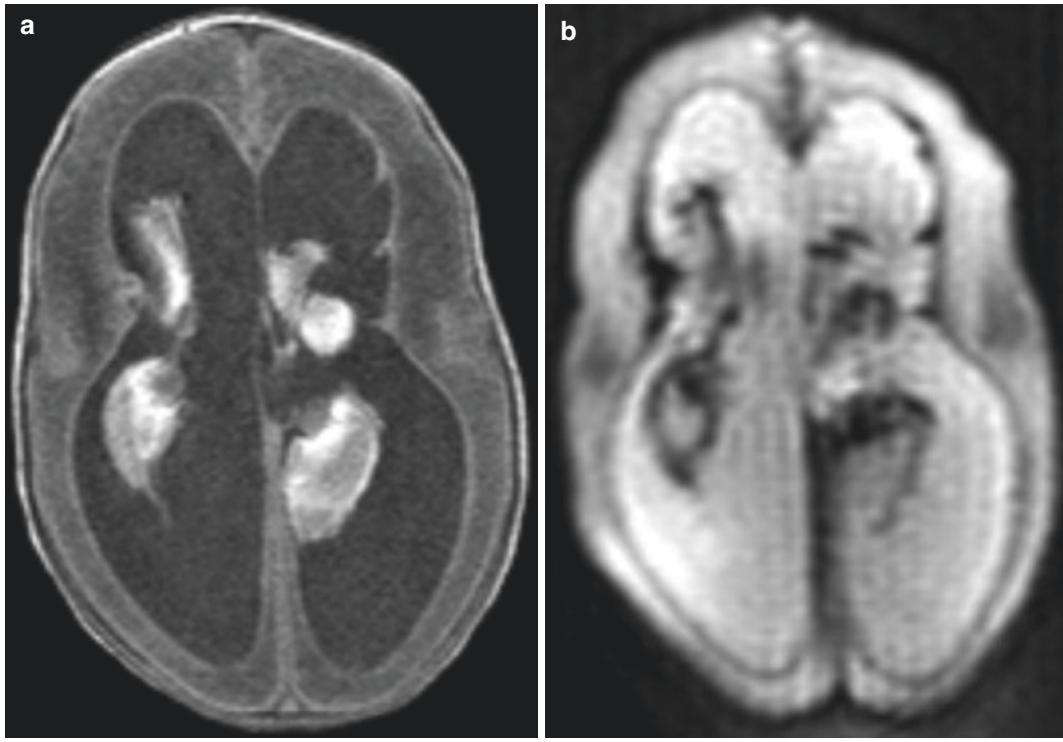

Fig. 13.3 Intraventricular haemorrhage in a 1-week-old neonate as depicted on MRI. (**a**) T1-weighted image demonstrates a hyperintense signal of blood within the ventricles. (**b**) Gradient echo T2* image demonstrates foci of low signal due to haemorrhage. Also note the hypointense staining along the margins of the lateral ventricles secondary to haemorrhage

rhage in the neonate is commonly graded using the classification of Papile et al. [22]. While this is commonly used on ultrasound (see Chap. 12), the same classification can be applied to magnetic resonance imaging as well. IVH encompasses four grades:

Grade 1: Subependymal haemorrhage only. These appear as focal areas of excessive hypointensity along the germinal matrix, most commonly in the region of the caudothalamic groove. The haematoma regresses over a period of days to weeks and may form a subependymal or germinolytic cyst.

Grade 2: Subependymal haemorrhage with blood in nondilated ventricles. Blood is seen extending into the ventricular system on MRI. The normal venous blood of the choroid plexus should not be confused with intraventricular haemorrhage on susceptibility sequences. In the chronic stages, hemosiderin staining of the ependymal margin of the ventricles may persist, but gradually decreases over time.

Grade 3: Subependymal haemorrhage with blood in dilated ventricles. Blood can fill part or all of a dilated ventricle. In the latter case, it may form a cast of the ventricle. Over time, the clot will resolve completely or persist as linear septations or bands within the ventricle. In more than two-third of patients, posthaemorrhagic hydrocephalus develops.

Grade 4: Subependymal haemorrhage with blood in dilated ventricles and intraparenchymal blood. The latter can be the result of haemorrhagic cerebral infarction rather than direct extension of blood from the germinal matrix [23]. This is mostly unilateral and is commonly detected in the frontal and parietal lobes on the same side as the intraventricular haemorrhage (IVH). Mass effect with shift of

the midline structures to the unaffected contralateral side may be present with large haemorrhages. The blood clot liquefies and retracts over several weeks, and in a matter of 2–3 months encephalomalacia develops. This can communicate with the ipsilateral ventricle. As the parenchymal haemorrhage, Grade 4, may be due to a different pathogenetic mechanism, it is sometimes regarded as a separate entity and not part of the original grading system by some authors [24].

Germinal matrix haemorrhage and intraventricular haemorrhage may be complicated by congestion and/or thrombosis of deep medullary veins in the white matter, leading to the white matter injury and periventricular venous infarction (PHVI) (Fig. 13.4). Intraventricular haemorrhage can also be detected in-utero utilising fast foetal MRI sequences targeted at detecting haemorrhage, including higher grades of IVH (Fig. 13.5). Detection of low grades of intraventricular haemorrhage is not uncommon on foetal MRI in our clinical experience. Nevertheless, it is important not to confuse normally prominent germinal matrices and developing deep venous structures in the foetus with IVH, as both may appear hypointense on T2*-weighted or echoplanar sequences.

In a report by the quality standards subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society based on comprehensive analysis of data from recent literature, Grade 3 and 4 IVH, cystic PVL and moderate-to-severe ventriculomegaly were found to be significantly associated with cerebral palsy at 2–9 years of age in VLBW preterm infants [25]. There was a tenfold elevation in the risk to develop cerebral palsy. The incidences of long-term neurologic sequelae of Grade 1–4 intracranial haemorrhage in the preterm infant are 5, 15, 35 and 90%, respectively [23]. In 90% of term infants with increased parenchymal echogenicity a neurologic sequel is to be expected [11]. Approximately 15% of all infants with IVH will develop PVHI. In 80–90% this develops within the first 96 h after delivery or 24–48 h after the appearance of germinal matrix haemorrhage on US particularly in clinically unstable neonates with metabolic acidosis [26].

Along with aqueductal stenosis, intraventricular haemorrhage is a common cause of

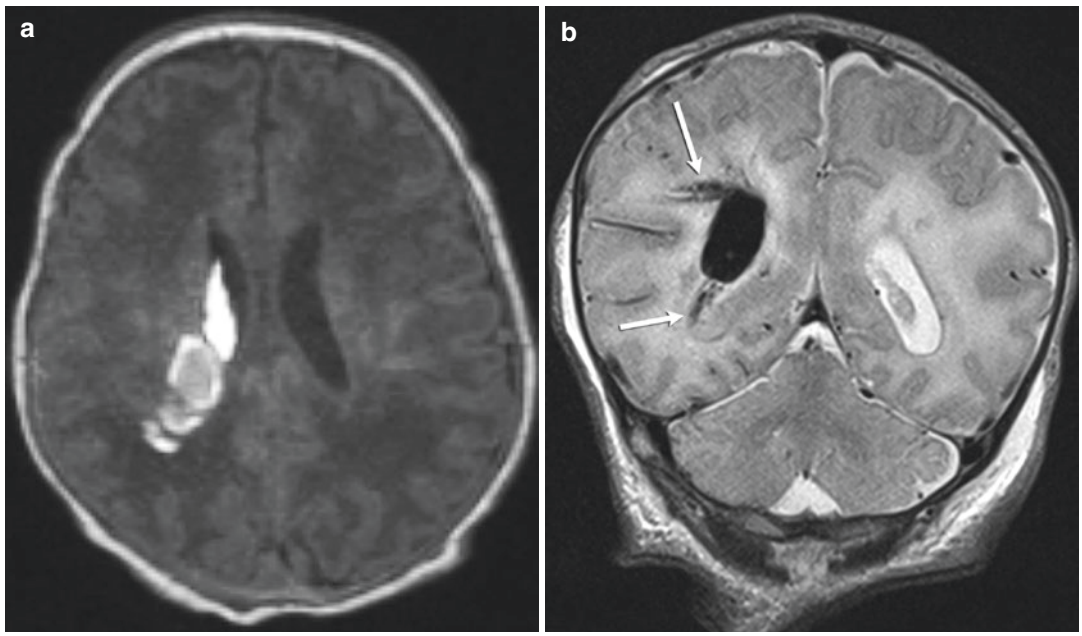

Fig. 13.4 In this patient with intraventricular haemorrhage (**a**), there is adjacent prominence and thrombosis of the medullary veins in the white matter (*arrows* in **b**), leading to periventricular haemorrhagic infarct

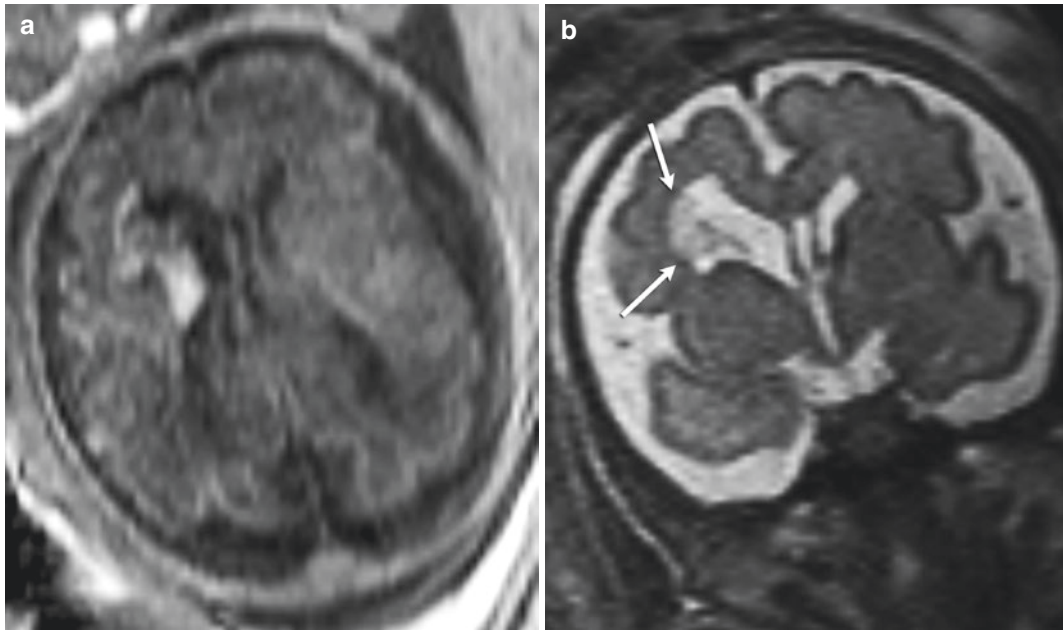

Fig. 13.5 In-utero grade 4 intraventricular haemorrhage on foetal MRI at 28 weeks gestation. (**a**) Axial T1-weighted image shows hyperintense blood within the right lateral ventricle extending into the adjacent parenchyma. (**b**) Coronal single-shot fast spin-echo T2-weighted image shows extension of blood into the brain parenchyma adjacent to the dilated ventricle and a thinned cortical mantle

neonatal hydrocephalus. Haemorrhage may result in obstruction of CSF flow through the ventricular system and CSF resorption at the level of the arachnoid villi, resulting in progressive ventricular dilatation, and both communicating and noncommunicating hydrocephalus. This can be delayed for days to weeks. The temporal horns, trigones and occipital horns often dilate before the frontal horns. The lateral ventricles dilate more than the third or fourth ventricles. Posthaemorrhagic hydrocephalus resolves in over half of the infants. Nevertheless, long-standing extensive ventricular dilatation can lead to white matter damage and atrophy.

Small subdural haemorrhages are extremely common in neonates, but almost cause mass effect or complications. These subdural haemorrhages are typically seen in the posterior fossa, along the tentorium, along the posterior falx and over the occipital regions. They are related to the birthing process. In the term infant, germinal matrix with resultant intraventricular haemorrhage is uncommon. On the other hand, isolated choroid plexus haemorrhage can occur in both the term and preterm neonate. Isolated parenchymal haemorrhage can occur and may be the result of traumatic delivery. The cortical haemorrhages may appear as a focal echogenic mass or cause diffusely increased gyral echogenicity on ultrasound (see Chap. 12). It can be easily detected on MRI. Over time, as the haematoma undergoes lysis and clot retraction, the hematoma mass decreases in size, and encephalomalacia may be a sequel seen on follow-up imaging.

13.5 Periventricular Leukomalacia and Neonatal White Matter Injury

Periventricular leukomalacia (PVL) is a general pathological description that is used without reference to a particular aetiology, and it is thought to typically affect the premature brain. MRI can detect signal abnormalities in the periventricular white matter early in the course of the injury. There is predilection for periventricular white matter. The MR findings of end-stage PVL are ventriculomegaly with irregular undulated margins of the body and

trigone of the lateral ventricles, reduced quantity of periventricular white matter particularly at the trigones with increased signal intensity on long TR sequences, delayed myelination, thinning of the corpus callosum and deep prominent sulci that abut or nearly about the margin of the ventricle with little or no interposed white matter (Fig. 13.6) [27]. In many cases, necrosis of

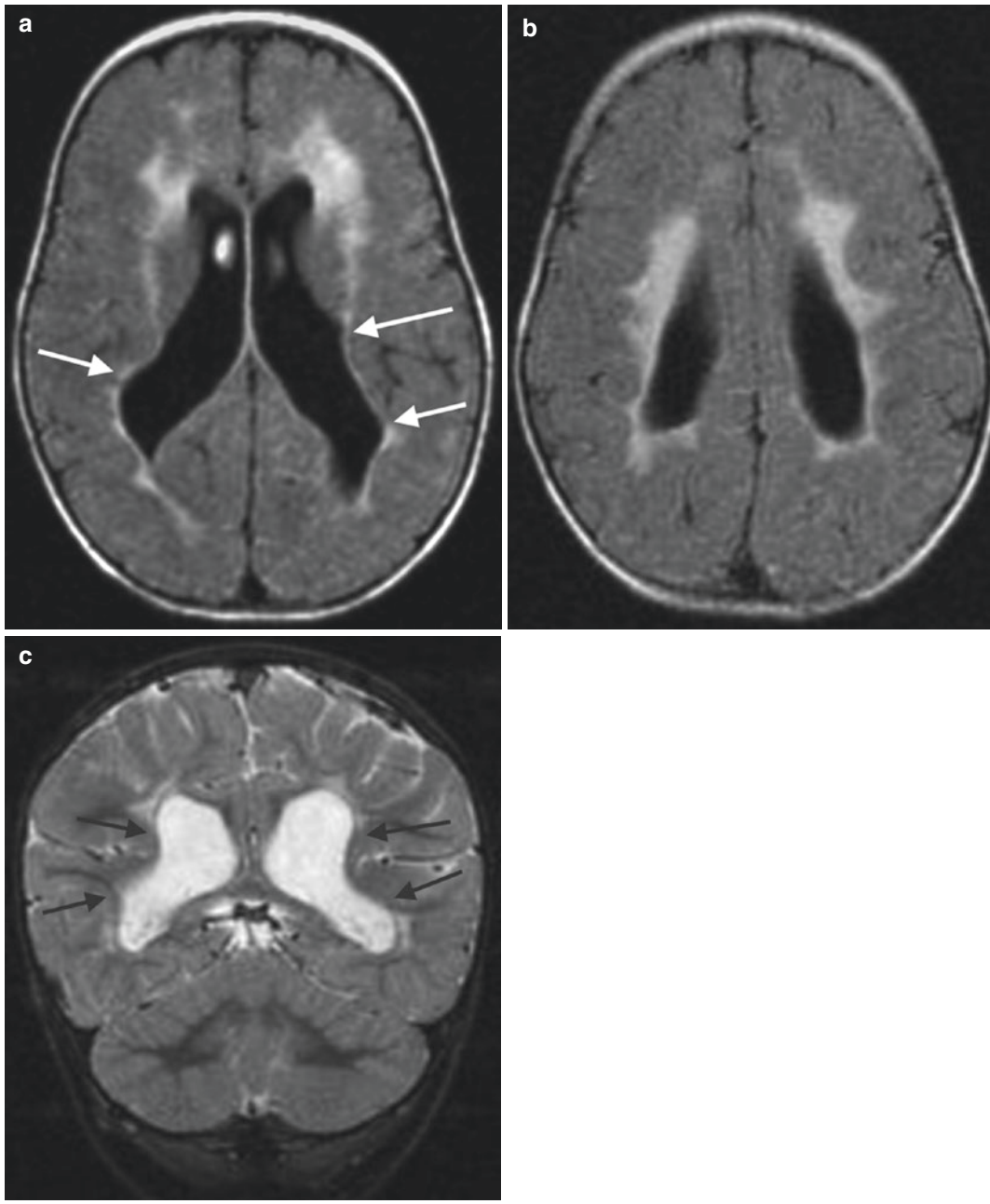

Fig. 13.6 Typical findings of periventricular leukomalacia. (**a**) The posterior lateral ventricles are distended within undulated margin (*arrows*), there is decreased white matter volume and there is periventricular abnormal white matter signal on FLAIR imaging (**a** and **b**). (**c**) Coronal T2-weighted image demonstrates decreased white matter volume, with approximation of the cortex to the margins of the distended lateral ventricles. (**c**) Sagittal T1-weighted image demonstrates associated sending of the corpus callosum

the immediate periventricular tissue occurs and cystic areas develop. The resulting cysts often later collapse or are incorporated into the lateral ventricles and the areas of signal abnormality come to lie closer and closer to the ventricular wall, until they finally disappear (Fig. 13.7). Compared with US performed on the same day, MRI of preterm neonates detects more white matter abnormalities in the first week of life [11, 28]. Contrary to findings in US in term newborns that later developed cerebral palsy, MRI can reveal a high rate of findings compatible with end-stage PVL [29].

There are other patterns of white matter diseases of prematurity as well [26, 28, 30]. Punctate white matter lesions may be seen at any gestational age including both in preterm and term patients. They are commonly seen in term neonates with cardiac disease or neuromuscular disease. Term neonates with severe cardiac anomalies have been shown to have delayed brain maturation [31]. These punctate white matter lesions are T1 hyperintense, often mildly T2 hypointense, and are most frequently detected along the corona radiata, the periventricular and deep centrum semiovale white matter and along the optic radiations [26]. They may occasionally also show restricted diffusion (Fig. 13.8).

Another less well-known pattern is termed diffuse excessive high signal intensity (DEHSI) within the white matter on T2-weighted MR imaging in premature babies at term-equivalent age, with signal intensity approaching that of cerebrospinal fluid [26, 32]. These were initially thought to represent abnormal white matter development without evidence of focal pathology on conventional MRI. However, more recent studies have shown that diagnosis of this entity is highly subjective [33], and there is no neurodeelopmental consequence in neonates with this appearance [34, 35]. On the other hand, cystic encephalomalacia and punctate white matter lesions were significant predictive of motor delay and cerebral palsy.

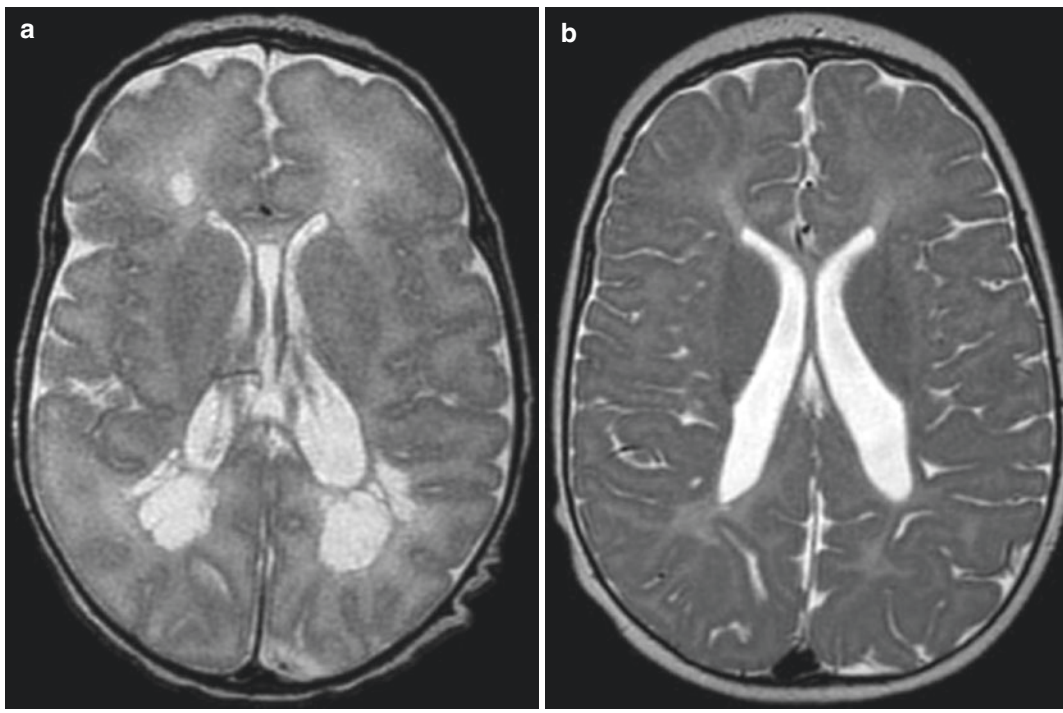

Fig. 13.7 (**a**) Axial T2-weighted image shows multiple foci of cystic periventricular leukomalacia in a 6-week-old infant. (**b**) Six months later, the cystic areas are no longer seen, but now depicted are undulated margins of distended posterior lateral ventricles and associated white matter volume loss

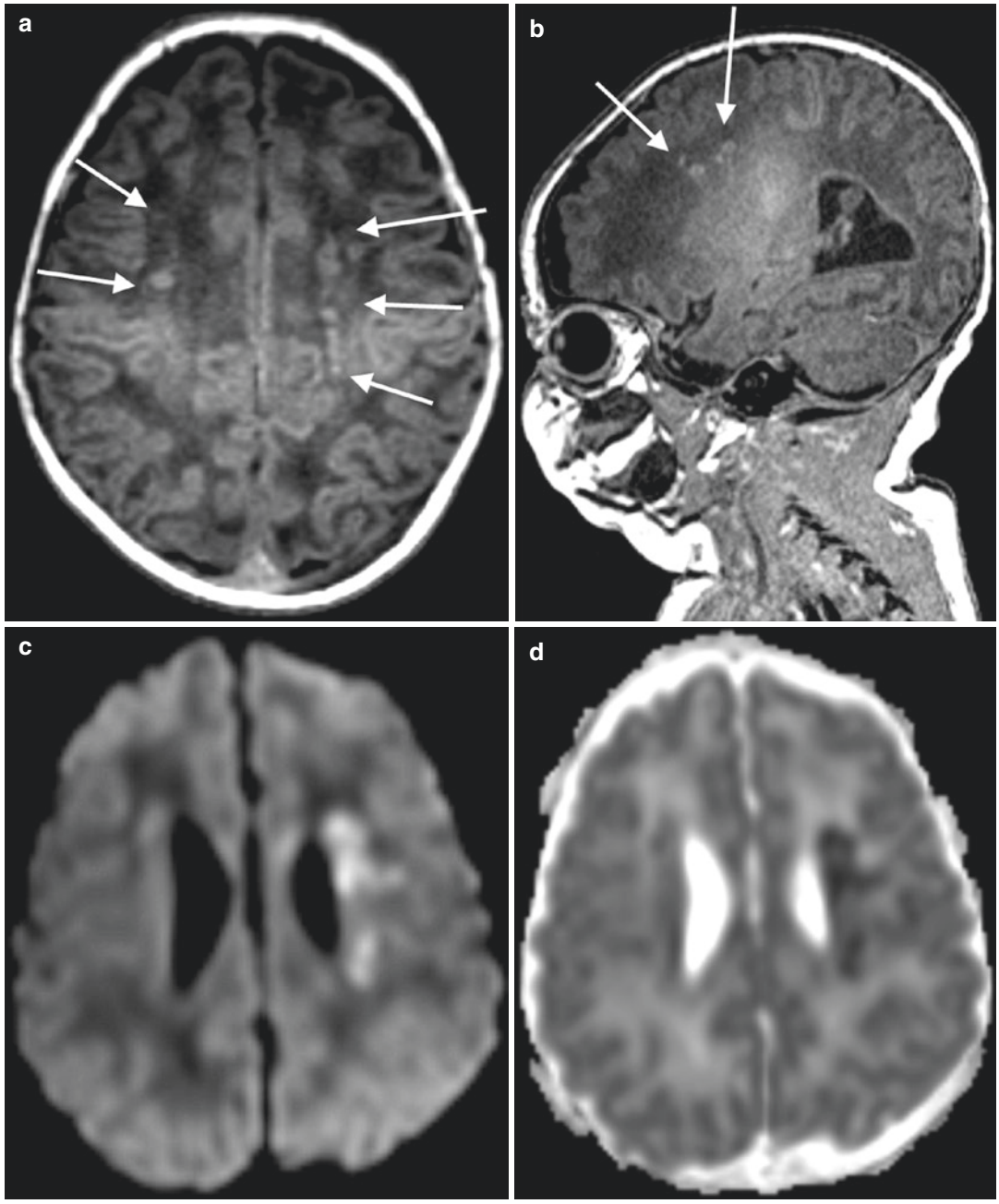

Fig. 13.8 Punctate foci of white matter injury in a term neonate with transposition of the great arteries. Axial (**a**) and sagittal (**b**) images demonstrate multiple small foci of abnormal high T1 signal intensity in the deep white matter. DWI (**c**) and ADC (**d**) images showed that a few of these foci demonstrate acute restricted diffusion

13.6 Hypoxic-Ischaemic Injury

Hypoxic-ischaemic injuries are another *aetiologic* category for CP. The use of MRI has been of great value in trying to determine timing of brain injury and recognition of patterns of injury [10, 36]. Nevertheless, there is some overlap in these patterns and the timing may not be as clear-cut. Presence of very wide subarachnoid spaces and interhemispheric fissure, ventricular dilatation, cystic lesions of the white matter and germinolytic cysts at birth or within the first week are some of the potential signs of prenatal injury (see Chaps. 5 and 12). The use of diffusion imaging has greatly assisted in timing of injuries to the brain. Diffusion-weighted imaging (DWI) assesses the movement of water molecules in tissue. It can detect acute injury to the brain and cytotoxic oedema resulting in reduced motion of water. High signal intensity on trace DWI maps and low signal intensity on the apparent diffusion coefficient (ADC) maps are often indicative of this acute injury. DWI is able to provide evidence of cerebral injury before conventional MRI in newborns with hypoxic-ischaemic encephalopathy [11].

The use of diffusion imaging has helped in assessing various patterns of acute injury to the brain [10]. The patterns of injury depend on the severity of the hypoxic event, presence or severity of hypotension, maturity of the brain, duration of injury and timing of the MRI relative to the acute injury episode. One major pattern of hypoxic-ischaemic injury to the brain in full-term neonates is seen in acute severe hypoxia. Diffusion-weighted imaging often shows restricted diffusion with high DWI and low ADC signal predominantly in the ventral lateral thalami and basal ganglia, putamina (most commonly posterior putamina) and also in the perirolandic cortices. Increased signal intensity in the deep grey structures including the thalamus and basal ganglia can develop on T1-weighted images (Fig. 13.9). There may be involvement of the hippocampi and brainstem. This pattern is usually seen as a result of a catastrophic event such as placental abruption, prolapse uterine court or ruptured uterus. In our experience, arterial spin labelling (ASL) perfusion often shows increased blood flow in the areas of injury by the time the patient is evaluated on MRI, likely as a result of luxury reperfusion. A second common pattern is the watershed predominant pattern of injury. This pattern is commonly seen following prolonged partial asphyxia. Often the watershed or border zone areas are involved, affecting the white matter and at least parts of the overlying cortex (Fig. 13.10). Another severe pattern, which is less common, includes extensive involvement of the cortex and subcortical white matter with relative sparing of the immediate periventricular white matter and central grey matter, referred to as the "*white cerebrum*" on diffusion imaging [10]. This type is often fatal though it may lead to multicystic encephalomalacia.

Hypoxic-ischaemic encephalopathy in the preterm neonate tends to affect the deep white matter at the level of the optic radiations adjacent to the trigones of the lateral ventricles and the frontal horns near the foramen of Monro and can result in periventricular leukomalacia (PVL). The sequel of PVL can be cystic encephalomalacia that can be identified about 2–3 weeks after the ischaemic insult. Only 15% of patients with increased periventricular echogenicity develop periventricular cysts. These can be single or multiple and communication with the ventricular system can occur when there is breakdown of the ependymal lining. PVL can be graded by the characteristics of the periventricular white matter [37].

With moderate or severe oedema, there may be poorly defined gyral-sulcal interfaces and slit-like ventricles. Later parenchymal atrophy,

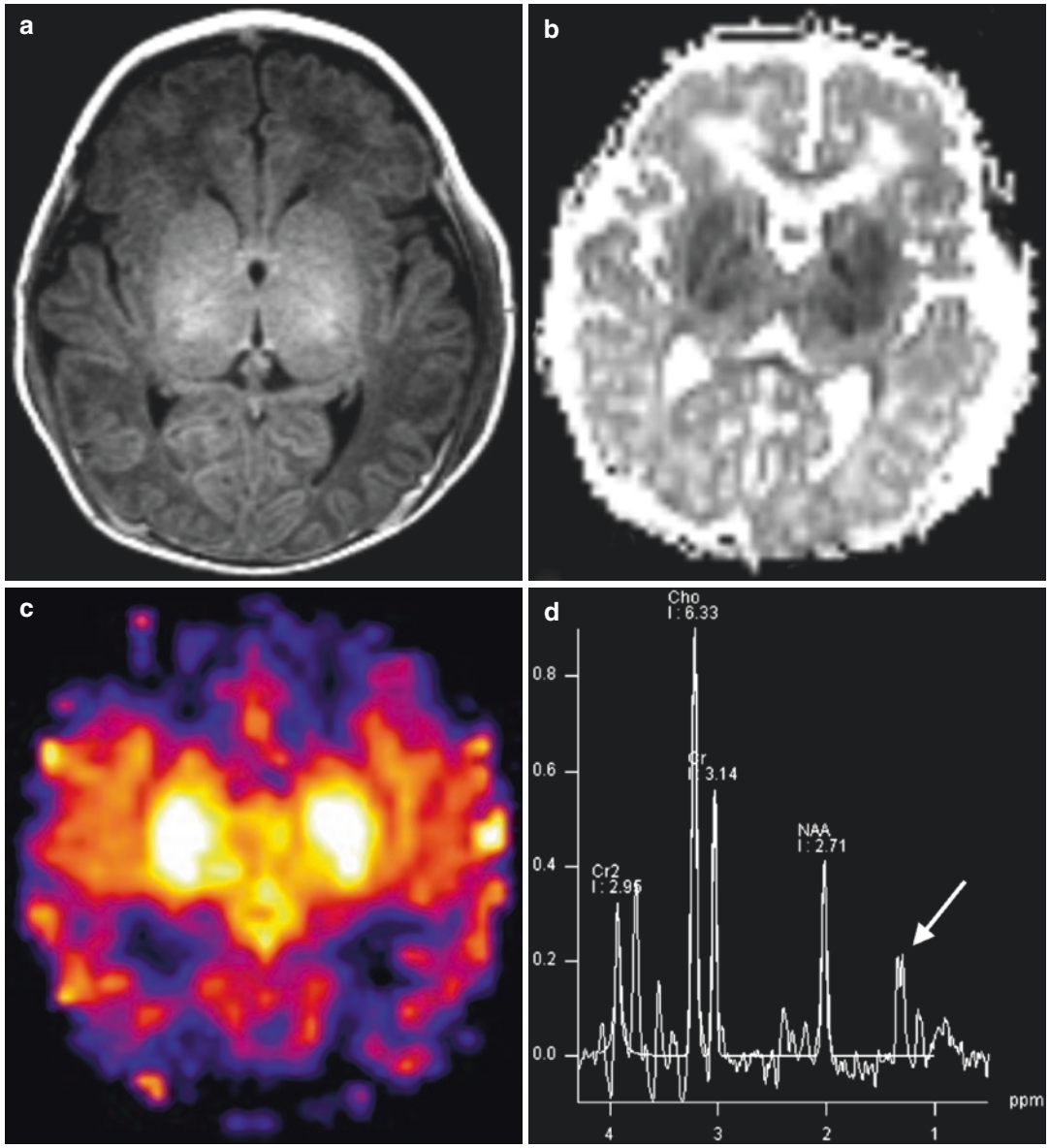

Fig. 13.9 Neonate with seizures after emergency caesarean section delivery due to close on full abruption, showing a deep profound pattern of hypoxic injury. (**a**) T1-weighted image demonstrates subtle increased signal in the basal ganglia and parts of the thalamus. Differentiating abnormal signal from normal myelination in the lateral thalamus and posterior limb of internal capsule may be difficult. (**b**) Apparent diffusion coefficient (ADC) map shows abnormally reduced diffusion in the basal ganglia and parts of the thalamus. (**c**) Arterial spin labelling (ASL) perfusion imaging demonstrates markedly elevated blood flow in the basal ganglia, corresponding to the areas of hypoxic injury on diffusion imaging. (**d**) Magnetic resonance spectroscopy demonstrates abnormally elevated lactate (*arrow*)

ventricular enlargement and cystic encephalomalacia may develop (Siegel et al. 1984). The cysts are mostly in the frontal and occipital lobes. In the term newborn, the thalamus and basal ganglia are vulnerable to hypoxic damage and if affected can be focally or diffusely echogenic on US [38] or

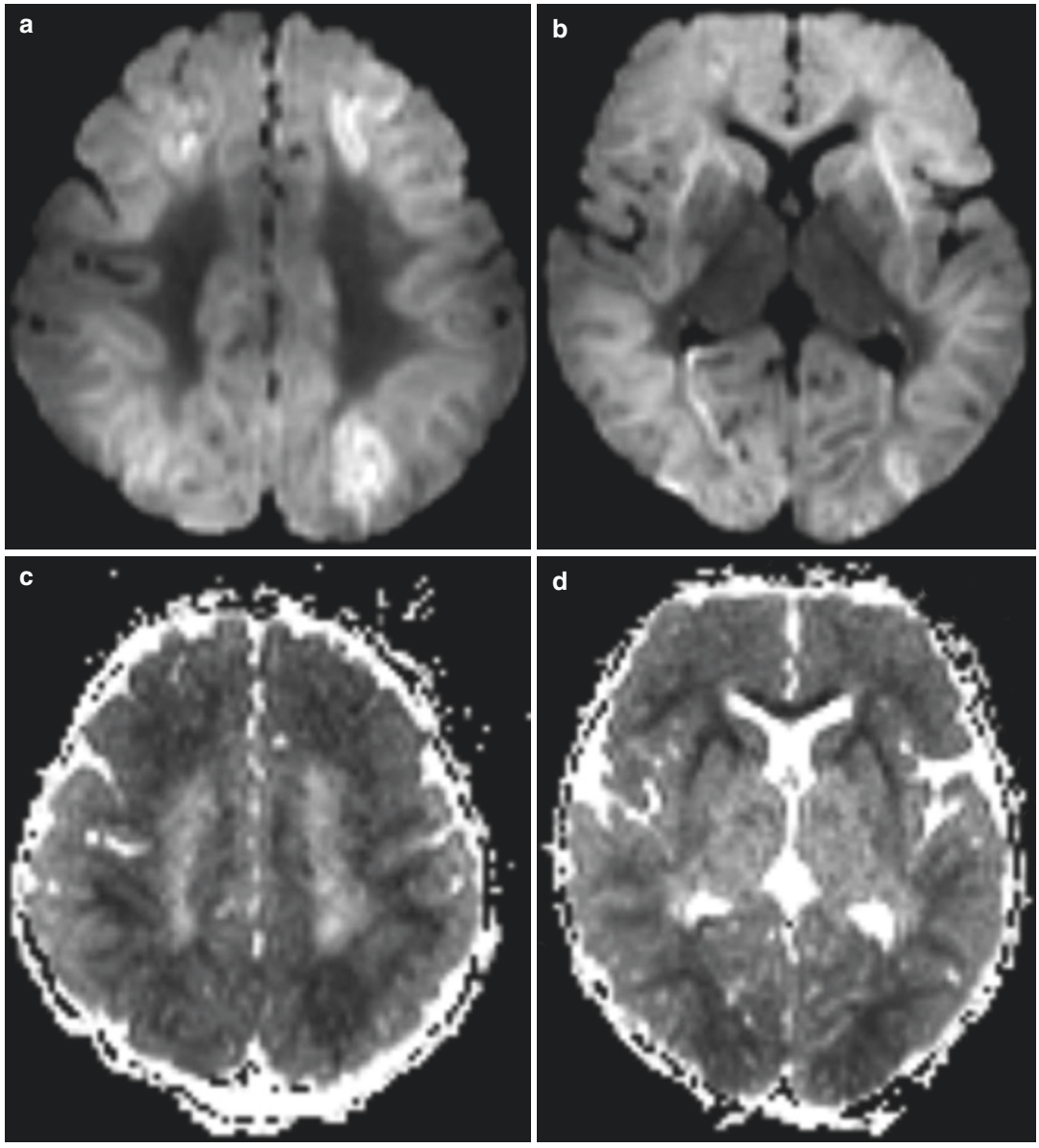

Fig. 13.10 DWI (**a** and **b**) and ADC (**c** and **d**) maps demonstrating a watershed-type injury to the brain, also involving white matter and parts of the cortex with relative sparing of the basal ganglia, thalami and other parts of the cortex

have abnormal signal on MRI (also see Chaps. 5 and 12). It should be noted that there may be cases of overlap between the different patterns of hypoxic-ischaemic brain injury. In the chronic phases after various types of injury, there may be cortical thinning and diminution of the underlying white matter with ex vacuo dilatation of the lateral ventricles. The affected areas of brain are shrunken and show high signal intensity on T2-weighted images compared to normal brain tissue.

13.7 Perinatal Ischaemic Stroke

Perinatal arterial ischaemic stroke and venous thrombosis can also be causes for damage to the brain leading to development of cerebral palsy. The incidence of perinatal stroke is between 2300 and 5000 births [39, 40]. As such, the neonatal period carries the highest risk for paediatric ischaemic stroke among all paediatric age groups. It is classified into arterial ischaemic stroke (confirmed by neuroimaging showing parenchymal infarct corresponding to an arterial territory) and neonatal cerebral sinovenous ischaemic stroke (confirmed by imaging showing thrombosis in the cerebral venous system and infarct corresponding to a venous territory). The aetiology of arterial ischaemic stroke in the neonate often remains unknown although placental factors are thought to be contributory [41].

Approximately half of neonates with a perinatal infract will develop hemiplegia [39]. The anatomic location and the size of infarct are obviously related to outcome. The presence of restricted diffusion along the descending corticospinal tracts is a sign of pre-Wallerian degeneration (diaschisis) (Fig. 13.11). The presence of pre-Wallerian degeneration at the time of acute arterial ischaemic stroke is a poor motor prognostic sign and often results in long-term motor weakness and signs of cerebral palsy [42].

The neonatal period is also a high-risk period for the development of cerebral sinovenous thrombosis (CSVT) [43]. These may involve the superficial or deep venous system. Adverse outcomes include postnatal epilepsy, cerebral palsy, visual deficits, cognitive impairments, posthaemorrhagic hydrocephalus requiring shunting and death. Outcome will be highly dependent on the location and extent of venous structures involved

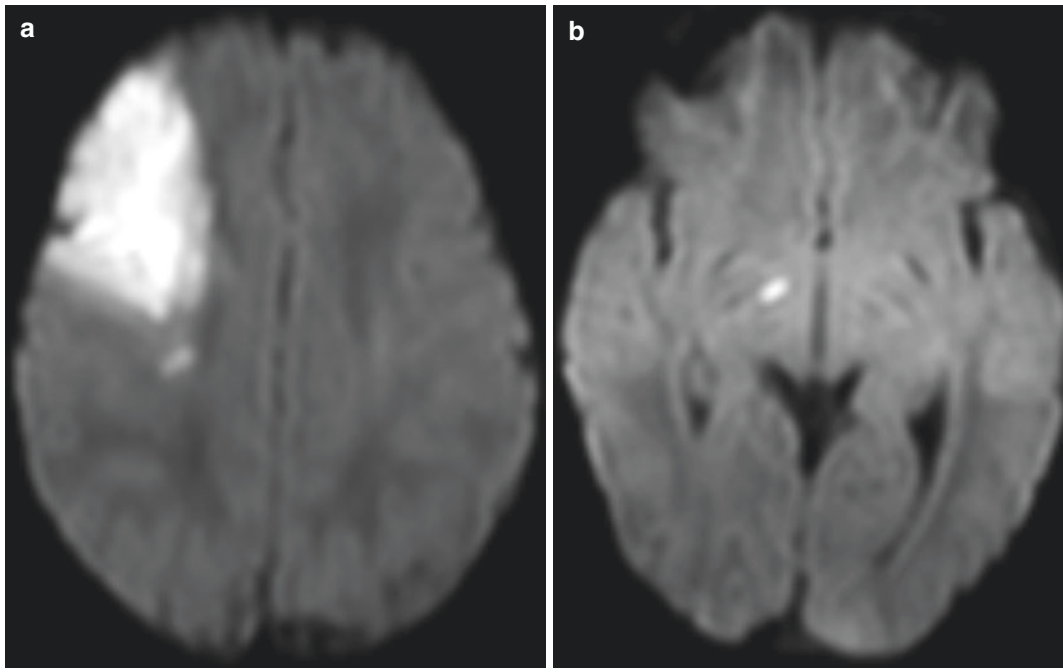

Fig. 13.11 Neonatal arterial ischaemic stroke (AIS) in a term infant. Diffusion imaging shows a large area of restricted diffusion in the right cerebral hemisphere in keeping with an infarct in the right middle cerebral artery territory (**a**). On a lower slice distant from the infarct zone (**b**), there is also focal restricted diffusion coursing along the descending corticospinal tract, in keeping with acute pre-Wallerian degeneration. The presence of this finding is a poor prognostic risk factor for motor outcome in neonatal arterial ischaemic stroke

and whether there are associated venous infarcts. Diagnosis can be made by detecting of abnormal signal intensity within the dural venous sinuses or cortical veins, demonstration of lack of flow on various magnetic resonance venographies (MRV) or filling defects within the dural venous sinuses on postcontrast MRI or CT studies. Of note, a number of artefacts and slow or turbulent flow may cause false positive or false negative results on various magnetic resonance imaging techniques.

In a subset of children, perinatal stroke may not be detected in the neonatal period for a variety of reasons [44]. They may present later with signs such as asymmetry in the use of an extremity and grasp, failure to reach normal developmental milestones, seizures and congenital hemiplegia. In these children, the diagnosis of presumed perinatal arterial ischaemic stroke (PPAIS) is made based on imaging appearance of a chronic arterial territory infarct (Fig. 13.12).

13.8 Advanced MRI Techniques

Newer MRI imaging methods have been utilised in evaluation of patients with brain disorders leading to cerebral palsy. These include metabolic imaging (MR spectroscopy, see Chap. 14), diffusion tensor imaging, volumetric MR imaging and functional connectivity MRI. These techniques have the ability or potential to provide additional pathophysiological insight into the biomolecular, cellular and systems processes that underlie development and outcome in children with cerebral palsy [45].

Widespread use of high-field magnetic resonance system and advances in MRI pulse sequences design has enabled acquisition of robust high-resolution 3D volumetric images of the brain. These images can be utilised in assessment of both global and regional brain volumes after segmentation. Thus, correlation of various

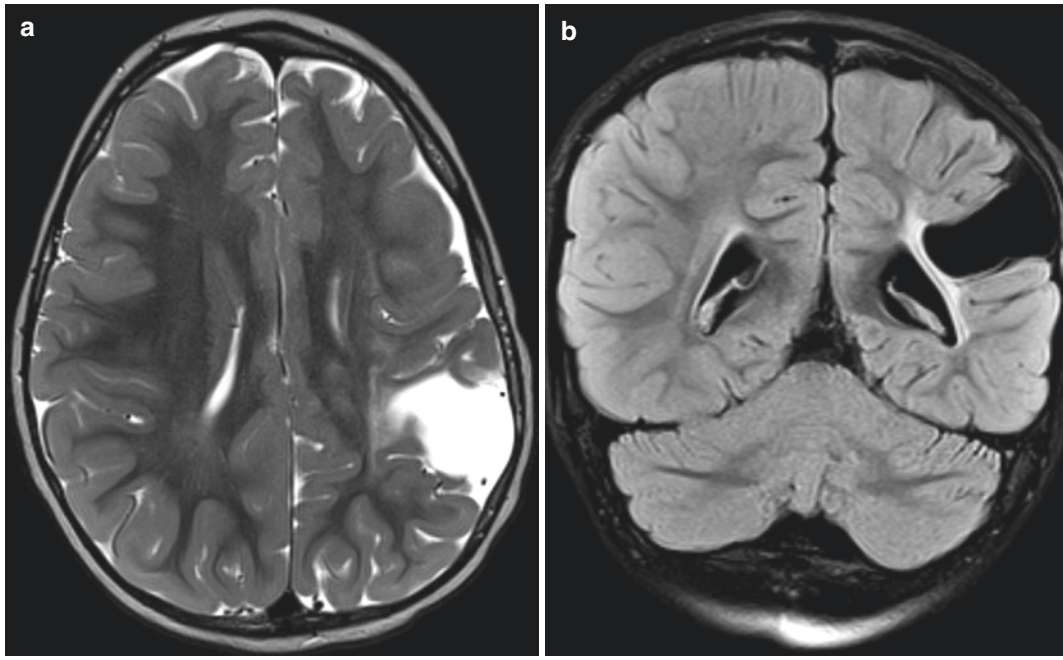

Fig. 13.12 Presumed perinatal arterial ischaemic stroke (PPAIS). A 15-month-old patient without a significant past medical history is brought to neurology clinic with preferred use of the left hand and shows some gait abnormality, with increased tone and reflexes in the right extremities. MRI shows chronic encephalomalacia in the left middle cerebral artery territory on axial T2-weighted (**a**) and coronal fluid-attenuated inversion recovery (**b**) sequences, with some surrounding gliosis. This is likely the result of a prior undiagnosed infarct, presumably in the perinatal period

brain segmental volumes with injury and outcome can be performed. The same data can be used for calculation of focal cortical thickness and analysis of the relationship with various diseases. The total brain and cerebellum volumes in children with cerebral palsy have been shown to be significantly reduced in comparison to controls [46]. In patients with periventricular leukomalacia, including those with spastic diplegia, cortical volume of the pre- and postcentral gyri and the paracentral lobule has been shown to be negatively correlated with motor function [47].

Proton MR spectroscopy (^{1}H–MRS) is an MR technique that has been applied extensively in the neuroimaging of newborns (see Chap. 14). This technique is most commonly applied by utilising single-voxel point-resolved spectroscopy (PRESS) or stimulated echo acquisition mode (STEAM) in evaluation of select predefined metabolites in the brain [10, 11]. Normally in the developing neonatal brain, there are higher concentrations of choline and lower concentrations of *N*-acetyl aspartate (NAA) compared to an adult or older paediatric brain, given the higher cell membrane turnover (choline) and lower neuronal concentration (NAA). Abnormally elevated lactate is commonly seen in patients with hypoxic-ischaemic injury to the brain (Fig. 13.7d) or in patients with certain metabolic diseases. The presence of elevated lactate may persist for days or weeks after the hypoxic event [10]. Lactate/creatine ratios of >1 in the first 18 h are more common in those infants with later neurologic findings consistent with hypoxic-ischaemic encephalopathy. Elevated lactate/NAA, lactate/creatine and lactate/choline ratios in the first 2 postnatal weeks have been found to be more common in infants with suspected neonatal encephalopathy than in age-matched controls [11]. Changes in metabolite ratios have been shown to correlate with neurodevelopmental outcomes [48].

Another recent advanced neuroimaging technique is diffusion tensor imaging (DTI) which utilises multidirectional diffusion information to reconstruct various quantitative parameters in regard to directionality of water diffusion, which is different in normal white matter and grey matter and in areas of brain injury. DTI is able to detect subtle changes not apparent on conventional MR imaging. DTI data could also be used in the depiction of white matter tracts using various tractography algorithms (Fig. 13.13). On a quantitative basis, alteration in various diffusion parameters in the corticospinal tract and corpus callosum are related to motor outcome [49]. Diffusion tensor imaging has been applied for identification of specific white matter tract injury in children with cerebral palsy and in association with periventricular leukomalacia [50]. In a more recent study, DTI parameters of the motor tract were shown to correlate with future motor function at mean age of 28 months [51]. DTI is being intensely investigated as a tool for assessment of brain function subsequent to various types of injury. The notion of structural connectivity as evaluated by diffusion tensor imaging can shed light into the extent of damage and pathophysiology in children with cerebral palsy [52]. In patients with periventricular leukomalacia, it has been shown although the fractional anisotropy DTI measure within most of the major white matter tracts were significantly lower than that of age-matched healthy controls, fractional anisotropy mainly within the bilateral corticospinal tracts and posterior body and isthmus of the corpus callosum showed more significant correlation with motor dysfunction than thalamocortical pathways [47].

Functional MRI is also being used in the evaluation of neonatal brain injury. Classically, fMRI involves performing certain tasks and observing the change in the blood-oxygen-level-dependent signal that results from vascular changes related to neuronal activation. These task-based methods are generally infeasible in the neonatal and infantile periods. However, it has been shown that even during periods of rest (no task), there is a temporal correlation between different parts of the brain that appear to function as different correlated networks. The method of analysis and characterisation in uncovering these correlated networks is known as resting state functional connectivity MRI. Patterns of aberrant functional

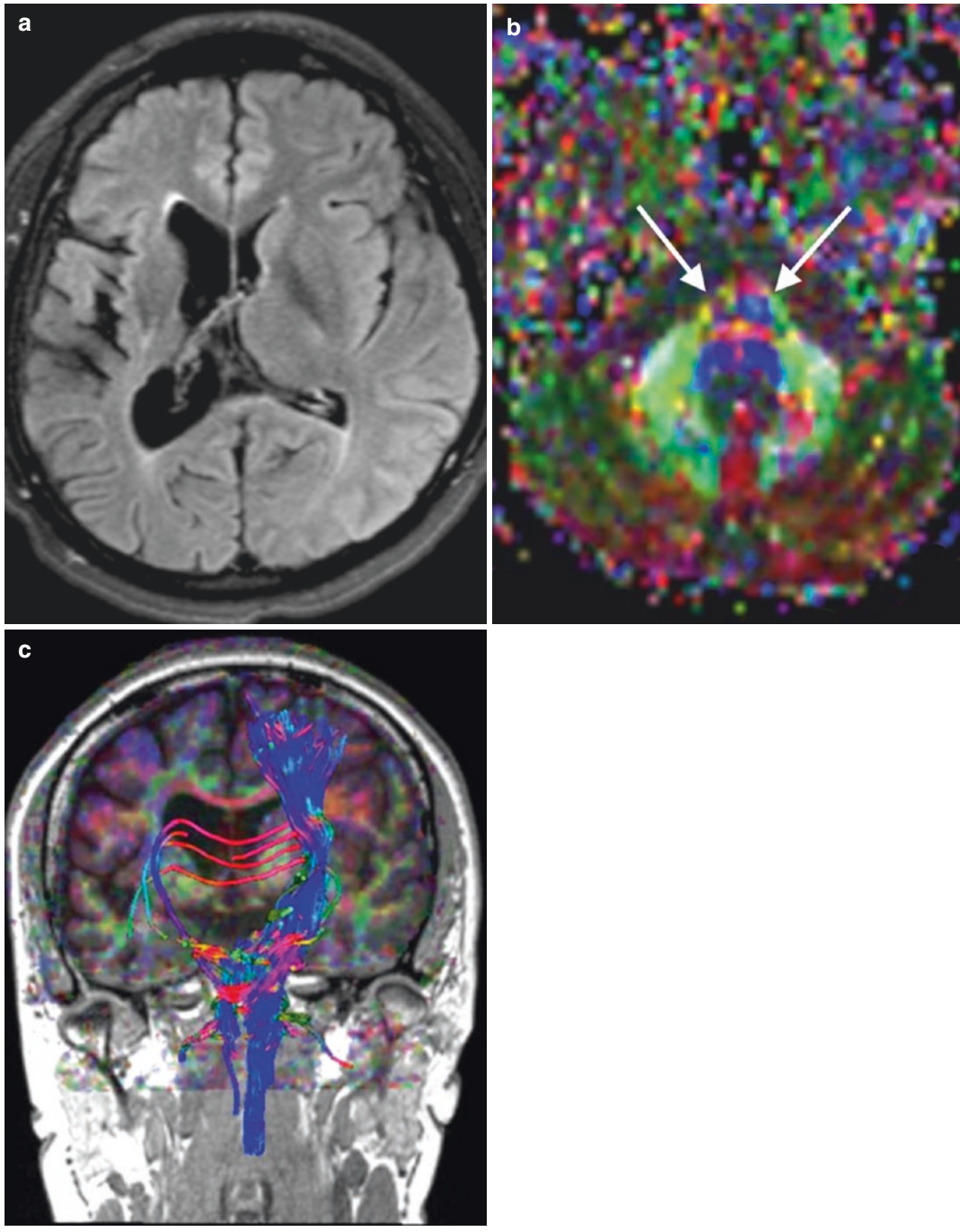

Fig. 13.13 Diffusion tensor imaging (DTI) in a patient with left hemiplegic cerebral palsy. Child with previous right-sided haemorrhage, with resultant volume loss and dilatation of the right lateral ventricle (**a**). (**b**) Colour-coded fractional anisotropy maps through the brainstem demonstrate markedly diminished right corticospinal tract (*blue*) compared to the left (*arrows*). (**c**) Tractography derived from diffusion tensor imaging superimposed on coronal anatomical images also shows markedly asymmetric and diminished right corticospinal tract compared to the left side

connectivity have been observed in premature neonates with white matter injury and depended upon injury severity [53]. In patients with PVL, the motor cortical connectivity was diminished mainly within the bilateral somatosensory cortex, paracentral lobule, cingulate motor area and visual in those with spastic diplegia [47]. More studies are required to assess the role of functional network derangements in patients with cerebral palsy due to a variety of aetiologies.

In conclusion, neuroimaging plays an important role in the evaluation of brain injury in preterm and term neonates and also as a tool in the investigation of motor and cognitive dysfunction. Further advances in neuroimaging have the potential to shed light on the pathophysiology of various types of injury and functional impairment in patients with cerebral palsy. In the combination of advanced techniques with conventional MR imaging techniques, the imaging findings have potential to be utilised beyond routine diagnostic and prognostic tools. They can be potentially employed as biomarkers of long-term motor and neurodevelopmental outcome and means to evaluate the efficacy of neuroprotective strategies and interventions.

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Nuclear and Molecular Imaging in Cerebral Palsy

14

Marc Hickeson and Efrosyni Sfakianaki

Abstract

Nuclear or molecular imaging (N/MI) is a functional imaging method, which utilizes radiopharmaceuticals (RPHs) to prepare the patient and special detectors to map and measure the distribution of the administered RPHs inside the body. RPHs are biologically active molecules labeled with radioactive isotopes (or radionuclides). They target either normal tissues or specific pathology (e.g., tumors, infection, etc.) and are administered in absolutely safe and harmless small quantities. N/MI provides a noninvasive evaluation of patients with or at risk of developing cerebral palsy and predicts outcome of these patients. It has also an established role for the localization of seizure foci in epilepsy, which is present in approximately two fifths of patients with cerebral palsy. Novel PET tracers that are used in some neurological centers image gamma-aminobutyric acid (GABA) receptor with ^{18}F-fluoroflumazenil and serotonin function with ^{11}C-alpha-methyl-L-tryptophan, and these have the potential to become the standard of care in the future.

14.1 Introduction

Nuclear or molecular imaging (*N/MI*) is a functional imaging method, which utilizes radiopharmaceuticals (*RPHs*) to prepare the patient and special detectors to map and measure the distribution of the administered RPHs inside the body. RPHs are biologically active molecules labeled with radioactive isotopes (or *radionuclides*). They target either normal tissues or specific pathology (e.g., tumors, infection, etc.) and are administered in absolutely safe and harmless small quantities. As such, they provide information about function, at the molecular, cellular, or

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organ level, but also about the presence, extent, and severity or grade of pathology.

In nuclear and molecular imaging, brain function and brain pathology are evaluated by the use of two techniques, which utilize different RPHs, labeled either with gamma/X-ray emitters or with positron emitters and different detectors (*cameras*): single photon emission computed tomography (*SPECT*), based on detecting single photons emerging from the body, and positron emission tomography (*PET*), based on detecting the two photons generated when a positron meets an electron and annihilate. In this chapter, we will review the clinical applications of these two imaging techniques as they apply to the evaluation of patients with cerebral palsy (*CP*).

14.2 Clinical Issues

Birth asphyxia is a significant problem in perinatal medicine and is associated with high rates of mortality and neurological and mental disabilities. The prevalence of asphyxia is estimated at between 2 and 4 per 1000 full-term newborn infants. Approximately 15–20% of such asphyxiated infants who develop hypoxic ischemic encephalopathy (*HIE*) actually die during the neonatal period, and of the survivors, 25% will exhibit permanent neuropsychological deficits. Thornberg et al. [1] reported that the clinical severity of HIE correlates with the outcome of the term infants. Mild HIE usually results in normal outcome and severe HIE usually results in either death or cerebral palsy [2]. Since, moderate HIE may result in a normal outcome or cerebral palsy [3], early prediction of future handicap is important when selecting infants for early interventions, which may be possible in the near future [4]. Epilepsy, which is often present in patients with cerebral palsy, will also be discussed.

The evaluation of the regional cerebral glucose metabolism (rCGM) by *FDG-PET* or the regional cerebral blood flow (rCBF) by *SPECT* may provide useful information in infants with clinical suspicion or evidence of CP and can be a powerful tool for early prediction of future handicap. Indeed, these methods accurately indicate focal brain damage or abnormal maturation as well as severity and extent by showing semiquantitatively the local absence/decrease in metabolism (rCGM) or blood flow (rCBF). Thus, they directly demonstrate the effects of ischemia and the lack of development of normal brain tissue as well as the exact locus, extent, and severity of the abnormality.

Before describing the limited clinical experience with SPECT and PET on such applications, it is important to review the topic of brain maturation as studied with these techniques.

14.3 Brain Maturation and Normal Metabolic Activity and Blood Flow

Under normal physiologic conditions, regional cerebral blood flow is closely matched to the resting regional metabolic activity of the tissue [5], although metabolic fluctuations are more pronounced than perfusion. Therefore, the distribution of the perfusion agents in SPECT is, in general, very similar to the distribution of FDG in PET, and both of these modalities will be discussed together in this chapter. Certainly, PET studies with FDG using dedicated PET brain units have greater advantages than SPECT when the objective is to detect small- or low-intensity differences in blood flow or metabolism.

When evaluating the pediatric brain function with *FDG-PET* or brain perfusion with *SPECT*, it is necessary to keep in mind the normal development of the brain in terms of regional metabolism and perfusion. Chugani et al. [6] using FDG-PET described the evolution of the regional glucose metabolism of the brain in infants during different stages of development. At age 5 days, the rCGM is highest in the sensorimotor cortex, thalamus, cerebellar vermis, and brain stem. During the first 3 months, the rCGM increases in the parietal, temporal, and occipital cortices, basal ganglia, and cerebellar cortex. Beginning at approximately 6 months, there is a gradual regional increase in the lateral frontal regions. The medial frontal and dorsolateral occipital cortical regions are the last cerebral regions to demonstrate a maturational

rise of regional glucose metabolism; this occurs at approximately 8 months. By 1 year of age, the distribution of FDG in the brain resembles that of the adult. Similar observations were made using SPECT and regional CBF studies [7].

Quantitative studies of the rCGM have been performed in infants. Kinnala et al. [8] also reported quantitatively similar observations during the first 6 months of life. They demonstrated that absolute values of regional cerebral glucose utilization also vary with age. Gray matter regions have low glucose utilization at birth (13–25 gm). These rapidly rise to reach adult values (19–33 μmol/min/100 gm) by 2 years.

It is interesting and important to notice that the regional cortical glucose utilization continues to rise until, by 3–4 years, it reaches values of 49–65 μmol/min/100 gm in most regions, higher than the adult values. These high rates are maintained until approximately 9 years, when they begin to decline, and reach adult rates again by the latter part of the second decade. The highest increases of regional glucose utilization over adult values occur in cerebral cortical structures; lesser increases are seen in subcortical structures and in the cerebellum. The rCGM also varies according to the gestational age; it gradually increases with post-conception age ([9].

14.4 Findings in rCGM and rCBF in Neonates and Young Children with CP

Decreased regional and global metabolism or blood flow to the brain is the typical finding in infants with *CP* on *PET* or *SPECT* imaging. Lee et al. [10] reported that nuclear medicine is complementary to MRI for the diagnosis of cerebral palsy. SPECT is more sensitive for the detection of hypoperfusion abnormalities in the cerebral gray matter, the subcortical nuclei, and the cerebellum, whereas MRI is the imaging modality of choice for the detection of white matter abnormalities. The findings demonstrated on nuclear imaging are not specific for CP as they may be observed in other cases of brain damage such as trauma, infection, and tumors. However, given the proper clinical presentation, they can be considered diagnostic of CP and indicative of the extent and severity of the damage and the lack of development of the brain. They may have prognostic significance and evolve as the child grows due to adaptations in brain function.

In another study, Shah et al. [11] studied the rCBF patterns with SPECT and ultrasound in neonates of 1–2 weeks of age with HIE and correlated the results with immediate neurological status and neurodevelopmental outcome at 3 months. The authors found that the commonest pattern of defect was parasagittal hypoperfusion, and the more severe the perfusion defect was, the higher was the incidence of difficult-to-control seizures and the higher was the duration of altered sensorium. They reported a positive predictive value of 75% for *SPECT* and for ultrasound, while the negative predictive value was 100% for *SPECT* and 76% for ultrasound.

Thorngren-Jerneck et al. [2] studied the correlation of the regional cerebral glucose metabolism (rCGM) on FDG-PET with the clinical severity of HIE and the clinical outcome [12]. In that study, there was a clear correlation between the rCGM and the clinical outcome [13]. They reported a sensitivity, specificity, and accuracy of 70%, 100%, and 96.5%, respectively, for adverse outcome with abnormal anteroposterior regional cortical perfusion.

Since the clinical subtype of CP depends on the location of damage or abnormal development of the brain and compensatory changes occur with brain maturation, the findings in patients with cerebral palsy on *SPECT* or *PET* brain imaging vary with the subtype of CP and the age of the patient.

14.5 Correlation Between rCGM/rCBF and Clinical Presentation

The findings of *SPECT* and *PET* studies closely parallel clinical abnormalities and allow further characterization of CP into different subgroups. Kerrigan et al. [14] correlated the finding of FDG-PET imaging in 23 children with 4 clinical

subtypes of CP: (a) spastic quadriparesis, (b) spastic diplegia, (c) infantile hemiplegia, and (d) choreoathetosis.

FDG-PET images were correlated with magnetic resonance imaging or computed tomography. Although the location of glucose metabolic abnormalities corresponded, in general, to abnormalities of brain structure demonstrated by structural imaging studies, the distribution of metabolic impairment almost invariably extended beyond the region of anatomic involvement.

The most prevalent finding on FDG-PET or brain perfusion SPECT is the hypometabolism or hypoperfusion of the thalamus occurring in approximately 98% of all cases of cerebral palsies [10]. Other interesting observations in some of the specific subtypes of cerebral palsy were determined with FDG-PET. In patients with spastic diplegia, FDG-PET revealed focal regions of cortical hypometabolism in the absence of apparent structural abnormality with MRI. In most patients with choreoathetoid cerebral palsy, a relatively normal pattern of cortical metabolism associated with marked hypometabolism in the thalamus and lenticular nuclei was observed. In patients with spastic unilateral, FDG-PET disclosed symmetric cerebellar glucose metabolism with absence of crossed cerebellar hypometabolism (diaschisis), which is often seen in adult patients with stroke [14].

Denays et al. [15] also studied 13 children with CP with ^{99m}Tc-HMPAO SPECT. They reported hypoperfusion of the hemisphere contralateral to the motor deficit in children in the hemiparetic group. Additionally, they reported normal findings in patients with mild bilateral hypoperfusion in the superior motor cortex in patients with moderate di- or tetraplegia (spastic bilateral) and bilateral reduction of perfusion in the superior motor, inferior motor, prefrontal, and parietal cortices in patients with severe di- or tetraplegia. In 36 children with bilateral spastic CP, Yim et al. [16] reported good correlation between the degree of developmental delay and the severity of hypoperfusion in the thalamus or the cerebellum, and they concluded that the measurement of rCBF by ECD SPECT could be valuable in the prognostication of gross motor development.

14.6 Compensatory Changes in rCGM in Children with CP

In older children, the findings on FDG-PET differ from those reported in neonates with HIE who subsequently manifested CP. Vandermeeren et al. [12] reported in children with congenital hemiplegia of subcortical origin a normalization or relative increase in rCGM in the ipsilateral sensorimotor cortex. In that study, a second but less intense cluster of increased FDG cerebral uptake was also observed in the contralateral side encompassing the primary motor cortex, the callosomarginal sulcus, and cingulate gyrus. Unlike in adult patients with previous stroke, contralateral diaschisis (*cerebellar cross abnormality*) was not observed in patients with congenital hemiplegia. This increased FDG uptake in the disconnected ipsilesional motor areas may reflect a long-term adaptation leading, for example, to an increased synaptic density and/or activity or to a change in the density of glucose transporters.

14.7 Prognostic Value of rCGM and rCBF in CP and Effect on Therapy

Functional brain imaging may be of value for the early diagnosis and prediction of outcome of neonates with high risk of CP, particularly when clinical examination and laboratory investigations, including CT and MRI, are inconclusive. In HIE within the first 24 h after birth, there is evidence of global increased cerebral blood flow, which decreases after 7 days [17]. This initial, transient cortical hyperperfusion is abnormal for infants less than 3 months old, as thalamic perfusion is expected to be greater than the cortical perfusion in that age group. This normally reverses as the child grows and telencephalic neocortical areas develop and cortical perfusion eventually becomes equal or greater than that of the thalamus, as was discussed earlier. As such, the pattern of cortical hyperperfusion as compared to that of the thalamus detected by ICBF SPECT within the first 24 h after birth appears to be a sensitive method for the early identification of HIE in children. Moreover,

this would indicate a poorer prognosis and would thus point toward minimally supportive management from the clinical perspective.

In accordance with this finding, local rCGM increase was observed utilizing FDG-PET scans in infants suffering from perinatal asphyxia and with moderate or severe HIE 2.5 days after birth [18]. The authors concluded that information indicating pathophysiological events could be extracted earlier with PET than with conventional anatomic imaging techniques. The pattern of transient hypermetabolism in neonates following perinatal hypoxia who later developed CP and eventually hypometabolism has also been described in the basal ganglia [19]. So, as with SPECT, the early evaluation of rCGM with a FDG-PET scan during the first 24–48 h after birth would also be valuable to identify HIE and predict the neurological outcome.

Neonatal brain perfusion (rCBF) defects can provide with prognostic information regarding the severity of cerebral palsy. In a study of 34 preterm infants, Valkama et al. [20] assessed rCBF with SPECT and ultrasound and compared the results with clinical follow-up. Perfusion defects measured by ^{99m}Tc-ECD SPECT predicted cerebral palsy with 82% sensitivity and 70% specificity, compared with 73% and 83% for ultrasound, respectively. In the same study, the sensitivity of SPECT in predicting moderate or severe CP was 100% and the specificity 67%; the corresponding results were 71% and 74%, respectively, for ultrasound. Based on those results, the authors concluded that brain SPECT is a highly sensitive modality for the identification of the most severe forms of CP in preterm infants at term age, which is associated with a lower sensitivity for the detection of mild CP.

Therapy using autologous bone marrow mononuclear cells is a potential novel treatment strategy complementary to rehabilitation for cerebral palsy. PET has also demonstrated its potential value for the assessment of treatment in cerebral palsy [21, 22]. The changes seen on imaging may be present before any objective clinical improvement becomes evident [23]. Future studies may be planned with PET imaging as a monitoring tool for those patients.

The rCBF and rCGM, as well as other *SPECT* or *PET* applications, which utilize the multitude of available RPHs, may provide needed additional knowledge and clinically useful information as therapeutic and preventive methods develop. Radiation exposure during the neonatal period is always an important concern. Regarding this matter, it should be underlined that most PET scans in neonates could be accomplished using effective doses approximately equal to the yearly background radiation exposure. The typical dose to the neonate from a PET scan would be approximately 5 mSv, which is 6 to 18 times less than that reported with CT scans [24]. By comparison, the average annual background effective dose amounts to 3.6 mSv in the USA [25].

14.8 Cerebral Palsy and Epilepsy

Approximately two fifths of children with cerebral palsy suffer from epilepsy [26] as compared to approximately 0.5–0.7% in the general population [27, 28]. Epilepsy is defined as a disease involving recurrent unprovoked seizures. In those patients, seizures are most commonly caused by brain injury. Seizures are often difficult to control, particularly in those with mental retardation [29]. In those patients with drug-resistant epilepsy, surgery involving resection of the epileptogenic focus should be considered.

Classification of seizures has been proposed and revised by the International League Against Epilepsy (ILAE) [30]. Seizures and epilepsies are considered as either partial (focal) or generalized. Partial seizures can involve the temporal, frontal, parietal, and occipital lobes. Generalized seizures are associated with bilateral initial hemispheric involvement.

Epilepsy surgery may be effective for the treatment of medically refractory epilepsy if the focus of seizure is properly identified and resected. The *greatest difficulty* of surgical management is to accurately localize the focus of seizure. Methods to detect the seizure focus include a complete physical and neurological examination, blood tests, electroencephalogram (EEG), single photon emission tomography (SPECT), positron emission tomography (PET), and magnetic resonance

imaging (MRI). Of all these methods, SPECT is the only clinically approved modality with the capability to evaluate the functional changes that occur during a seizure. Brain SPECT is most commonly performed using one of the following brain perfusion agents: ^{99m}Tc-hexamethyl-propylene-amine-oxime (HMPAO) or ^{99m}Tc-ethyl cysteinate dimer (ECD). ^{18}F-Flurodeoxyglucose (FDG) is most commonly used for PET imaging of CP.

FDG-PET of the brain is done in the interictal phase and provides superior spatial resolution as compared to brain SPECT. Unlike SPECT, it is not feasible to perform an ictal PET due to the slow accumulation of the FDG to the target site. With interictal FDG-PET, the seizure focus is identified as a hypometabolic site (Fig. 14.1). FDG-PET is considered most valuable when the findings on MRI are negative or discordant with the ictal electroencephalography [31]. The sensitivity of FDG-PET is up to 90% for localization of the seizure focus in temporal lobe epilepsy and approximately 55% for extratemporal epilepsy [32]. Multifocal seizure foci pose a significant challenge for the presurgical evaluation in epilepsy. Functional imaging has the purpose to correctly identify the seizure focus and to differentiate it from non-epileptogenic lesions. In those cases, ictal SPECT is most helpful for the presurgical evaluation.

Ictal SPECT assesses the cerebral perfusion during or shortly after onset of seizure. The purpose is to establish with absolute certainty the site of the seizure activity for surgical planning. The principle of ictal brain perfusion imaging is that partial seizures are associated with an up to 300% increased regional cortical perfusion at the site of the seizure focus [33]. True ictal SPECT with the tracer injected immediately after the onset of the seizure demonstrates a hyperperfused focus at the site of the seizure focus with hypoperfusion surrounding that focus. This hypoperfusion may be attributed to the steal phenomenon, in which the blood flow is diverted to the seizure focus, or due to a protective mechanism, in which an inhibitory zone limits the spread of seizure [34]. The tracer should be injected within 30 s, ideally 20 s, after the onset of seizure through a previously placed intravenous line. The sensitivity of ictal SPECT

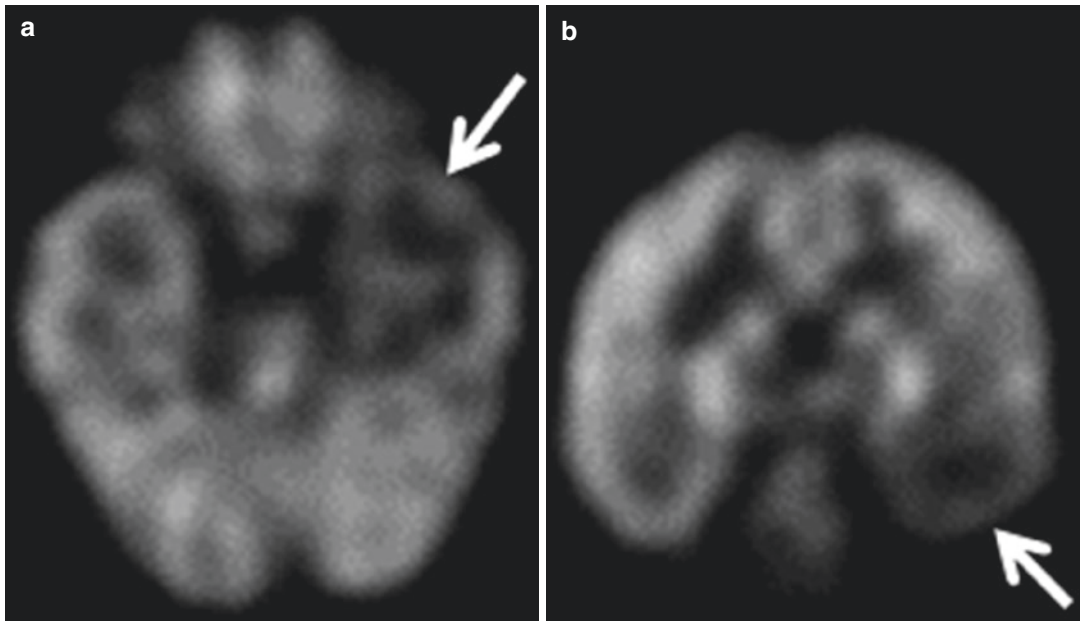

Fig. 14.1 This 22 year old with history of medically refractory recurrent episodes of seizures had undergone FDG-PET scan of the brain. Transaxial (**a**) and coronal (**b**) images demonstrate hypometabolism in the left temporal lobe (*arrow*). The patient subsequently had undergone anterior left temporal lobe resection and had been seizure-free since then

is estimated at up to 90% in temporal lobe epilepsy and approximately 66% in extratemporal lobe epilepsy [32].

Interictal SPECT assesses the cerebral perfusion in the resting state when the patient is not having seizures. During that time, the focus of seizure is often associated with hypoperfusion at the site of the seizure focus. However, the interictal study should not be used as the sole imaging procedure for the identification of seizure focus unless it is impossible to perform ictal SPECT and if FDG-PET is not available. The sensitivity for the detection of the seizure focus is less than 50% [32]. It is most helpful when done in conjunction with the ictal SPECT. The interictal images can be subtracted digitally from the ictal images using a three-dimension standardized coordinate system of the brain. This technique may improve the accuracy of identifying the focus of seizure.

14.9 Molecular Imaging Beyond rCBF and rCGM

There is growing evidence suggesting that besides FDG-PET and brain perfusion scintigraphy, other RPHs are demonstrating potential value for the investigation of patients with CP. These are mainly RPHs acting on the GABA receptors and those acting in the serotoninergic pathway.

Cerebral gamma-aminobutyric acid (GABA) receptor PET radiopharmaceuticals include ^{11}C (R)-PK11195 and ^{18}F-fluoroflumazenil. These showed that increased GABA(A) receptor binding in the ipsilateral motor cortex and increased binding in the brain stem in CP patients of spastic type may be an important adaptive mechanism after prenatal brain injury and have adverse effect on the development of motor plasticity [35, 36]. Activated microglial cells express peripheral benzodiazepine receptors and may be helpful as a screening biomarker for detecting patients at risk of developing cerebral palsy due to a perinatal insult [37]. Other investigators reported ^{18}F-fluoroflumazenil and GABA expression and binding might be also utilized, along with the patterns of glucose metabolism, for the monitoring of the therapeutic effect of future medications or intervention methods, such as hypothermia and stem cell transplantation. For the evaluation of epilepsy, some neurological centers in Europe have adopted ^{18}F-flumazenil as the tracer of choice for the evaluation of patients with refractory seizures using PET [38]. ^{18}F-flumazenil PET has been shown to delineate the focus of seizure smaller and more accurately than with FDG-PET during the interictal phase [39] (Table 14.1).

Table 14.1 PET and SPECT imaging methods, radiopharmaceuticals, and indications

Agent	Function	Clinical utilization
SPECT (single photon computed tomography)		
(a) HMPAO (Ceretec) (^{99m}Tc-hexamethyl-propylene-amine-oxime)	Regional cerebral blood flow	Ischemia, seizures, maturation, trauma, cerebral palsy, etc.
(b) ECD (Neurolite) (^{99m}Tc-ethyl cysteinate dimer)	Regional cerebral blood flow	Ischemia, seizures, maturation, trauma, cerebral palsy, etc.
(c) Thallium (^{201}Tl)	Tumor imaging	Tumors
(d) ^{123}I-IMP(^{123}I N-isopropyl-p-lodo-amphetamine)	Tumor imaging	Tumors
(e) Receptor-specific studies	Receptor studies	Receptors, ischemia, tumors
PET (positrons emission tomography)		
(a) ^{18}F-FDG (^{18}F-fluoro-deoxy-glucose)	Regional glucose metabolism	Seizures, dementia, stroke, tumors, maturation
(b) ^{11}C (R)-PK11195	Benzodiazepine analog	Asphyxia and cerebral palsy
(c) ^{18}F or ^{11}C-flumazenil	GABA (A) receptor binding	Asphyxia, cerebral palsy, and seizures
(d) ^{11}C-AMT (^{11}C-alpha-methyl-L-tryptophan)	Amino acid analog	Seizures

^{11}C-alpha-methyl-L-tryptophan (^{11}C-AMT)-PET has also been shown to be helpful for the identification of the focus of seizure in children [40]. With this radiotracer, the epileptogenic regions demonstrate increased uptake interictally. Thus ^{11}C-AMT does not require tracer injection during the ictal phase to show increased uptake at the focus of seizure unlike FDG and other radiopharmaceuticals. The increased AMT uptake is more restricted to the site of the focus of seizure than the corresponding hypometabolism demonstrated on FDG-PET. In the brain, ^{11}C-AMT is converted to ^{11}C-alpha-methyl-serotonin, which is not a substrate for the degradation by monoamine oxidase and, as such, accumulates at the serotoninergic terminals.

Conclusion

In conclusion, molecular imaging has demonstrated its value for the evaluation of brain injury in the neonatal period following birth asphyxia and for the evaluation of the seizure focus in patients suffering from epilepsy, which is more prevalent in patients with cerebral palsy as compared to the general population. There are novel tracers that have the potential to become the standard of care for the evaluation of these patients.

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Muscle Biology of Contractures in Children with Cerebral Palsy

15

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Abstract

Muscular contractures are routinely observed in children with cerebral palsy. The natural progression of gait leads to a reduction in passive range of motion. Here we discuss the physiological properties of skeletal muscle tissue and the recent advances in the biological basis of contractures. Skeletal muscles are highly organized structures composed of muscle cells, i.e., myofibers, arranged in parallel and series. Myofibers in turn are made up of the basic contractile proteins, actin, and myosin that form sarcomeres. Sarcomere length and force production are intricately associated such that at very long and short sarcomere lengths, there is a reduction in force-generating capacity. During normal postnatal development, stretch-induced longitudinal skeletal muscle growth by addition of sarcomeres is mediated by bone growth. In children with cerebral palsy, sarcomere lengths are overstretched, and sarcomere number is lower, associated with a limitation in joint range of motion, suggesting reduced ability for muscle growth. Increase in muscle extracellular matrix content and increase in passive mechanical stiffness of fibers and fiber bundles are also observed. Satellite cells are resident stem cells indispensible for postnatal development, repair, and regeneration of skeletal muscles. The satellite cell population is dramatically reduced in contractured muscles. Overall these findings suggest that impaired muscle growth and contractures in children with cerebral palsy are related to a reduced muscle stem cell number.

15.1 Introduction

Cerebral palsy (CP) is the most common developmental movement disorder and affects 2–4 children per 1000 live births [1]. CP is an umbrella diagnostic term, and the functional abilities can be best understood using the Gross Motor Function Classification System (*GMFCS*)

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levels [2], which vary from I to V, with V being those children who are nonambulatory requiring maximal assistance and I being the children who have minimal impairments. Distinctions among GMFCS levels are based primarily on functional impairments, ability to ambulate independently, the use of assistive devices for walking, and the use of wheelchairs for mobility (for more, see Chap. 22). Spasticity is the largest subcategory, and 70–80% children with CP have spasticity either unilaterally or bilaterally [3]. Although the primary neurological injury in these children is nonprogressive, significant secondary impairments develop in the musculoskeletal systems. Specifically, muscle weakness and contracture are seen in the upper and lower extremities that limit the available range of motion at the joints [4]. Common walking patterns in children with spasticity are equinus gait associated with contractures of the plantar flexors that limit ankle dorsiflexion and crouch gait associated with knee flexors and hip flexors contractures that limit knee extension and hip extension [5] (Fig. 15.1).

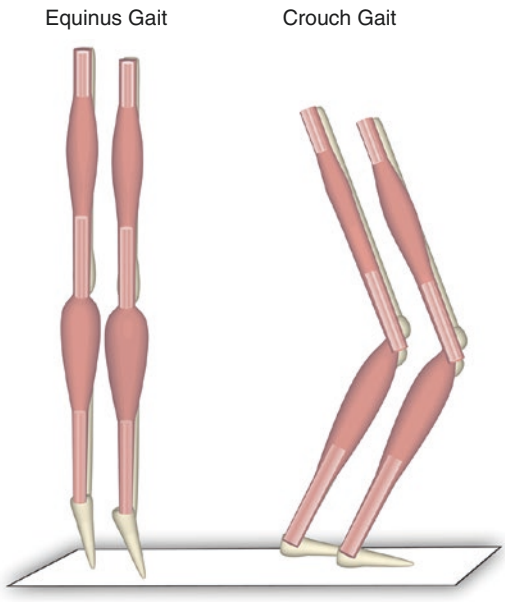

Fig. 15.1 Contractures in gait impairments. Equinus and crouch gait are common gait patterns seen in children with CP, associated with muscular contractures of the plantar flexors, hamstrings, and hip flexors. The contractures limit the available excursion at the hip, knee, and ankle joints

Similarly, elbow flexion and wrist flexion contractures are seen in the upper extremity, associated with limitations in elbow extension and wrist extension [6].

Contractures may be dynamic initially, i.e., accompanied by spasticity, but this changes with age when they become static with limited range of motion permissible at the joints. Broadly speaking, population-based studies have shown that spasticity increases in children with age till the age of four, after which there is a steady decline in muscle tone [7], and older children show limitations in range of motion presumably more associated with change in properties of skeletal muscles [8]. Even in younger children, spasticity does not appear to be the only contributor to contractures, and changes are observed in passive mechanical properties, i.e., passive joint torque [9]. Importantly, while spasticity is a contributing factor, elimination of spasticity by selective surgical dorsal rhizotomy does not in of itself prevent contracture development [10]. In their 10-year follow-up, these investigators observed that surgical dorsal rhizotomies reduced spasticity and improved passive range of motion in the short term but did not prevent development of contractures in the long term (for more, see Chap. 26). Similarly, in children undergoing botulinum toxin injections for local reduction of spasticity, there were short-term gains in range of motion and spasticity reduction, but long-term follow-up 1–3 years later showed a decline in range of motion [11]. These studies suggest that development of contractures is not simply caused by the presence of spasticity.

The natural progression of walking in children with cerebral palsy over a 2–4-year period, without surgical intervention, leads to a gradual reduction in permissible joint excursion and a crouch gait pattern [12, 13]. Correspondingly, lower limb passive range of motion decreases from early childhood to adolescence [8], suggesting an inability to align muscle growth with bone growth (discussed in the section on sarcomere addition below). Muscle growth and volume in children with cerebral palsy are significantly lower than in children with typical development (TD) [14] even in children 15 months of age

[15]. Longitudinal bone growth is also reduced in children with CP [16]. Specifically, tibial length is reduced in ambulatory children with CP compared to children with TD and is lower in children who are more severely affected, i.e., GMFCS level IIIs. In addition, abnormal torsion along the femur and tibia is reported, either due to failure for typical postnatal developmental changes such as in femoral anteversion or is acquired due to muscle force abnormalities [4, 17]. Consequently, most clinical treatments for children with CP are focused toward promoting appropriate muscle and bone growth and preventing muscular contracture [4].

In recent years, progress has been made to understand the biology of muscle contractures from human studies utilizing biopsies from children and animal studies, which we review here.

15.2 Longitudinal Growth and Sarcomere Addition

Skeletal muscles are structurally hierarchically organized tissues composed of bundles of fascicles, which in turn are bundles of muscle cells, i.e., myofibers, which are made up of myofibrils, composed of a collection of sarcomeres [18]. Sarcomeres are the basic functional units of muscles composed of contractile proteins actin and myosin whose interaction via the cross-bridge cycle is responsible for force generation. Sarcomeres are organized in series to provide length and in parallel to provide cross-sectional area to the myofibers. The force-length relationship is an important predictor of active force generation such that increased or decreased sarcomere length relative to optimum lead to reduced force while an optimal sarcomere length, reflecting an maximal overlap between the actin and myosin filaments, produces maximal force [19].

15.2.1 Postnatal Development

Postnatal muscle development is characterized by both longitudinal and cross-sectional myofiber growth [20]. Longitudinal growth increases the range over which a muscle functions, while cross-sectional growth increases muscle contractile force [21]. It is important to note that during postnatal development, in mammalian muscles, the number of myofibers does not increase [22]. In a series of seminal murine studies [23–26], Williams and Goldspink studied the role of sarcomere length and sarcomere number on myofiber longitudinal and cross-sectional development. They reported increased myofiber cross-sectional area by addition of myofibrils [23]. We recently showed [20] that, in mice between postnatal day 1 and day 28, there was an almost twofold increase in myofibrillar packing, a sevenfold increase in myofiber cross-sectional area, and a fourfold increase in muscle mass [20].

Longitudinal myofiber length increases by the addition of sarcomeres in series such that the force-length relationship is maintained (Fig. 15.2). Measurements in mouse muscles have shown that there is a fivefold increase in sarcomere number during the postnatal period [20, 24]. Sarcomere addition is difficult to measure directly in humans, but a clinical case has shown, in a child undergoing distraction osteogenesis, that there was a corresponding sarcomere number increase with bone growth [27]. In this case, with a twofold increase in fiber length, there was a similar increase in sarcomere number showing that the increase in fiber length was not purely just a case of stretching existing fibers and creating fibers with increased sarcomere length (Fig. 15.2).

15.2.2 Sarcomere Adaptation

Serial sarcomere number is a dynamic property even in mature adults. This can be seen by addition and subtraction of sarcomeres in response to maintaining a muscle in a lengthened and shortened position of immobilization, respectively. When a muscle is maintained in a stretched position for 2–4 weeks, it will stretch the myofiber and increase its length. Initially the existing sarcomeres are in a lengthened position but, over the course of several weeks, will add new sarcomeres such that sarcomere lengths return to optimal [26]. *Similarly*, if a muscle is maintained in a

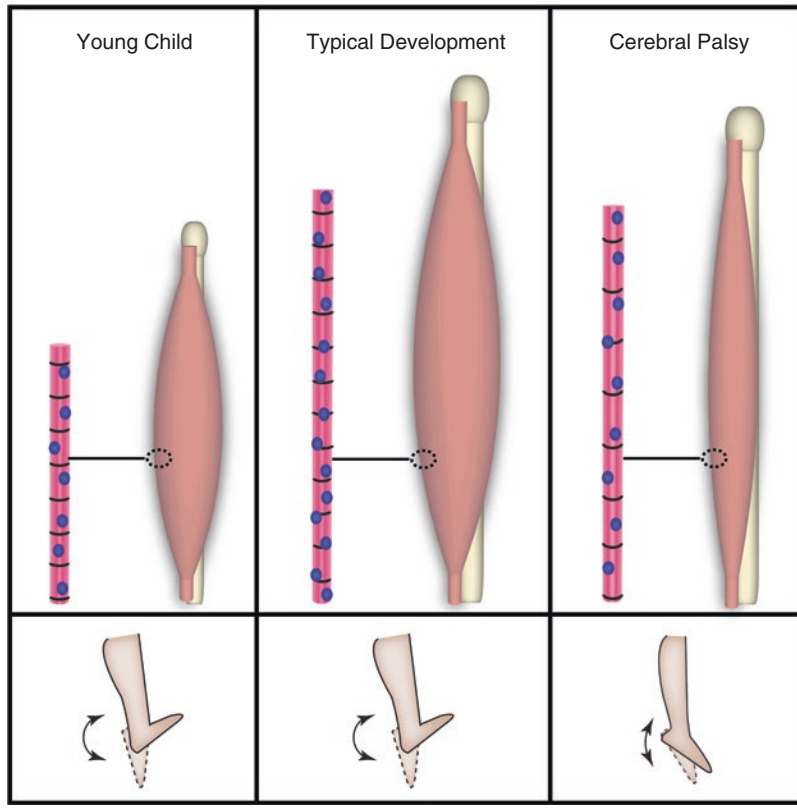

Fig. 15.2 Muscle growth and contractures**.** During postnatal development as a young child's muscle (*left*) grows, in typical development (*middle*) there is an increase in the myofiber length associated with an increase in the serial sarcomere (distance between the black bands) number and myonuclei (*blue*). This allows for maintenance of range of motion (*bottom*). In the case of children with CP, there is an increase in myofiber length with an increase in sarcomere length and decreased sarcomere number (*right*) along with a reduced increase in number of myonuclei. This results in a decreased capacity for muscle excursion leading to reduced range of motion and contractures (*bottom*). The distance between black bands of a myofiber represents a sarcomere, and the serial sarcomere is the number of sarcomeres along the length of the myofiber. Note the differences between the child with TD and CP

shortened position, myofiber length will reduce over several weeks and will lose sarcomeres such that the sarcomeres are no longer in a shortened position [26]. If a growing muscle is prevented from increasing in length by maintaining a shortened position for 3 months from a few days after birth, it does not increase serial sarcomere number. However, if it is then allowed to recover [25, 26] by removing the immobilization, subsequent stretch and growth resulted in rapid serial sarcomere number increase similar to the contralateral side. These experiments demonstrate that the postnatal period is particularly plastic for adaptation and serial sarcomere addition. This finding leads to the idea of using serial casting in children with CP to increase the range of motion and muscle length, presumably by the addition of sarcomeres [28].

15.2.3 Sarcomeres in Children with CP

Sarcomere length measured in vivo during surgical correction of wrist contractures in children with CP revealed an interesting pattern. These muscles showed seemingly contradictory patterns of overlengthened sarcomeres although the joints were in static contractures, i.e., having markedly reduced range of motion at the joint.

The sarcomere length of the flexor carpi ulnaris was ~45% increased compared to non-contractured muscles in control subjects [29]. Intraoperative sarcomere length is highly correlated with the degree of contracture, i.e., maximal permissible passive range of motion such that the children who have the worst contractures also have the longest sarcomere lengths [30]. Sarcomere lengths of the antagonistic extensor carpi radialis brevis are also increased but not correlated with the degree of maximal range of motion, consistent with the idea that the imbalance between the larger flexors and smaller extensors drives the adaptation.

Sarcomere length measured in contractures in lower limb muscles (gracilis, semitendinosus, and soleus) was also increased by 20–50% [31, 32]. The popliteal angle, measuring degree of hamstring contracture, is negatively correlated with sarcomere length. Similar to the finding in wrist flexion contractures, sarcomere lengths were longest in children who had the more severe contractures [32]. This suggests an inability in the ability of the growing contractured muscle to add sarcomeres in series to increase the length of the muscle fiber and an overlengthening of the existing sarcomeres. Consistent with this logic, we see that when serial sarcomere number of contractured muscle is calculated, it is approximately 40% lower compared to typically developing children [31]. In children with TD, the bone grows and stretches myofibers which respond by addition of new sarcomeres to maintain the capacity for excursion of the fiber and consequently range of motion (Fig. 15.2). In contrast, it is our hypothesis that, in the case of children with CP, with muscle stretch, there is an increase in myofiber length without concomitant increase in sarcomere number that is reflected by similar fiber length with overstretched sarcomeres (Fig. 15.2) and development of contracture (Fig. 15.1). Transcriptional studies from both upper and lower limb muscle contractures show a significant upregulation of genes related to embryonic and perinatal myosin heavy chain isoforms [33, 34], routinely not seen during later postnatal development [20]. This implies either a reduction in overall muscle development or impaired muscle regeneration that could be related to contracture development.

15.3 Extracellular Matrix

Extracellular matrix (*ECM*) is the connective tissue that surrounds the muscle fiber, fiber bundles, and whole muscle and connects to the tendon. Traditionally, it is described as having an endomysium (surrounding individual myofibers), perimysium (surrounding fiber bundles), and epimysium (surrounding the whole muscle), which, while convenient, may not be very helpful to understand the true organization and how force interaction and transmission occur from the contractile proteins to the tendon and bone [35]. The microstructure and function of normal ECM is complex, and we only discuss some aspects relevant to what is known in children with CP. Readers seeking more detailed information are referred to reviews [35, 36]. Briefly, collagen is the major protein of the ECM with Types I and III being the major components although other types such as Type IV, glycoproteins, and proteoglycans also play a significant role.

Children with CP have a significant increase in ECM material around myofibers seen by immunohistochemical evaluation of sections of contractured muscles. Labeling for collagen I and laminin (component of the basal lamina) shows a marked qualitative increase compared to muscles from children with TD [32] (Fig. 15.3). Quantitative analyses for collagen using hydroxyproline assays also showed a significant increase in extracellular matrix content in contractured muscles [32]. However, histological evaluation, which might not have the resolution to detect differences, has not shown such changes in intramuscular connective tissue in contractured muscles of the upper extremity [38]. Interestingly, there is some evidence to suggest that children with moderate–severe spasticity have a greater collagen content [39]. At the level of transcription, contractured muscles of both the lower and upper extremities demonstrate an increased gene expression related to the ECM, specifically in collagens and laminin [33, 34]. In

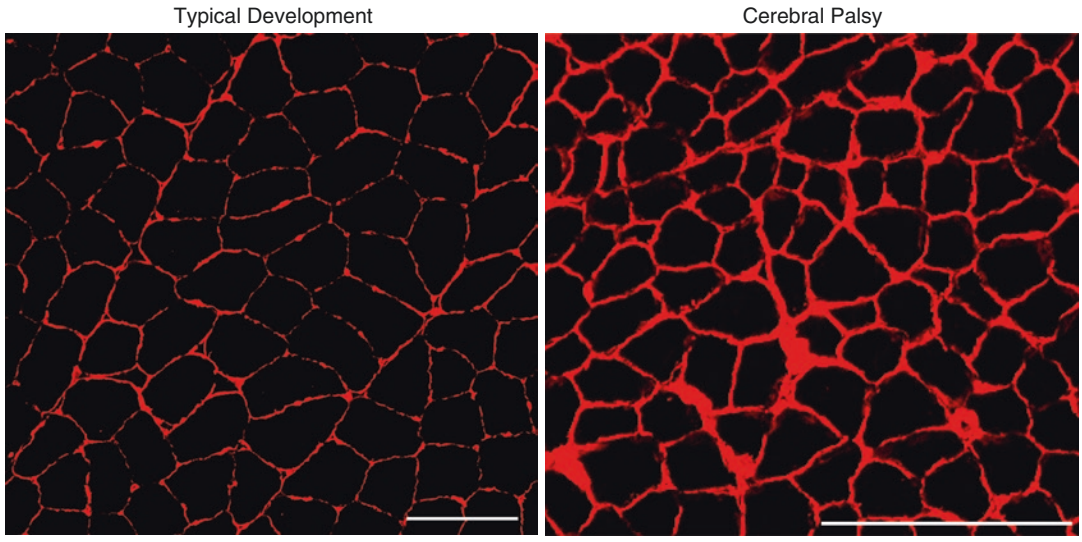

Fig. 15.3 Extracellular matrix is qualitatively increased. Representative images showing Laminin labeling for the basal lamina from semitendinosus muscle section in a child with typical development (*left*) and cerebral palsy (*right*). Note that the scale bars indicate 150 μm in both images showing markedly reduced myofiber areas as well in the child with CP (Data from [37])

addition, there is increased expression of some genes related to the breakdown and maintenance of the ECM, such as metalloproteinases, its inhibitors, and other associated glycoproteins, suggesting dysregulation in the microenvironment of the ECM.

15.4 Passive Mechanical Properties of Muscle Fibers and Bundles

One way to test the stiffness of skeletal muscles is to dissect fiber bundles (~20 fibers) or single fibers from biopsies, secure them with a force transducer on one end and a stable base on the other side, stretch them to various sarcomere lengths, and measure the development of passive stiffness [40]. The use of single fibers and fiber bundles helps observe if any observed differences in stiffness compared to controls are due to a change in the ECM material or due to properties inherent to single fibers (e.g., intracellular large protein titin, which secure the myosin filament to the Z-disc of the sarcomere). Increased passive stiffness could contribute to development of contractures and any increase in stiffness observed during clinical evaluations of passive range of motion such as popliteal angle measurement.

The stiffness of single fibers of various contractured muscles from the upper extremity combined together was slightly higher than control muscles [41]. However the control muscle bundles had dramatically greater stiffness than the bundles from muscle contractures. Importantly, qualitatively the amount of ECM observed was much greater in the bundles compared to controls. This suggested that although the spastic contractured muscles in the upper extremity had greater ECM content, they generated much less stiffness under conditions of stretch, i.e., their material was not organized in the same way as control muscles. Passive stiffness was measured in fibers and bundles from specific medial hamstring muscles rather than combing different types of muscles [32]. This revealed that, in both gracilis and semitendinosus muscles, there was a significant increase in bundle stiffness but not in single fibers compared to controls and no difference seen in mass of the intracellular protein titin. This supports the idea that increased ECM content, mentioned in the previous section, was associated with the increased stiffness of the

bundles rather than any change in intracellular stiffness. Interestingly, gracilis passive stiffness was far greater than of the semitendinosus although they were both different from control muscles, illustrating the idea of variability between different muscles with contractures.

In the case of gastrocnemius and soleus muscles, fiber stiffness was greater than control muscles, but no differences were observed in the fiber bundles. The mass of the titin was greater in children with CP, contradictory to what would be expected with greater stiffness since it would suggest more compliant fibers. Interestingly titin molecular mass was not correlated with the observed fiber stiffness. All of these studies using passive mechanical properties and extracellular matrix measurements show that, while it is clear there are differences in children with CP compared to children with TD, it is not clear how they related to contractures. As mentioned, in the previous section, even in healthy muscles, there is a poor understanding of how all these components create passive force transmission from the muscle to the tendon as well as overall muscle excursion capabilities.

15.5 Muscle Stem Cells, Postnatal Development, and Contractures

Satellite cells are the primary resident muscle stem cells responsible for muscle development, repair, and regeneration throughout the lifespan [42]. Satellite cells were so named, based on their peripheral location in the myofiber, sandwiched between the sarcolemma and basal lamina [43] (Fig. 15.4). In *contrast*, multiple myonuclei of myofibers are present within the sarcolemma. During postnatal development there is an increase in myonuclear number [47]. *However* adult (mature) myonuclei are terminally differentiated, i.e., unable to divide, proliferate, or regenerate. Consequently there must be other myogenic tissue-specific stem cells that can make the skeletal muscle. Indeed, the source for postnatal increase in myonuclei comes from proliferation, differentiation, and fusion of mononucleated satellite cells to existing myofibers [48]. By definition, an adult tissue stem cell has two properties—the ability to differentiate to create new tissue and the ability to self-renew [49].

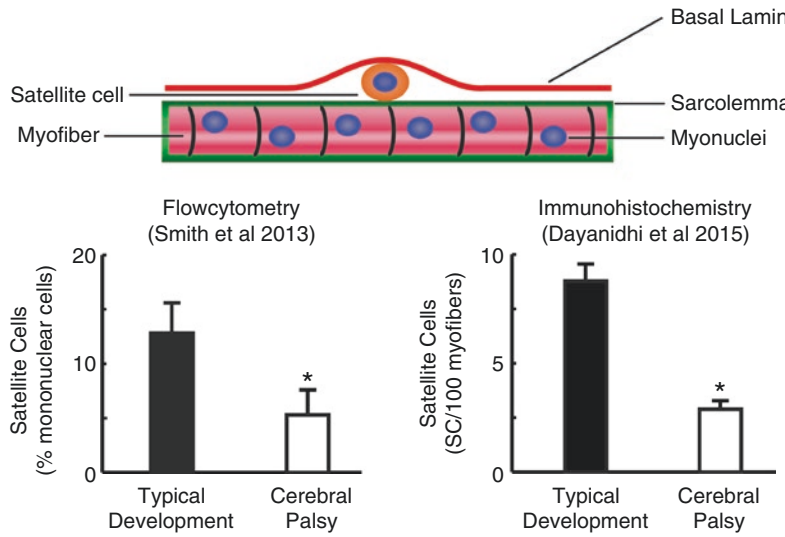

Fig. 15.4 Muscle stem cells and contractures. Satellite cells are muscle stem cells located in their niche between the basal lamina of the extracellular matrix and the sarcolemma of the myofibers. They are the source for myonuclei and are indispensible for growth and regeneration throughout life. In contractured muscles in children with CP, the satellite cell population is lower by 60–70% compared to children with TD demonstrated using two different methods (flow cytometry and immunohistochemistry) in two different cohorts of children (Modified from [44–46])

The ability to self-renewal is a critical feature that allows all stem cells to maintain their presence and functionality throughout life, without which their population would be depleted as they are used over time. Satellite cells were visually identified back in the 1960s, but it was not until the 2000s, after new molecular markers such as the Pax7 transcription factor were identified [50], that it was convincingly shown that the satellite cells are indeed the primary muscle stem cell capable of self-renewal and differentiation [51].

15.5.1 Role of Satellite Cells

Satellite cells are normally quiescent but become activated during growth or, in the case of repair, proceed down the so-called myogenic pathway, i.e., proliferate, differentiate, and create new myoblasts that fuse with the existing myofibers. Satellite cells have a large number of activation factors [52] including mechanical stretch, which are important in the postnatal period during bone-mediated muscle growth. Postnatal muscle development is critically dependent on satellite cells [53, 54]. Pax7 null mice demonstrate a dramatic reduction in both myofiber size and in satellite cell number during the postnatal period. Using a transgenic mouse that conditionally inactivates Pax7, Lepper et al. [53] show that myoblasts from Pax7 lineage fuse into myofibers and are indispensible during the postnatal period. Conditional satellite cell inactivation during the postnatal period results in severely compromised muscle regeneration after injury. A number of studies [55, 56] conclusively show that Pax7-expressing satellite cells are critical for long-term muscle repair capability even in adult muscle. Satellite cells have similarly been shown to contribute to routine maintenance in uninjured fibers during adulthood and aging [57].

15.5.2 Satellite Cells in Children with CP

It is clear that CP muscle has reduced capacity for longitudinal and cross-sectional growth during the postnatal period. In light of the discussion above where we presented evidence that satellite cells play a significant role in muscle growth, we speculate that contracture formation may, in part, be due to satellite cell dysfunction. Using flow cytometry of muscle biopsies from children with CP [46], we showed that, compared to typically developing children, children with CP had a significantly reduced (~60%) satellite cell population (Fig. 15.4). However, as noted, children with CP have extracellular matrix (*ECM*) abnormalities that may systematically bias flow cytometry results in that it may be more difficult to extract satellite cells from the CP muscle. To test this idea, we used the much more labor-intensive in situ immunohistochemistry method to quantify satellite cells [44] using antibodies for satellite cells (anti-Pax7), the basal lamina (anti-Laminin), and a nuclear stain (*DAPI*). By systematically sampling large volumes of tissue, we quantified satellite cell number in situ without significant tissue manipulation. The satellite cell number quantified from these sections, as number per 100 myofibers, similarly showed a 70% decrease compared to age-appropriate controls (Fig. 15.4). These two studies using different methods and different human subjects demonstrate that it is highly likely that there are significant changes in the satellite cell population in children with CP and suggest possible future avenues for therapeutic intervention using regenerative medicine.

Satellite cells are primary muscle stem cells, but they do not act independent of other mononuclear cell types such as fibroblasts, macrophages, etc. [58]. Recent evidence from animal studies suggest that satellite cells negatively regulate the extracellular matrix (*ECM*). Murphy et al. demonstrated that interaction between satellite cells and fibroblasts is important for appropriate muscle regeneration after injury [59]. More recently, Fry et al. [60] showed that activated satellite cells are important regulators of ECM changes in response to muscle overload. Similarly, with age, lack of satellite cells leads to increased ECM content and fibrosis [60]. One proposed mechanism is that satellite cell activation is associated with upregulation of interstitial collagenases, which allow ECM remodeling and satellite cell migration [61].

As previously discussed, compared with children with typical development, muscles of children with cerebral palsy have increased collagen content, increased bundle passive stiffness, and qualitatively increased levels of ECM—consistent with muscle fibrosis [32]. These contractured muscles also have significantly reduced satellite cell number [44, 46], providing support for the idea that increased ECM might be related to decreased satellite cell number. With reduced satellite cell number, it appears as though this process of ECM regulation could fail and result in the development of muscle contractures. Recently, we showed that under conditions of stretch, limited sarcomere addition can occur in satellite cell-specific transgenic mouse models in the presence of a reduced number of satellite cell, but there is also considerable proliferation of the ECM and fibrotic changes [62].

15.6 Summary

Children with CP have poor longitudinal muscle growth and develop contractures. This is associated with increased sarcomere length, decreased serial sarcomere number, and changes in the extracellular matrix. The number of muscle stem cells, responsible for postnatal development, repair, and regeneration, is significantly reduced in contractured muscles. Future avenues will utilize regenerative medicine to provide novel therapeutics for improving the muscle stem cell function to prevent development of contractures.

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16 Physiotherapeutic Interventions: Bobath, Vojta, and Motor Learning Approaches

Dieter Karch and Karl Heinemann

Abstract

This chapter describes different approaches to physiotherapy in children with cerebral palsy (CP) and the principles of learning processes. Bobath and Vojta developed their concepts in the 1960s. These were based on the level of knowledge at that time, regarding normal motor development and its restrictions in cerebral lesions. Their objective was to improve the abnormal neurophysiological function in patients with cerebral movement disorders and to avoid development of such abnormal function by early therapy. Several controlled studies designed to evaluate this therapeutic approach could not prove the special effects of these "process-oriented" therapies, amongst others, due to methodological reasons.

Based on current knowledge, motor learning is considered to be a basic principle of therapeutic interventions intended to improve the patient's ability to accomplish age-appropriate, adequate tasks and self-initiated activities. The learning processes involved depend on the following elements: control of motor function and cognition, storage of learning objectives, and a central reward system to improve motivation, neuroplasticity, and reorganisation. Therefore, Bobath's therapy was modified, and the focus of attention shifted to individual learning objectives, improving the child's autonomy in small steps and supporting social integration. Controlled studies of the effectiveness of these "goal-directed" or "task-oriented" interventions indicate that a specific effect is quite likely, at least for children with mild to moderate CP.

16.1 Introduction

Physiotherapy, like occupational therapy, completes a number of important tasks and specific goals in the treatment of children with CP: promoting sensorimotor development, improvement of abnormal posture and movement control in all

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activities, prevention of deformities, finding the best possible position when standing, sitting and lying (even during sleep), advice in the adaptation of orthotics and assistive technology, and support for the patient and family to cope with the demands of everyday life. There are various therapeutic approaches, which are based on different theoretical principles and use different techniques and methods.

CP is caused through damage to the developing brain, which can occur prenatally, perinatally, or in the first months of life (see also Chap. 6). One main symptom is abnormal muscle tension, which, according to the type of CP, occurs with limited passive range of motion (pROM)—partly depending on the speed of movements—or only with active or intended movements. It also affects posture when moving into a sitting or standing position. The insufficient control and regulation of muscle tension, posture, and movements are also influenced by the emotional state of the child. Disorders of the sensory circuit and sensorimotor and cognitive deficits are found simultaneously.

16.2 Physiotherapy Approaches

- Approaches to modifying the neurophysiological basis
- Approaches based on the principle of motor learning
- Approaches to treat specific symptoms of the disease
- Alternative and complementary approaches

16.3 Approaches to Modifying the Neurophysiological Basis

Therapy approaches which claim to influence or improve the neurophysiological basis of the disease and to prevent the development of abnormal postural and movement patterns or to mitigate their effects are, from today's perspective, no longer appropriate. They have, however, the great advantage that they are plausible and understandable for patients and therapists and that the resultant therapeutic techniques are not complicated and can be easily learned and implemented. Therefore, these techniques are considered to be promising and are, along with the *Vojta* approach (see below), part of so-called alternative therapy approaches. One example is *neurological reorganisation*, which is based on the hypothesis of Fay [1] and Doman et al. [2].

16.4 Vojta Approach

Vojta [3] developed his ideas through the observation of therapeutic intervention for children of average intelligence with CP. Through defined changes of their head position against resistance, it was possible to provoke regular movements of the extremities, and vice versa. Specific changes in posture lead to certain changes of posture and awoke movement pattern. From this he concluded that there had to be a complex reaction pattern affecting the whole body. This *coordination complex* [4] was seen as partially a function of locomotion, in the sense of *Reflexlokomotion* . It is likely that these are innate patterns of movement ("central pattern generator") (www.vojta.com/Reflex Locomotion). This reflex movement is activated through the three basic positions, namely, prone position, supine position, and sidewards. To provoke movements, ten zones described by Vojta, located on trunk and extremities, are used. Of importance is the correct starting position and the angle of the joint to provoke and activate *Reflexkriechen* (reflex creeping) and *Reflexumdrehen* (reflex turning). Furthermore, resistance is important, set by the therapist to limit and reduce active movement and generate isometric muscular activity. Stimulation of each of the ten zones then leads to activation of different muscle patterns of the entire body.

Vojta assumed that in children with CP, a blockade of motor development exists; this is equivalent to the function of a 6-week-old infant. The postural disturbance leads to abnormal regulation of muscle tone, which is expressed mainly in the lack of trunk stabilisation during standing. The regular provocation of coordination

complexes should enhance the development of postural control, the so-called "postural ontogenesis", and help to overcome the blockade. It is assumed that the regulation and control of the coordination complexes on the supraspinal level happens through frequent repetitions and will eventually become permanent. The main goal of therapy is to improve the highly differentiated posture of the spine as a basis for the function of extremities.

Vojta refused to enhance sitting or standing with the child before a sufficient control of posture is achieved, as this would unnecessarily encourage the use of abnormal movement and posture. It is assumed that the CNS is able to take the offered *ideal* movement pattern in the free play situation in a "normal" surrounding and improve the child's motor abilities, and therefore it is expected that treatment according to Vojta's concept stimulates a self-initiated learning process. The Vojta concept of using the complex coordination complex in an isometric manner also facilitates an increase in muscle strength.

The therapy has an impact not only on the musculoskeletal system but also on other areas, such as swallowing, chewing, breathing, and autonomic functions, and indications have been expanded over time. The Vojta concept is now used to treat a range of conditions including neuromuscular disorders, diseases of the peripheral nervous system (e.g., plexusparesis), myelomeningocele, etc.

In *Vojta's* opinion it should be possible, if the treatment starts early, to influence the development of cerebral palsy, even potentially eliminating symptoms. He developed a diagnostic system for the first year of life. Posture control is evaluated in seven defined positions, the so-called *Lagereaktionen*, based on innate motor behaviours (e.g. *Landau* or *Peiper-Isbert* reactions). If there are 6–7 abnormal postural reactions or five abnormal reactions and a hemiparesis, treatment is immediately indicated.

Vojta's ideas of physiotherapeutic treatment on a neurophysiologic basis are in many aspects contrary to *Bobath's* concept, leading to heated discussions amongst physicians, therapists, and parents, especially in Germany. Although the treatment techniques differed significantly, both were originally based on very similar theoretical ideas about motor control and neurological development. Both are based on a hierarchical reflex-oriented model of motor control, as it corresponded to the knowledge of the 1940s and 1950s. In view of the recent knowledge on the importance of motor learning (see below) regarding effectiveness, physiotherapy according to the Vojta concept for CP is only indicated under special conditions, such as significant physical limitations and considerable mental deficits (see Table 16.2).

16.5 Bobath Approach or Neurodevelopmental Therapy (NDT)

When providing treatment to an adult patient with spastic hemiplegia, *Berta Bobath* observed a stereotyped flexion movement pattern, which occurred involuntarily and in response to psychological and physical stress situations. The spastic movement patterns could change with certain *reflex inhibitory* body positions. The therapy was therefore attempted to inhibit the abnormal movement patterns from defined "key points", while more variable movement patterns were facilitated. The stereotyped pattern used by a patient with spastic hemiplegia could be best treated by using the shoulder as a key point.

Reduction of muscle stiffness (spasticity) occurred during one treatment session. The posture of the hand and minimal voluntary movements of the fingers could be observed, and the patient felt improved sensation in his hand.

The patient with cerebral palsy not only shows persisting primitive motor patterns and insufficiently developed postural reflex mechanisms but also an abnormal postural tone. The development of postural reactions, such as head righting, equilibrium reactions, and many other adaptive and protective postural reactions, are impaired [5]. The most important aims of treatment should therefore be:

- To develop normal postural reactions and postural tone against gravity for support and control of movements
- To counteract the development of abnormal postural reactions and abnormal postural tone
- To give the child, by means of handling and play, the functional patterns he/she will use later on for feeding, dressing, washing, etc.
- To prevent the development of contractures and deformities [5]

Berta and Karel Bobath [6] described their therapeutic approach to children's normal sensorimotor development as neurodevelopmental treatment (*NDT*). In general, pediatricians use the terms Bobath Therapy and NDT synonymously. In young children with infantile cerebral palsy, no prior motor experience exists, so matching normal motor development should guide the motor development and treatment goals. The previously expected normalisation of posture and improvement of sensation and movement failed. Adequate transfer of skills achieved in a therapeutic situation into daily use was only possible to some extent. The Bobaths recognised that the child's development represents a learning process that is determined by the experience of dealing with daily demands, which they described as "the child can only use what he knows" [5]. They therefore recommend that therapy should be increasingly dynamic and they treat mainly in everyday life using functionally oriented movement sequences.

If through neurological examination (including neuroimaging techniques; see Chap. 13) and observation of behaviour the diagnosis of CP is confirmed, intensive treatment should start immediately. Upon suspicion that the child is developing CP, the first step should be to guide and advise the parents how to handle the child. According to various research findings [7–9], it is possible to diagnose severe movement disorders already in the first 3 months of life through the assessment of general movements (GM; see Chap. 9).

The therapy according to the *Bobath* concept has spread worldwide. In most countries neurodevelopmental therapy has adapted its methods and techniques to the up-to-date concepts concerning the effectiveness of the therapy. However, treatment techniques vary from country to country, and different schools prefer different approaches [10, 11]. Bobath emphasised the need for repetition to achieve an effective learning process. Therefore, therapists train parents and carers in ways to assist their child to achieve best performance.

In general, advanced motivation and inspiration of the intrinsic activity of the child is the focus of therapy, so that an increased sensorimotor experience and thus functional improvement will be achieved. However, the influence of controlling by the therapist will be reduced so that the patient becomes the active part in the setting (www.ibita.org/Theoretical Assumptions and Clinical Practice). Priority is given to the accomplishment of everyday tasks, largely independent of the quality of the movement sequences. Particularly, with increase of age pathological movements are more accepted. In this respect the Bobath concept is open to conclusions based on actual neurophysiological knowledge and to therapeutic interventions in terms of a learning process. However, only few studies concerning the evaluation of a *NDT* concept, which is based on the concept of motor learning, have been presented up to now.

16.6 Methods to Encourage Motor Learning

16.6.1 Neuropsychological Models of Learning

From the neuropsychological point of view, motor learning is determined by action planning, which depends on top-down programming and on sensory feedback systems. Existing movement patterns are constantly modified and adapted to the actual task and request. A skilful movement should be accurate, goal oriented, smooth, and continuous. The simplest conceptual model considers two feedback systems, one from the periphery of the musculoskeletal system and one as a reference copy of the segmental programme in the spinal cord or on the executive level, which allows the comparison of each movement with the stored pro-

grammes, a process known as closed loop control. Detailed concepts about the learning process and the neurophysiological correlates of information processing and action planning were developed [12, 13]. Schmidt postulates two programmes or patterns concerning motor learning: a generalised motor programme and a motor action pattern. With a generalised programme, he means a spatio-temporal pattern of muscle activation which is retrieved with intended activities since each motion is not controlled by a separate programme.

16.6.2 Method According to the Concept of Motor Learning

Based on current knowledge, motor learning is considered a basic principle of therapeutic interventions, which shall motivate patients to accomplish age-appropriate, adequate tasks and self-initiated activities. The learning processes involved depend on the following elements: control of motor function and cognition, storage of learning objectives, as well as a central reward system to improve motivation, neuroplasticity, and reorganisation. The approaches HABIT and CIMT are also based on motor learning [14, 15].

Prerequisites for the therapeutic work on the basis of the principles of motor learning described above, important prerequisites for practical work can be derived:

- Motivation for independent and reasonable activities
- Illustration of the desired movement or activity also by specific demonstration and motivation for imitation
- Fostering of the body feeling and recognition of own and object-related position in the room
- Choice of adequate and reasonable short-term and long-term objectives in order to increase motivation as well as compliance during therapy and in everyday life
- Positive feedback even for minor achievements to encourage the joy of learning and repetitions and adequate therapy breaks to improve and consolidate the storage of learning contents

16.6.3 Goal-Directed Interventions

Goal-directed or task-oriented interventions (see below) are increasingly used to achieve special purposes in order to improve the child's autonomy in everyday life. Goals are set by the child, the parents, and the therapist working together. This applies to physiotherapy as well as other therapy methods, for example, occupational therapy with or without constraint-induced movement therapy (*CIMT*). Goal Attainment Scales (*GAS*) can be compiled to define the objective and assess the learned effects. For this purpose, items from the International Classification of Functioning, Disability and Health (*ICF*) can also be used, both for children with different *disabilities* [16, 17] and with cerebral palsy [18–21].

16.6.4 Evaluation of Treatment Effects of Physiotherapy

In the 1970s, studies on the effectiveness of neurophysiologically based physiotherapy in children with CP were published; their statistical methodology was, however, not reliable from today's point of view. In a review article on 18 studies, Parette and Hourcade [22] stated that in more recent studies with more stringent methodology no positive effects could be scientifically proven. Turnbull [23], who analysed 14 studies concerning the effectiveness of early intervention, came to the same conclusion. *Also*, Butler and Darrah [24], in a meta-analysis of methodologically correct studies commissioned by the American Academy for Cerebral Palsy and Developmental Medicine (*AACPDM*), found no significant effects of the neurodevelopmental treatment (*NDT*) approach. The studies were classified according to their "levels of evidence". There was no significant difference between therapy and control in studies with a randomised controlled group or in the randomised single-subject comparison (Level I, by [25–28]; see below), but in two studies with nonrandomised control groups (Level II, Table 16.1), a difference was found. A systematic review of different intervention categories confirmed the results [29].

Table 16.1 Features of the effect studies (evidence level according to "The Oxford 2011, Levels of Evidence", http://www.cebm.net/index.aspx?o=5653)

Term	Up-to-date concepts	Methodology	Evidence level	Setting/therapist
Neurodevelopmental therapy (NDT)	The original approach (*Bobath* concept) has shifted to the task-oriented motor learning concept	Different techniques are used depending on the individual goals which should be achieved	2 (downgraded to level 3)	1–2×/week the therapist treats the child, adapts technical aids, and gives advice to integrate the techniques in daily activities or coaches the parents to train at home
Vojta therapy	Using reflex locomotion, motor development is encouraged	Repetitive triggering of reflex creeping and reflex turning	3	1–2×/week by physiotherapist and 2–3×/day reflex locomotion at home

The effects of *Vojta's* therapy were evaluated in two Japanese studies with control groups. A retrospective study carried out by Kanda et al. [30] found that children with spastic diplegia who received treatment before the ninth month could walk earlier and better than children who got treatment later. In a follow-up study of premature infants (birth weight <2000 g), Kanda [31] compared five children who received sufficient physiotherapy with five children who received insufficient physiotherapy. At the time of evaluation (age range from 52 to 62 months), four of the children in the first group could stand still or walk, while none of the children in the second group achieved these skills. Hayashi [32] investigated the effects of Vojta's therapy in 90 children with CP. Of the 27 children who received treatment before 7 months of age, 84.6% could walk. However, only 40% of the 63 children who received treatment after 7 months of age learned to walk. In both studies, control groups were not randomly assigned, in accordance to the criteria of *Sackett*. A specific effect of the Vojta method could not be proven, as all were treated with the same concept. Studies regarding prevention of CP for children at risk by early Vojta therapy had little significance, as the children on therapy and the control children had unequal risks and because there was an inadequate number of children [33, 34]. Wu et al. [35] carried out a combined *Vojta* and *Bobath* therapy of high-risk infants with brain damage. The control group without preventive therapy had a significantly slower motor development, although CP did not occur in either group. On an overall basis, the evidence of these studies complies with level 3 according to *The Oxford 201 Levels of Evidence*.

In 2013, Novak et al. [36] published another systematic literature analysis regarding the effects of very different interventions in the treatment of children with CP. In only 16% of the studies (21 out of 131), effects could be reliably detected for bimanual training, botulinum toxin, casting, constraint-induced movement therapy, context-focused therapy, fitness training, goal-directed training, hip surveillance, home programmes, occupational therapy after botulinum toxin, selective dorsal rhizotomy, pressure care, and pharmacologic treatments, while 58% (76 out of 131) showed possible effects (*yellow light*), e.g. for the Vojta therapy. Seven studies were quoted as a justification. However, only four studies related to the Vojta therapy [31, 33, 35]. Conversely, no effects were substantiated for the neurodevelopmental therapy or the Bobath therapy, so that there was advice not to use them (*red light*). This review was repeatedly criticised, especially as the use of the traffic light symbolism for derived recommendations in favour of or against a therapeutic use was too undifferentiated. Further, other results arise with closer analysis of some of the studies [37, 38]. Regardless, Damiano [39] recalls that there were great individual differences in symptoms, aetiology, and living conditions that became apparent during the group comparisons of the so-called *RCT* studies. She therefore demands studies considering these individual factors and which not only answer the question "what works but also what works best for whom".

Additional studies demonstrating lack of evidence of effects of the NDT or Bobath therapy include two systematic reviews and a meta-analysis [24, 40, 41]; however, according to Ganley [37], "all three stated that there was not enough evidence to determine the efficacy or inefficacy of the treatment approach". Only three of the quoted studies quoted by *Butler* and *Darrah* [24] complied with evidence level I. In two of these NDT studies, the specific effects of the arm and hand motor function were tested with "inhibitive casting to maintain a specific joint in a functional position" [25, 26]. The studies by Palmer et al. [27] compared the effects of NDT (*group A*) with intensive support of the gross and fine motor and cognitive and linguistic development (*group B*). After 6 months, the children of group A with NDT showed a significantly less motor progress than those of group B. However, the NDT followed the former concept of the Bobath therapy (see above). The results are therefore no longer relevant.

Myrhaug et al. [42] published a literature analysis regarding the extent to which intensity and context influence the therapeutic effects. Older studies were aimed at improving gross motor function with the Bobath therapy. Recent studies focused on hand function, usually using constraint-induced movement therapy (*CIMT*). Exercise intensity was higher than in the older studies. A clear answer was not possible as most of the studies were affected by "risk of bias", except in two older studies (again with therapeutic techniques following the earlier Bobath concept) regarding gross motor function [43, 44] and three CIMT studies.

16.6.5 Task-Oriented Interventions

Considering the updated concepts of Bobath therapy, the study by Bar-Haim et al. [45], level 2 evidence according to "The Oxford 2011 Levels of Evidence", is of importance. The NDT effects were compared with those of "motor learning coaching (MLC)". After 3 months of therapy, both concepts resulted in significant improvements. However, the effects on the gross motor function, which corresponds to an increased transfer of mobility performance in outdoor environments, in the MLC group remained unchanged after 6 months, whereas the effect in the NDT group was decreased. This does not automatically lead to the conclusion that NDT is ineffective and not advisable, particularly taking into account that the actual Bobath concept and the therapeutic techniques overlap with those of task-oriented motor learning.

Feasibility studies [46, 47] were published and also several studies—with level 2 evidence according to "The Oxford 2011 Levels of Evidence"—regarding the effects of "task-oriented interventions" with individually planned objectives to improve autonomy and inclusion, partly with instruction and assistance of the parents at home, as, for example, for standing and body balance [48, 49], for posture control while sitting [50], for everyday skills [20, 51], or for psychomotor development [52, 53]. Franki et al. [20] and Brogren et al. [54] realised that despite the positive results, the scientific evidence has to be proven by further RCT studies due to methodical limitations.

Significant results can probably only be achieved with therapies adapted to individually agreed objectives that are relevant for the child [55]. Nevertheless, physiotherapy has been and still is often carried out according to the traditional concepts. The indirect effects of each therapeutic intervention might be responsible for this. Over months and years, therapists, patients, and parents (usually the entire family) develop a personal relationship that is sustained not just by the hope of improvement but also by the need for help and advice in managing everyday life (Activity of Daily Living "*ADL*"), the adjustment or application of appliances, social integration, and participation.

Further, it is difficult to determine in each case whether the progress was achieved spontaneously or as a result of the therapy. Harris [56] and others criticise that evaluation criteria such as eating behaviour—which are important for everyday life as well as for integration and participation—are hardly examined in these studies. Also basic objections are raised against the strict methodological requirements regarding studies

for therapy evaluation and their classification according to "levels of evidence", which [57] stated and assessed in an editorial. *RCT* studies can only determine whether a therapy method in a specifically defined collective can—compared with a control group—significantly improve specific parameters.

Considering the variability of the requirements in the course of development or life, long-term evaluation of intervention would be important.

16.6.6 The Role of the Modern Therapist

He has to be an analyst, catalyst, and family adviser. He should have knowledge about normal and abnormal motor functioning as well as psychological behaviour and the range of compensatory devices. The therapist and the physician work together to achieve the main goal: autonomy depending on the extent of disability. He does not treat CP; he "manages" the functional restrictions, improves skills, and encourages integration in family, school, and work. He follows the guidelines:

- Achieving the most accurate prognosis in all areas
- Indicating the problems which might be eliminated or alleviated
- Assessing the child's daily life situation
- Using this assessment to list the most important aims and how these might be achieved

16.7 Summary

From a huge variety of different methods and approaches, an individual selection is necessary and important. The best method depends on the capabilities of the available therapist. The decision is essentially determined by the following factors: severity and form of CP, cognitive abilities, the intrinsic motivation and readiness for cooperation of the members, and the circumstances of life (Table 16.1).

Neurodevelopmental therapy (*NDT*) or Bobath therapy, based on the concept of motor learning, requires good patient cooperation as well as a good understanding from the integrated relatives (Table 16.2). At most, the NDT concept can be used with patients with all forms of CP with mild and moderate severity. As the Vojta therapy is based on more simple techniques, it could be used in providing treatment for children with severe spastic CP and significant mental retardation. However, the therapy has to be tolerated by the child and the family members who provide the technique. The Vojta therapy is less recommended for choreoathetosis.

Table 16.2 Therapy indication (evidence level 5)

	NDT/motor learning	Vojta therapy
Spasticity distribution		
Diparesis	+	(+)
Tetraparesis	+	+
Hemiparesis	+	(+)
Choreoathetosis	+	(+)
Ataxia	+	(+)
Contractures	(+)	+
Scoliosis	+	+
Mental status		
Normal	+	(+)
Severe abnormal	(+)	+
Motivation		
Normal	+	(+)
Severe abnormal	(+)	+
Psychosocial resources		
Normal	+	(+)
Severe abnormal	(+)	(+)

+ recommended, (+) possible, but not recommended

The evidence of the effectiveness of the therapies was partly documented by randomised controlled trials (*RCT*). However, all such trials suffered from considerable limitations.

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17 An Overview of Evidence-Based Occupational and Physiotherapy for Children with Cerebral Palsy

Christine Imms and Noula Gibson

Abstract

This chapter focuses on school-aged children and adolescents and is presented in two parts. The first part introduces the foundational principles and practices for occupational and physiotherapy for children with cerebral palsy. The second part provides an overview of evidence-based interventions that aim to optimise participation outcomes, reduce activity limitations or minimise body structure or function impairments of children with cerebral palsy.

17.1 Part I: Principles and Practices of Occupational Therapy and Physiotherapy

17.1.1 Introduction

17.1.1.1 Occupational Therapy

Occupational therapy is the art and science of promoting health and well-being through enabling occupation for people who are experiencing problems due to illness, injury or significant disadvantage [1, 2]. Occupations include all the activities that people undertake in their daily lives including those related to recreation, self-care, learning or work. Occupational therapy is an ecologically based, client-centred therapy that considers how to enable clients to undertake all the things that they need to, have to or want to do in their daily lives. Theoretically, occupational therapy practice is informed by ecological models that consider the dynamic interaction between the person,

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the occupation (or *activity*) and the environment in which they are situated [3, 4]. Reasons for difficulty in undertaking or achieving activities that are important in daily life may arise from problems or impairments within the person (physical, emotional, cognitive), aspects of the activity that require adaptation or modification or the presence of environmental constraints. Occupational therapists may apply therapies to support changes at the level of the person, the activity or the environment, but their primary focus is on modifying the occupation or the environment to better support activity engagement [2].

17.1.1.2 Physiotherapy

The World Confederation for Physical Therapy's (*WCPT*) contemporary definition of physiotherapy is (1) services that develop, maintain and restore people's maximum movement and functional ability. They can help people at any stage of life, when movement and function are threatened by ageing, injury, diseases, disorders, conditions or environmental factors. (2) Physiotherapist help people maximise their quality of life, looking at physical, psychological, emotional and social well-being. They work in the health spheres of promotion, prevention, treatment/intervention, habilitation and rehabilitation [5].

The concept of movement has remained a focus of theoretical premises of physiotherapy. Motor control and dynamic system theories further inform the focus on movement in physiotherapy, emphasising the role of the environment or context as well as the individual psychosocial influences on movement acquisition [6]. These theoretical frameworks are well placed to describe the theoretical premise of physiotherapy in CP, whereby active involvement of the child in movement is essential to maximising potential and outcomes [7].

17.1.2 International Classification of Functioning Disability and Health: Children and Youth

The ICF-CY provides both a theoretical framework and a classification system to understand the characteristics of health and functioning [8]. The classification system allows the recording of problems

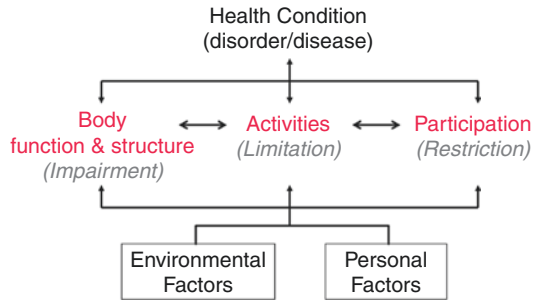

Fig. 17.1 The International Classification of Functioning, Disability and Health [8]. Reprinted with permission from: Towards a Common Language for Functioning, Disability and Health: ICF The International Classification of Functioning, Disability and Health (Geneva: WHO, 2002). WHO/EIP/GPE/CAS/01.3 http://www.who.int/classifications/icf/icfbeginnersguide.pdf?ua=1

involving body structures and functions (called impairments), activity (called limitations) and participation (called restrictions). The framework describes the influence of a health condition and contextual factors (environmental and personal) on functioning in the domains of the body structure and function, activity and participation (see Fig. 17.1). The ICF defines functioning as an *umbrella term* that describes the positive outcome of the dynamic interaction between each element of the model and disability as the negative aspects of this interaction. That is, disability or functioning occur as a consequence of a dynamic interaction between the person with a health conditions' body structure and function, their activity and participation, environmental factors and personal factors. The ICF-CY provides a way of classifying and considering where a person's difficulties may be primarily situated. For example, a person who is blind and who is trying to board a bus may experience most problems due to the features of the environment, or a person with chronic pain may experience most restrictions in participation because of lack of pain management which is a problem in the body.

Although the ICF-CY defines participation as 'involvement in a life situation', and separates the concept from activity in the framework, in the classification system there is no separate system for classifying participation and participation restrictions. This suggests that additional qualifiers are needed in the ICF-CY to further understand how activity limitations differ from participation restrictions. The family of Participation-Related

Constructs (f*PRC*) [9] is proposed as a mechanism for assisting therapists and researchers to articulate both the focus of their interventions (the mechanisms by which interventions are intended to work) and the intended outcomes. In the fPRC, participation is defined as *attending* and *being involved in* life situations and is distinct from activity competence which can be defined in terms of capability, capacity or performance [9].

17.1.3 Evidence-Based Practice

Evidence-based practice is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient (p. 71), [10]. Evidence-based practitioners integrate research evidence with clinical expertise, client values and preferences and service-level resources [11]. To maintain currency of knowledge requires therapists to access and synthesise new research evidence into their practice context. Although it is commonly acknowledged that changing practice in response to new knowledge is challenging [12], it is an imperative for every therapist and service organisation.

Critical new knowledge about the scientific basis underlying therapy for individuals with neurological impairments has increased exponentially in the past decade. Prior to these advances, therapy was dominated by neurodevelopmental techniques that now have evidence they are not effective [13]. It is time to stop providing neurodevelopmental therapy and focus on contemporary evidence-based therapies which are task related and provide structured opportunities for intense practice of desired skills and abilities. Evidence for specific therapeutic interventions is reviewed in *Part* II of this chapter. Assessment of the level of evidence was undertaken following the Oxford Centre for Evidence-Based Medicine Levels of Evidence [14]. The levels of evidence related to intervention effectiveness range from Level 1, systematic review of randomised controlled trials (*RCT*) or n-of-1 trials; Level 2, randomised trial, or observational study with dramatic effect; Level 3, non-randomised controlled cohort/follow-up study; Level 4, case series, case-controlled studies or historical study; to Level 5, mechanism-based reasoning [14].

17.1.4 Family-Centred Care

Family-centred care is best practice in paediatric healthcare and rehabilitation [15, 16] and involves professionals applying caring, respectful attitudes and behaviours that acknowledge and work with the uniqueness of each family. Families and professionals collaborate in making decisions about the child's care in the context of the family as a constant in the child's life. Family-centred care takes a strength-based approach to setting therapy goals that dignifies, values and prioritises the family and child's preferences and choices and works to provide flexible services founded in good quality information sharing [15]. In developing a family-centred partnership for practice, therapists aim to learn about and consider the family's supports and routines, assist them in accessing appropriate resources to achieve their goals and provide interprofessional services in ways that considers the health and well-being of the whole family, in particular the primary caregiver [15, 16].

17.1.5 Developmental Considerations

The importance of taking a lifespan approach to positive child development outcomes with all children and families is emphasised. This means working to address the issues of today, with the knowledge that development is a complex transactional life-long process, influenced by much, much more than any therapy provided. *Recent* models, such as the life-course health development model, put development of 'health' as a critical resource for living and provide a broad framework for intervention planning and goal setting [17]. Table 17.1 provides an overview of how therapy focus might change over time for children with CP.

17.1.6 Complexity of Motor Change in Cerebral Palsy

Cerebral palsy defines the condition as a disorder of movement and posture. At the time of identification of CP, many parents are concerned with their child's potential for motor development,

Table 17.1 Changes in focus of therapy over time

Factor	Early intervention	School age	Young adult
Theoretical underpinnings of approach	Habilitation—harness plasticity, minimise maladaptive plasticity Prevention of secondary impairments Activity and participation	Rehabilitation—focus on activity and participation; focus on establishing life-long habits Monitor muscle length changes and contracture carefully Use of aids and equipment	Rehabilitation—establishment of life habits to prevent effects of inactivity on premature ageing; activity for exercise Use of aids and equipment
Family	Promote attachment Promote family cohesion Parent driven goals, impact of diagnosis on well-being, planning for health of caregivers over the long term	Encourage autonomy Mutual parent/child goals, focus on family lifestyle habits Family and caregiver well-being	Independent of family Individual goal directed
Dose	High intensity, high frequency, identifying and embedding in daily routines	Frequency and intensity limited by other demands of school	Lifestyle approaches—minimum daily requirements—e.g. equivalent of 45 min vigorous physical activity
Individual characteristics	Child parent bonding Temperament, family and child preferences	Gradual disengagement from parents—need to start early Adaptive behaviours	Preferences, strengths, motivation, individual resources and resourcefulness
How delivered	Contextual and functional/participation (goal) driven Activity goals BoNTA	Contextual and functional/participation (goal) driven Activity and lifestyle based BoNTA ↓ Surgery ↑	Contextual and functional/participation (goal) driven BoNTA ↓; surgical ↖↘

often centring on their potential to be able to walk [7, 18]. The development, validation and longitudinal evaluation of the Gross Motor Function Classification System (*GMFCS*) [19] for CP was seminal in assisting families and clinicians to understand the potential prognosis for gross motor abilities (for more see Chap. 22). While the brain lesion associated with CP is non-progressive, failure to reach full motor potential can occur due to several interacting factors associated with the complexity of motor acquisition. When considering the complexity of these factors for influencing motor skill acquisition, it is also important to note that deterioration in motor ability and posture can occur secondary to inactivity and musculoskeletal impairments. For the most part, medical or rehabilitation treatment does not improve the person's motor performance to the extent that they are classified at a milder *GMFCS* level, but intervention can prevent the person from deteriorating and being reclassified at a more severe *GMFCS* level [7, 20, 21].

17.1.7 Embedded Assessment

Embedding assessment into practice aims to ensure that interventions are guided by current need and that they are successful at achieving the goals of the family and child. Assessments are about data gathering. Assessing the level of the family, child and environment (or context) ensures that interventions are goal directed, are individually tailored and address the wide-ranging factors that promote function (Fig. 17.2).

Assessment of the child with CP should be strength-based and focused on identifying the child and family goals for therapy and supporting their achievement. Identification of factors that limit goal attainment, including those related to the environment, context or activity, as well as impairments of body structure or function, is required. Evaluations need to be valid, reliable and meaningful to the child and family. In addition, because assessment drives intervention, evaluation needs to be relevant to the service mandates and funding bodies.

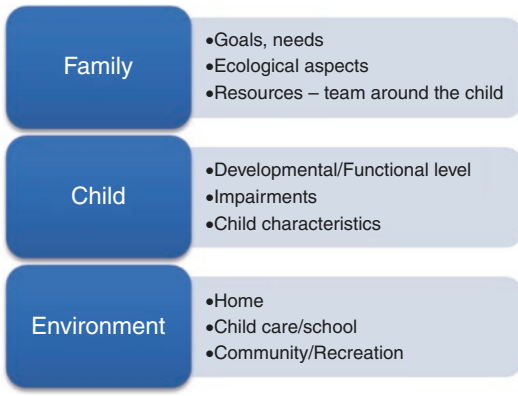

Fig. 17.2 Assessment at all levels of the child's ecosystem is critical

17.1.7.1 The CP Functional Classification Systems

The classification systems that have been developed to reliably and validly describe the functional performance of children and adolescents with CP provide a critical contribution to clinical reasoning. It is an internationally accepted standard that all therapists and other healthcare providers know and use the classification systems. By providing a description of the levels of performance (*functioning*) of individuals, the systems enable clarity of communication with individuals, families and varied service providers, support focused knowledge generation related to future prognosis and enable families and therapists to collaborate on strategic goal setting [22].

Each system has five levels ranging from Level I which describes the highest level of ability in which individuals require little support to achieve daily activities, to Level V which describes individuals who will always require assistance in aspects of daily living. It is important to note that an individual's performances will vary across the systems, that is, a child classified at Level V on the GMFCS, might also be classified at Level II on the MACS, Level III on the CFCS and Level I on the EDACS. Therefore, assumptions should not be made about performance simply on the basis of the GMFCS [23, 24].

Each of the classification systems is designed to be rated by someone familiar with the individual's performances—they are not assessments that require 'test-taking', and the level determined should be that of the usual performance in daily life. Four of the key classifications are briefly described here, although therapists working in the field of CP should be aware that new systems are in development.

17.1.7.2 Gross Motor Function Classification System

The Gross Motor Function Classification System (*GMFCS*) classifies gross motor function with emphasis on a child's self-initiated movement and need for mobility aids [25] (for more see Chap. 22). The GMFCS is applied within four age bands: (1) before the 2nd birthday, (2) between the 2nd and 4th birthday, (3) between the 4th and 6th birthday and (4) between the 6th and 12th birthday. Evidence supports the validity and reliability of the GMFCS [19, 26, 27], its clinical utility [21, 28], its stability over time [27, 29] and its prognostic ability [30]. The updated, extended and revised GMFCS (GMFCS E & R) includes an additional age band of "between the 12th and 18th birthday" [31]. Content validity of the GMFCS E & R has been established, and there is a good agreement between the GMFCS and GMFCS E & R, suggesting that the GMFCS E & R can be compared to the GMFCS level collected prior to the updated release [32]. The five levels of the GMFCS are:

Level I: Walks without limitations
Level II Walks with limitations
Level III: Walks using a hand-held mobility device
Level IV: Self-mobility with limitations. May use powered mobility
Level V: Transported in a manual wheelchair

17.1.7.3 Manual Ability Classification System

The Manual Ability Classification System (MACS) [33] is used to describe an individual's ability to handle objects in daily life. Growing evidence supports the validity, reliability and stability of the MACS [34–37] (see Chap. 22). The five levels are:

Level I: Handles objects easily and successfully
Level II: Handles most objects but with somewhat reduced quality and/or speed of achievement

Level III: Handles objects with difficulty; needs help to prepare and/or modify activities
Level IV: Handles a limited selection of easily managed objects in adapted situations
Level V: Does not handle objects and has severely limited ability to perform even simple actions

17.1.7.4 Eating and Drinking Ability Classification System

The Eating and Drinking Ability Classification System (*EDACS*) [38] is more recently developed and therefore has a smaller body of evidence in its support. The methods used however provide a foundation for ongoing establishment of validity and reliability, and the tool provides an important mechanism for considering this area of performance in children and adolescents. The five levels of the EDACS are:

Level I: Eats and drinks safely and efficiently.
Level II: Eats and drinks safely but with some limitations to efficiency.
Level III: Eats and drinks with some limitations to safety; there may be some limitations to efficiency.
Level IV: Eats and drinks with significant limitations to safety.
Level V: Unable to eat or drink safely—tube feeding may be considered to provide nutrition.

17.1.7.5 Communication Function Classification System

The Communication Function Classification System (*CFCS*) classifies a person's communication capacity within everyday situations with distinction between levels based on the person's ability to send and receive information with familiar or unfamiliar communication partners, time required and effectiveness of communicating the message [39]. The CFCS is also a relatively newer classification system and therefore has a smaller body of evidence of support. It has good inter-rater reliability between professionals [39, 40] but poorer reliability between parent and professional classification with parents tending to classify their children's communication as being more effective than professionals [39].

The five levels of the CFCS are:

Level I: Sends and receives with familiar and unfamiliar partners effectively and efficiently
Level II: Sends and receives with familiar and unfamiliar partners but may need extra time
Level III: Sends and receives with familiar partners effectively, but not with unfamiliar partners
Level IV: Inconsistently sends and/or receives even with familiar partners
Level V: Seldom effectively sends and receives, even with familiar partners

17.1.7.6 Individualised Goal Setting Tools

The importance of goal setting in therapy to motivation and successful therapy outcomes is well established [41]. Setting goals is both part of an effective intervention and an evaluative approach [7, 13, 42]. The critical link between individualised goal setting and motivation and success of therapy is embedded in self-determination theory in which autonomy (ability to choose and make decisions), relatedness (ability to be connected and supported) and competence (experience of mastery) drive motivation and goal-directed behaviour [41]. Individualised goals recognise the priorities of the individual and/or family.

Two widely used goal setting tools are the *Goal Attainment Scale* (*GAS*) [43] and the *Canadian Occupational Performance Measure* (*COPM*) [44]. Both tools have strong evidence; they are valid and reliable for use with children with CP and their families [45]. Because of the importance of client-focused, meaningful goal setting to therapy outcomes, ensuring there is sufficient time to set goals for therapy is important. Tangible, feasible, time-limited goals may be set that address participation restrictions, activity limitations or body function impairments. When establishing goals, care is needed to ensure that goals are worded according to the level of the ICF-CY on which the goal is focused. For example, participation goals need to be about attendance or involvement in activities; activity-level goals can be related to capacity or performance of cognitive, physical or affective skills; and

Table 17.2 Assessments with evidence of validity and reliability for children and/or adolescents with CP

Participation	Activity	Body structures and function
Children's Assessment of Participation and Enjoyment (CAPE) [46]	ABILHAND-Kids [47]	Fitness • Aerobic with Modified Shuttle Test [48] • Anaerobic with Muscle Power Sprint Test [49]
Participation and Environment Measure for Children and Youth (PEM-CY) [50]	Activities Scale for Kids (ASK) [51]	Hip surveillance [126]
	Agility (10 × 5 m sprint test) [49]	HOUSE assessment of thumb deformity [52]
	Ambulatory capacity • Timed Up and Go (TUG) [53] • Functional Mobility Scale (FMS) [54] • 6 min walk test (6MWT) [174] • 10-m fast walk test (10mFWT) [55] • 1 min walk test [56] • Gillette Functional Ambulation Questionnaire (FAQ) [57]	Joint measurement/muscle lengths • Active range of movement (AROM) [58] • Passive range of movement (PROM) [58–60]
	Assisting Hand Assessment (AHA) [61]	Functional Strength Test (30 s sit to stand, 30 s lateral step up, 30 s ½ kneel to stand) [62]
	Caregivers Functional Use Survey (CFUS) [63]	Muscle strength • Grip strength dynamometry [64] • Hand-held dynamometry for lower limb strength [65, 66] • Oxford Scale
	Children's Hand Use Questionnaire (CHEQ) [67]	Spasticity measures • Australian Spasticity Assessment Scale (ASAS) [68]
	Gross Motor Function Measure (GMFM) 88 or 66 [69]	Spinal Alignment and Range of Motion Measure (SAROMM) [70]
	High-Level Mobility Assessment Tool (HiMAT) [71]	
	Melbourne Assessment-2 [72]	
	Paediatric Balance Scale [73]	
	Paediatric Evaluation of Disability Inventory: Computer-Adapted Test (PEDI-CAT) [74–76]	
	Quality of Upper Extremity Skills Test (QUEST) [77]	

body function goals about changes at the level of the body. Both long- and short-term goals need to be considered.

17.1.7.7 Standardised Assessments

Standardised assessments enable therapists to identify targets of intervention, objectively evaluate improvements or deterioration in the child with CP over time, or in response to interventions, and provide objective evaluation to funders on the impact of services. A list of commonly utilised standardised assessments is displayed in Table 17.2. Standardised measures that identify the strengths and needs of children with CP across the domains of the ICF framework are available. Any chosen measure must be valid for the population (*including* the age and type of CP), be reliable and have good clinical utility [78].

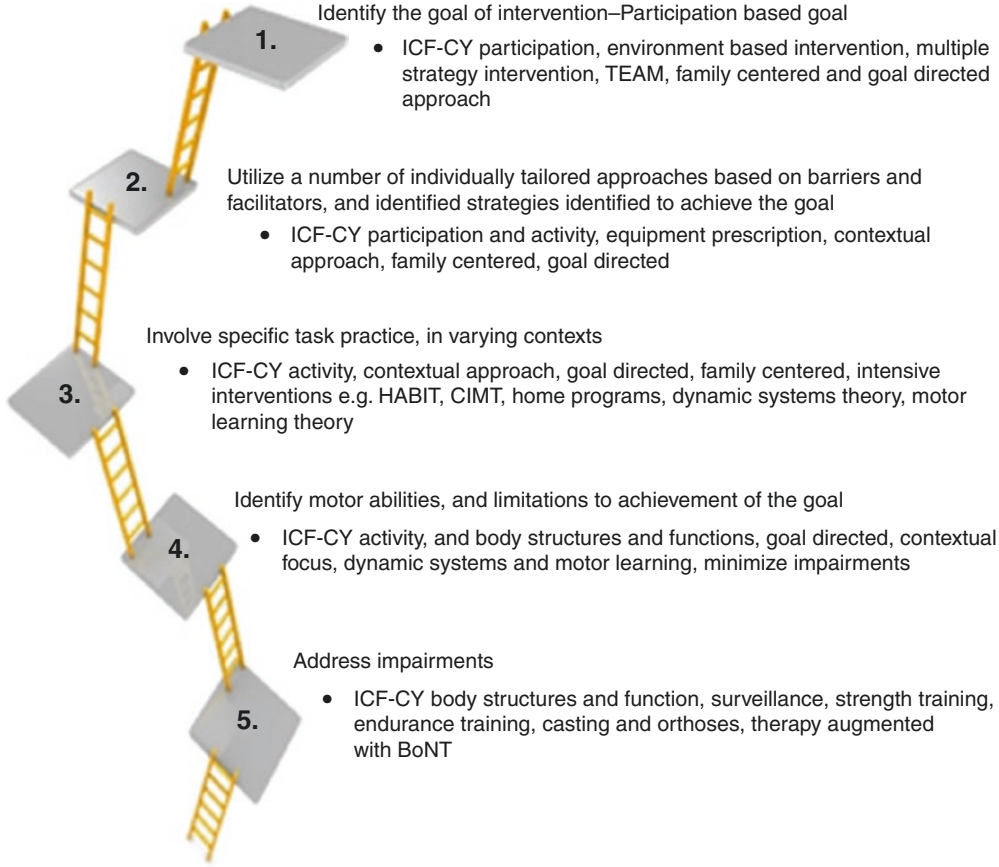

Fig. 17.3 Top-down approach to therapy in cerebral palsy

17.1.8 Theory-Driven Practice: Top-Down Approaches

Figure 17.3 illustrates the top-down approach to interventions. Performance-based or 'top-down' approaches to interventions focus directly on specific task training in activities of interest and are not primarily focused on underlying impairments of body structures or function. Most evidence generated in the last 10 years about effective therapy for CP describe top-down approaches aimed at improving participation, activities and performance and inducing neuroplasticity [13]. These approaches include functional goal-directed training and are underpinned by principles of intense practice, motor-learning and dynamic systems theory. Impairments can worsen with age in children with CP, and therefore assessing and intervening to ensure no loss of function is important. However, evidence to date suggests that effective treatments are those that are directed at the activity level [79].

17.1.8.1 Intensity of Therapy

In activity- and goal-directed interventions, intensity of practice is described by the number of repetitions required to learn functional and meaningful skills with the aim that these skills will be incorporated into daily routines. Ensuring the child spends sufficient time practising an activity in natural environments is important for learning [80].

In Part II the timeframes for delivery of different interventions will be described, but in essence, time for practice of new skills must be found. Children with CP require much more practice to learn some motor skills than their peers with typical development. Situated within a framework of family-centred partnership, therapists can work to support and coach the family to use naturally

occurring learning opportunities to teach specific skills to achieve functional outcomes for the child and the family.

17.2 Part II: Interventions

17.2.1 Optimising Participation

Since the publication of the ICF in 2001, there has been a strong interest in enhancing participation outcomes following health interventions. A recent systematic review of interventions that aimed to increase participation found that interventions that focused directly on changing participation outcomes, rather than aspects of body structure or functions, or activity performance, were more likely to be effective [81]. Effective interventions included group and individualised approaches and often involved coaching.

Three studies that have been published since the review reinforce the importance of working with individuals with impairments to build their capacity to assess their own participation context and choose and apply strategies that will support their own participation. Further research is required in this area, and the pilot work described below provides early (Level 4) evidence of the developments in this area.

17.2.1.1 Environment-Based Interventions

Definition: Anaby et al. [82, 83] describe a *solution-focused* intervention approach in which strategies to overcome environmental barriers or activity limitations are sought in collaboration between the therapist, the adolescent and a parent to enhance leisure participation outcomes. Using a coaching approach, the therapist then continues to work with the youth and family to implement the strategies and achieve the participation goals.

Theoretical rationale: Because environmental factors have been strongly implicated as a barrier to optimal participation, the theory is that directly intervening at the level of the environment, or by adapting the activity (rather than trying to 'fix the impairment'), will enable increased participation of youth with impairments.

Evidence: Pilot studies [82, 83] using interrupted time series designs provide preliminary positive Level 4 evidence of the effect of the intervention. The evidence suggests that individual goals can be achieved (measured using the COPM [44]) and that frequency of participation can be improved (measured using the Participation and Environment Measure-Children and Youth (PEM-CY) [84]). There was little evidence that the intervention effected change in involvement. The authors hypothesised that this was due to the time-limited intervention period and that involvement may take longer to change. Further research is required to substantiate the findings, consider lower age limits to whom it is applicable and extend the follow-up period to determine ongoing effectiveness.

How to, volume of therapy: This intervention was offered over a 12-week period during which three individualised leisure goals were set and addressed in turn (4 weeks per goal). The process involved (1) setting a client-centred leisure goal using the COPM; (2) identifying and evaluating environmental barriers/facilitators of participation; (3) therapist, youth and parent collaboration to explore strategies to modify the environment or activity demands and to implement the strategies; and (4) coaching with parents and adolescents about utilising strategies to seek information and advocate for the adolescent's inclusion (p. 84), [82].

Who the intervention was designed for: The intervention was designed for adolescents of any MACS/GMFCS level and is implemented in the home and community setting most appropriate for the goal. Adolescents with cognitive and communication impairments require greater engagement and support of a parent/carer during implementation [82].

How you know it is working: Outcomes can be measured using participation specific measures, such as the PEM-CY, as well as individualised goal setting tools such as the COPM, provided the goals are articulated as participation-based goals (rather than activity performance or skill based goals).

Therapist training requirements: No formal training to implement the intervention has been identified as necessary.

17.2.1.2 Project TEAM: Teens Making Environment and Activity Modifications

Definition: Project TEAM (Teens Making Environment and Activity Modifications) was designed to teach individuals with intellectual/developmental disabilities to systematically identify environmental barriers and supports, develop strategies to address barriers and request reasonable accommodations (p. 259), [85]. Project TEAM is an intervention that aims to develop self-advocacy skills to enable greater participation.

Theoretical rationale: Developed in collaboration with adolescents with impairments, the intervention is founded on theoretical work that supports the importance of self-awareness, goal setting and self-monitoring on participation outcomes. The programme takes a cognitive skills development approach, teaching adolescents to apply the meta-cognitive strategy of Goal-Plan-Do-Check [86] to setting a participation goal (Goal), developing a plan to identify environmental barriers and strategies for overcoming them (Plan), an implementation strategy (Do) and a review of the effectiveness of the plan to achieve the desired goal (Check). The particular focus of Project TEAM is on teaching adolescents to systematically identify environmental barriers to participation along with the five modification strategies for overcoming the barriers: (a) planning ahead, (b) teaching others about disability, (c) using things differently, (d) doing activities differently and (e) changing spaces (p. 260), [85].

Evidence: Project TEAM is still in development [85, 87]. Pilot evidence using a single-group design suggested that youth enjoyed the program, that knowledge about environments and strategy use could be increased (measured using a knowledge quiz) and that progress towards participation goal achievement (measured using GAS [43]) was made. Formative evaluation of the intervention supports ongoing development and refinement of the intervention package to either reduce the cognitive demands of the learning activities or more carefully select appropriate individuals into the program. In addition, the need for providing further opportunities to practise the strategies was identified.

How to, volume of therapy: Project TEAM involves a 14-week manualised programme: (a) initial assessments and goal setting, (b) 9 weeks to deliver seven modules of training, (c) progress assessment, (d) 4 weeks of coaching and field trips and (e) a final module of training followed by outcome assessment. The intervention is delivered by two individuals, one of whom is an occupational therapist, and utilised student volunteers for additional support for delivery.

Who the intervention was designed for: Adolescents aged 12–17 years with intellectual and developmental disabilities. The adolescents need to be able to attend to tasks for at least 10 min and follow two-step directions. A feasibility study found further development of the materials was needed to support adolescents with less cognitive ability [85].

How you know it is working: The intervention explicitly involves pre- and post-assessment of goal achievement—using Goal Attainment Scaling (*GAS*) [43] and the Child Occupational Self-Assessment (*COSA*) [88].

Therapist training required: As the intervention is still under development, it is not clear what training for interventionists will be required.

17.2.1.3 Multi-strategy Approach to Optimising Leisure Participation

Definition: The optimising leisure participation [89] intervention programme utilises a multi-strategy approach embedded within the ICF framework [90].

Theoretical rationale: Participation occurs as a consequence of a dynamic interaction among (1) an individual's personal factors (preferences, age, gender), (2) environmental factors, (3) activity performance competence of the individual and (4) body structure and function [90]. The focus is on providing family-/youth-centred practice to find the best fit between person factors and participation goals, to apply a solution-focused problem-solving approach to addressing environmental factors, and applying motor and general learning principles to enhancing activity performance skills of the individual. Body structure/function impairments may also require intervention to

support participation outcomes, but this participation intervention is primarily focused on addressing the first three elements [89].

Evidence: Only one small pilot study has been undertaken that provides very preliminary (Level 4) evidence that adolescents with physical impairments are able to achieve some of their leisure goals [89]. Further research is required.

How to, volume of therapy: The programme is a 40-week intervention provided by an occupational therapist. The first 8 weeks are focused on providing weekly individualised support to the youth and a family member or support person. The second 8 weeks comprises a weekly group programme conducted by two occupational therapists. The group focused on the participants' learning how to solve problems in participation and to obtain peer support. Through the remaining 24 weeks, periodic individualised support was provided by the occupational therapist that was tapered off over time.

Who the intervention was designed for: Adolescents with physical impairments who may also have learning difficulties or an intellectual impairment. The pilot included those aged 12–19 years. The tailored individual programme is suitable for individuals of all levels of impairment. The group-based programme is suitable for those with sufficient cognitive ability who are able to communicate with sufficient skill to engage in the group-based learning environment (e.g. Communication Function Classification System Levels I–III [39]).

How you know it is working: Formal goals are set using the COPM [44] or GAS [43] and evaluated at the end of the 8-week individualised programme, the 8-week group-based programme and the end of the 24-week follow-up period.

Therapist training required: The programme is still under development.

17.2.1.4 Equipment, Adaptive Technology and Environmental Modifications

Definition: Equipment adaptive technology and environmental modifications involve prescription or adaptation of equipment, including technology and changes to the environment that are designed to enable an individual's access to the environment.

Theoretical rationale: The theoretical premise is that equipment and/or environmental modifications can be used as a strategy or solution for supporting the individual with movement, body posture or accessibility to enhance participation. Although the usual goal of equipment and environmental modifications are participatory, there may also be goals related to supporting body structures and function, for example, to maintain skeletal alignment or symmetrical posture to prevent, accommodate or correct skeletal deformity, control abnormal movement and/or manage the effect of pressure on skin and soft tissues.

Evidence: Specialised equipment and adaptive technology has received relatively little research attention with many published studies lacking robust methodological quality [91, 92]. There is Level 2 evidence that adaptive seating and adaptive technology can improve activity and participation in the home environment [91, 93] and that devices should be provided as an intervention early in life [93]. Further research to investigate the effectiveness of equipment, adaptive technology and environmental modifications to improve participation, particularly in children and young people with CP, is required. There is also limited evidence about the effectiveness of equipment to improve body structure and function outcomes; again, most studies are of low level, poor methodological quality [94, 95].

How to, volume of therapy: Equipment prescription can include, but is not limited to, specialised seating, standing and tables; equipment for car travel including car seating and/or specialised and/or suitable car, with or without modifications; mobility devices including manual and/or motorised wheelchairs, specialised bikes, modified strollers, ambulatory aids including crutches and walkers; communication devices; technology and electronic software, switches and their mounting devices, splints and orthoses; medical devices, for example, suction machines; equipment to support eating and drinking, toileting, bathing, dressing and

sleeping; home modifications; and specialised toys and recreational device modifications. Frequently prescribed equipment includes mobility devices and positioning equipment [96]. Frequency, duration and equipment use schedules are individually determined based on the goal of the equipment.

Who the intervention was designed for: Equipment prescription is not limited by *GMFCS* or *MACS* level, movement disorder type or age; however, the largest users of equipment and modifications reported in the literature are children in GMFCS Levels III, IV and V [91, 96] and those with dyskinetic movement disorders for computer access modifications [91].

How you know it is working: Equipment and environmental modifications to improve participation outcomes can be assessed using COPM [44] or GAS [43] plus relevant functional or impairment measures if the goal of equipment prescription includes improvement at the body structure or function level.

Therapist training required: There is no formalised training; however, equipment prescription is a specialised area which requires knowledge of local therapeutic goods, governance policies, funding models and resource availability, in addition to an ability to assess the needs of the child. Professional development through workshops is recommended.

17.2.2 Maximising Activity Competence

Activity competence is defined as being able to execute an activity according to an expected standard and involves the use of cognitive, physical and affective skills and abilities [9]. Competence is often considered from the perspectives of capacity, the best ability of the child in an ideal environment; capability, the skills and abilities the child can use in daily environments; and performance, the skills and abilities the child actually uses in daily environments [8, 9, 97]. A recent systematic review found moderate positive evidence (Level 1) that intensive, activity-based, goal-directed interventions are more effective than standard care in improving upper limb and individualised outcomes (p. e175), [98]. Standard care does not appear to provide sufficient intensity of training.

17.2.2.1 Goal-Directed Training

Definition: Goal-directed training is an activity-based approach to therapy whereby child-/family-selected goals are used to drive the movements required to successfully meet the desired outcome of the goal-directed intervention [99].

Theoretical rationale: Goal-directed training is underpinned by dynamic systems theory that acknowledges the interrelationship of motivation of the individual and the role of family in effecting motor change [100]. The involvement of the individual (child) in goal setting means that the motivation of the child to achieve the goal results in the child being an active participant instead of a passive recipient of treatment [101]. Meaningful goals harness the engagement of the family thus increasing opportunities for practice of activities [102].

Evidence: A growing body of evidence shows that goal-focused therapy results in greater intensity of practice that is incorporated into the child's daily routines and results in improved activity performance outcomes [100, 101, 103].

How to, volume of therapy: Goal-directed training includes an initial planning session devoted to determining the goal and identifying factors in the task, environment and/or child that were hindering the child's performance. These constraints are identified collaboratively through an analysis of observed task performance. Treatment is then designed to address the constraints that are most amenable to change. The therapist identifies with the parent, and child where possible, opportunities to practise the tasks in natural environments (e.g. home, school, community). Remediation of the child's impairments may or may not be included. Instruction and training is provided and structured/timed follow-up visits planned.

Who the intervention is designed for: Goal-directed therapy is not restricted to any GMFCS Level, MACS Level or age. The setting is individualised and determined by the goals and the opportunities for practice, which might occur in the home, school or community setting.

How you know it is working: Outcomes can be measured using individualised goal setting tools such as the COPM [44], or GAS [43], provided the goals are stated as activity-based goals. A standardised activity measure related to the outcome and age of the child, for example, the GMFM [69] or PEDI-CAT [74] measures, can also be used. Measurement should occur before and after a specified period that goal attainment is expected to occur.

Therapist training required: No formal training is required, but professional development through workshops or through peer-mentoring in goal setting is recommended. In particular, training that supports learning to administer the goal setting tools as well as to analyse the child's task performance to determine which child/task and/or environmental elements might be improved can assist in developing and implementing goal-directed intervention.

17.2.2.2 Bimanual Training

Definition: Bimanual training aims to assist the child to improve the coordinated use of the two hands together. Therapy is underpinned by establishing child-centred activity—or participation-level goals—and focused on providing sufficient practice of hand skills to elicit changed performance. Hand-arm bimanual intensive training (HABIT) and occupational therapy-based bimanual training are related forms that have some differences in application.

Theoretical rationale: All forms of bimanual training are underpinned by the principles of neuroplasticity and motor learning in which intensive, structured practice is used to ensure the child uses both hands together in bimanual tasks [104]. In addition to specific motor-learning principles, HABIT also involves principles of shaping to guide the development of the most efficient movement to complete the task [63].

Evidence: A strong body of RCT evidence (Level 2) supports the effectiveness of bimanual training both when provided as HABIT and as intensive occupational therapy [63, 105–107].

How to, volume of therapy: In research, bimanual training has been provided in either a block of weekly therapy plus home programme practice or as an intensive day camp model. Therapy blocks are typically provided for between 8 and 12 weeks with studies suggesting 1–3 sessions per week [104, 108]. Day camp models have been conducted for 2- or 3-week periods, in which 6 hours of daily training is provided for 5 days per week [63, 109]. Day camps may be themed (e.g. magic or circus) to provide a motivational environment.

Who the intervention is designed for: Bimanual training is suitable for children with either unilateral or bilateral motor impairments and for those with varying levels of motor impairment. Research has tended to exclude children with complex communication and cognitive impairments. In addition, most research has included children with unilateral impairments (typically *MACS* Levels I–III). Bimanual training is pertinent from approximately 6–8 months of age, throughout life, and can be conducted in all settings including home, school, therapy.

How you know it is working: Goal-focused intervention approaches are supported by measurement tools such as the COPM [44] and/or GAS [43], and for this intervention, improved bimanual performance should also be measured. The Assisting Hand Assessment (AHA) series, including Mini-, Kid's- and Adolescent-AHA [61, 110, 111] are valid, reliable and responsive and are available for children with unilateral impairment from infancy to older adolescents. A version for those with bilateral impairments (Both Hands Assessment; BoHA) is under development. Additional bimanual activity measures, such as ABILHAND-Kids [47], would be pertinent to use.

Therapist training required: These bimanual approaches have not been manualised and situated within a training module—there is no requirement for training. However, professional development through workshops or through peer-mentoring within existing programmes is recommended to assist in implementing the approach.

17.2.2.3 Constraint-Induced Movement Therapy

Definition: Constraint-induced movement therapy (*CIMT*) is designed for those with unilateral upper limb impairment and involves constraining the use of the less-impaired limb while implementing an intensive motor-learning-based training programme to enhance the movement skill development of the more impaired limb [112].

In a recent consensus-based guideline related to CIMT, four forms of CIMT were described: forced use, modified CIMT, signature CIMT and hybrid CIMT [113]. In all forms, the less-impaired limb is constrained from use for some period within the intervention program:

- In forced use, no other targeted therapy is implemented.
- In modified CIMT, intensive practice is offered for less than 3 h per day.
- In signature CIMT, intensive practice is offered for more than 3 h per day for at least two consecutive weeks.
- In hybrid CIMT, a period of constraint-induced movement training is combined with a period of bimanual training of individualised activity goals [113].

Theoretical rationale: Two essential premises underlie these approaches: (1) that the ability of the more impaired upper limb is influenced by learned non-use, sometimes called developmental disregard in children and (2) that intense task-based practice will lead to increased skill associated with use-dependent cortical reorganisation that supports retention and generalisation [108, 113]. In addition, in the hybrid CIMT, there is an assumption that practice of bimanual goals will provide an opportunity for the child to establish the strategies for successful goal achievement once improved unilateral hand use is available [114, 115].

Evidence: Strong Level 1 and 2 evidence (systematic reviews and randomised controlled trials) support the positive effect of modified CIMT, CIMT and Hybrid CIMT to improve skill development [13, 107]. Future research is guided towards understanding the optimal dose and timing of intervention. Eliasson et al. (2014) consensus statement identified no clear benefit of one model over another: benefits were seen in each model, each model has been implemented using varied methods, and no direct comparisons have been undertaken [113].

How to, volume of therapy: In all forms of the constraint approach, the less-impaired limb is constrained by a device that aims to limit the use of the hand while handling objects. Constraint devices vary in the research and have included a mitt or glove that prevents grasp, a sling that prevents both hand and arm use or a full arm cast. As there is no evidence that one form of constraint is more effective than another: safety, comfort, fit and compliance are important considerations when selecting the constraint device [113].

While wearing the constraint, an intensive task-based movement training programme is implemented to engage the child in use of the more impaired upper limb. Training sessions are designed to ensure the selected activities elicit unilateral movements and skills. In some forms, shaping of movement is embedded and carefully guided by the trainer to facilitate learning of efficient movement solutions. In all forms, the activity or task itself is used to stimulate the child's engagement in unilateral play and movement problem solving.

The frequency or 'dose' of therapy has varied in research and can be described as intensive where a therapy is provided with high frequency (*daily*) over a short time period (2–4 weeks) or in a distributed mode where therapy is provided for a longer period (*several weeks*) less frequently (1–2 times per week) [107]. In hybrid CIMT, the period of training using CIMT principles is followed by a period of goal-focused task practice without the constraint. This training period is for bilateral skill development and enhances goal achievement [116].

Who the intervention is designed for: CIMT in its various forms is for those with a unilateral impairment, or, in the presence of bilateral impairment, where one limb is more affected than the other. Typically applied with children who have moderate impairment, it has been trialled across the paediatric age ranges.

How you know it is working: For assessment of change in bimanual performance, the suite of Assisting Hand Assessments are valid, reliable and responsive and are available for children across a wide range of ages [61, 111]. For unimanual performance, outcome measures used in research include the Melbourne Assessment 2 (formerly called the Melbourne Assessment of Unilateral Upper Limb Function) [72], the Box and Blocks [5] and the Jebsen Taylor Test of Hand Function [117].

Therapist training required: The CIMT approaches have not been manualised and situated within a pre-specified training module or certification procedure. However, professional development through workshops, or through peer-mentoring within existing programmes, is recommended to assist in implementing the approach.

17.2.2.4 Home Programmes

Definition: Home programmes are prescribed home-based intervention programmes where the therapist serves as a coach to the child and parents, who in turn implement the actual treatment/intervention at a prescribed frequency in the home environment. Implicit within the definition of a home programme is an embedded goal of achieving a desired outcome.

Theoretical rationale: Home programmes are utilised to compliment direct intervention and to assist in achieving the necessary intensity of practice to effect the desired outcome of the intervention [98, 118]. Dose of therapy, which includes the intensity and duration of therapy [119], is closely related to clinical outcomes [107], with evidence suggesting that the dose of therapy may be just as important as the type and context of therapy [120]. In children with CP, home exercise programmes can account for 50–80% of the total therapy received [107]. As well as increased intensity of practice, other benefits of home programmes include increased involvement of parents in goal setting and training and improved general education about the health condition [118, 121].

Evidence: In a randomised controlled trial of home programmes in CP, positive effects of home programmes were found compared with no home programme [118]. A systematic review [120] demonstrated that interventions that included home programmes to increase intensity of practice were more likely to result in significant improvements in therapy outcomes. A more recent RCT comparing equal doses of hybrid CIMT with traditional occupational therapy plus a home programme found no difference in outcomes between the groups [116].

How to, volume of therapy: To be effective home programmes must involve parent education and active involvement in training [118, 120, 121]. Parents are more likely to engage with home programmes when it is clear that the activities improve outcomes are enjoyable without adverse effects (pain, discomfort), not too complex, minimise disruption of the affective or recreational family relationship, and the programme addresses the real needs of family [121].

At the initial session, the family and therapist identify goals, determine therapeutic activities and prepare a home programme document with accompanying explanations and illustrations. Frequency of practice, strategies to embed practice and a follow-up schedule form part of the home programme [121]. The frequency of the therapist's follow-up will vary depending on the type of goals identified, the ability or confidence of the parent as coach to grade activities and stimulate progress and the expected progression of goal attainment.

Who the intervention is designed for: Home programmes are suitable for all children at all MACS and GMFCS Levels and all ages. While parent and family involvement in establishment of home programmes is relevant for all children, in younger children or those with limited cognitive ability, goals and adherence to the home programme are more reliant on parent and family involvement. Although home programmes suggest that the intervention occurs in the context of the 'home', the environmental context can be broadened to include other settings such as school and community using the same principles.

How you know it is working: Outcomes are measured using individualised goal setting measures such as the COPM [44] or GAS [43], plus a specified targeted measure based on the type and goal of the intervention embedded in the home programme (e.g. aerobic fitness measure or upper limb function measure). In addition, engagement can be recorded using a programme diary or logbook.

Therapist training required: There is no requirement for training. However, professional development through workshops or through peer-mentoring with goal setting and measurement of goals can assist in developing and implementing home programmes.

17.2.2.5 Context-Focused Therapy

Definition: Context therapy involves identifying client-centred goals and then providing interventions that are focused on only changing the task or the environment [122]. This is a family-centred approach in which a primary therapist is identified to work with the child and family to set goals, typically using the COPM [44]. Following this, the therapist, family and child work together to identify strategies to adapt the task the child is trying to achieve or modify the environment so that the child's success at the task is enhanced. There is no provision of therapy aimed at remediating impairments of the child [122].

Theoretical rationale: This therapy is supported by theoretical premises of dynamic systems theory that describes a person's success at functional tasks as arising from a dynamic interaction between the person, the task and the environment. In addition, family-centred care principles underpin the process of therapy [122].

Evidence: One high-quality randomised controlled trial provides evidence (Level 2) that context therapy is as effective as child-focused therapy in achieving increased scores in functional outcomes related to mobility, self-care and participation [123].

How to, volume of therapy: Context therapy involves three phases: goal setting, assessment of the task performance and implementation of the intervention strategies. An episodic intervention approach is taken, that is, short bursts of intense therapy (perhaps over a few days) followed by periodic follow-up from the therapist [122]. In the RCT, a 6-month period of intervention was offered, in which 18–24 sessions were held [123].

Who the intervention was designed for: The RCT [123] included young children (aged 12 months to 5 years) who were classified at all levels of the GMFCS [25] thus suggesting that this intervention is appropriate for a wide range of children. However, children with complex impairments, including those with cognitive impairments, have been identified as more challenging to engage in context therapy.

How you know it is working: Outcomes should be measured using individualised goal setting measures such as the Canadian Occupational Performance measure [44], as well as activity-level measures such as the GMFM [69], or PEDI-CAT [74].

Therapist training required: The developers of this intervention suggest that therapists find it difficult to stop providing interventions that aim to remediate impairments of the child and require training to ensure they focus on only changing the task or the environment. *Training* in administration of the goal setting tool—Canadian Occupational Performance Measure—as well as in analysing the child's task performance to determine which task and/or environmental elements might be changed was provided to the therapists in the study [123].

17.2.3 Minimising Body Structure and Function Impairments

One role of therapy for children with CP is to minimise musculoskeletal impairments and maximise function. Although children are not born with musculoskeletal impairments, loss of range of movement can be evident from before age 3 years and progresses throughout childhood [124, 125]. Therefore, surveillance to detect progressive musculoskeletal impairment is a critical role of therapists to ensure interventions occur early [126, 127]. Secondary impairments include contracture and pain which impact 80% of children with CP. Those at greatest risk are children with spasticity [92, 128].

Surveillance should occur from the time that CP is identified. In the early years, botulinum neurotoxin (BoNT) to decrease the influence of spasticity may play a role in minimising progression of contracture in gastrocnemius and hamstring and delay or minimise the need complex lower limb surgical intervention in the school age years [129]. However, it is important to note that there is no good evidence showing that there is a long-term benefit of using BoNT to prevent contractures in CP [130] (for more see Chap. 22).

17.2.3.1 Surveillance

Definition: Surveillance is the process of monitoring and identifying the critical early indicators of secondary and tertiary impairments that can occur in CP. Hip surveillance involves monitoring

and identifying indicators for progressive hip displacement [126].

Theoretical rationale: Children with CP often present with decreased mobility and with movement occurring in shortened ranges. This paucity of movement may be crucial to the development of secondary musculoskeletal impairments, with the inactivity of the limb having a greater impact on the secondary impairments than the initial brain lesion.

Therapists play a key role in monitoring because of the progressive nature of musculoskeletal impairments with growth in CP. Monitoring includes routine measurement of ROM and muscle lengths; ongoing hip surveillance until skeletal maturity, routine measurement of strength and endurance; annual video recording of gait and/or function; and monitoring deterioration or change in ambulatory or functional status.

Deterioration of locomotion skills is a pronounced problem in adolescents and adults with CP and requires surveillance (see Sect. 17.2.6). Self-reported causes of deterioration are pain, fatigue and lack of adapted physical activity, while strong predictors are severe neurological involvement [128, 131]. Pain and fatigue levels are higher in people with CP compared with their typically developing peers [132, 133]. Nearly 70% of adolescents with CP self-report some pain over a typical week [128]. A key barrier to engaging in physical activity in children with CP is presence of pain during exercise [128]. Children with CP, including those who are independently ambulant, are more likely to have decreased physical activity levels and less aerobic capacity when compared to their typically developing peers [134]. Increasing physical activity levels in children with CP has been found to be effective at improving pain and fatigue levels [132].

Children with CP are at risk of hip displacement [135]. Hip dysplasia is silent and therefore requires monitoring of critical indicators that include GMFCS Level, age, gait classification (WGH IV) and migration percentage measured by X-ray [127]. Hip dislocation can lead to pain, difficulty with positioning and seating, loss of function and decreased quality of life [127].

The incidence of scoliosis in CP has been reported as 15–65% in school age children with CP [136] (see Chap. 20). Age is the most important factor in predicting progression, and in most children, scoliosis was diagnosed after 8 years of age with progression most prevalent after 12 years of age [137]. Risk of scoliosis is also associated with GMFCS level: the risk of developing scoliosis increases with GMFCS level and age [137, 138]. Children in GMFCS Level IV or V had a 50% risk of having moderate or severe scoliosis by 18 years of age, whereas children in GMFCS Level I or II had almost no risk [138].

The prevalence of respiratory co-morbidities in people with CP has only become known since the introduction of CP registries. Respiratory disease is the leading cause of hospital admissions and deaths in children with CP [139, 140]. Despite improvements in medical care and technology over the past 40 years, survival of children with CP is much the same as it was in the 1970s [139, 140]. The onset of serious respiratory disease is often gradual and insidious, and children may not be identified as being at risk until it is too late. Therefore, although the concept of surveillance of respiratory impairments is relatively new, it is an important role of the physiotherapy (for more see Chap. 29).

Evidence: Since the introduction of surveillance programmes, there has been a reduction in the need for complex surgery and a reduction in repeated and salvage surgery [141]. There is population-based evidence to show that hip surveillance can prevent progression to hip dislocation by identifying timely intervention [141], and multilevel surgery for muscle contracture can be prevented by identifying timely intervention [129].

How to and frequency: Routine surveillance includes clinical examination and documentation of joint range of movement, muscle strength and muscle lengths. Standardised assessment should be used [48, 58, 62, 142, 143]. Routine hip surveillance that includes clinical examination with an X-ray is the only way that hip displacement can be identified. The Australian Guidelines for hip surveillance in CP provide detailed information on how to conduct hip surveillance [127]. Every child with CP must have an initial hip X-ray between 12 and 24 months as hip subluxation can occur by age 2 years, and subsequent surveillance regimes depend on GMFCS level and age [127, 135, 141].

There are no evidence-based guidelines for timing and frequency of surveillance to detect changes in ROM, muscle strength, endurance and monitor pain levels; however, it is suggested that this should occur at a minimum twice yearly for children under 6 years of age and then continue annually after 6 years of age [129, 144].

Guidelines for scoliosis and spinal surveillance are yet to be determined, but as with hips, follow-up programmes for early detection of scoliosis should be based on the child's GMFCS level and age. Any complaint of lumbar pain in children with CP, particularly if dyskinesia is present, should be investigated with an X-ray as stress-related spinal musculoskeletal disorders such as spondylolysis, and vertebral endplate lesions are commonly found in the lumbar spine of patients with dyskinetic CP [145].

Guidelines for respiratory surveillance in CP are being developed [146]. A checklist for the early identification of severe respiratory disease in children and young people with CP has been developed and is currently being validated [146]. Until evidence-based guidelines are available, it is recommend that the therapists monitor respiratory symptoms and refer for early medical attention when negative signs are evident.

Who surveillance is for: Musculoskeletal surveillance, including hip, spine and affected limbs, should be routine for every child with CP. Annual recording of motor ability and screening for pain and fatigue levels should be incorporated into surveillance. Frequency of follow-up is dependent on the motor type and GMFCS Level.

How you know it is working: The goal of surveillance is to minimise impairments and to identify secondary impairments early to intervene early. With respect to the hip, the goal of surveillance is to identify progressive displacement early. Therefore, identification of progressive hip displacement, where all options for management remain possible, is one indication that hip surveillance is working.

Therapist training required: There are no specific training requirements; however, it is recommended that clinicians regularly benchmark ROM, muscle length and muscle strength assessments against colleagues to determine and maintain inter-rater reliability. The integrity of determining change in hip X-ray measures is dependent on inter-rater reliability, and therefore assessors of hip X-ray migration percentage need adequate exposure to hip surveillance to maintain their measurement skills [147, 148].

17.2.3.2 Strength Training

Definition: Strength training should be more correctly termed resistance training, and it refers to the use of progressively more challenging resistance to muscular contraction to build muscle strength and anaerobic endurance.

Theoretical rationale: The rationale for resistance training is that muscle weakness in CP is a contributor to decreased function and that by addressing muscle weakness in children with CP there will be an associated improvement in function [79].

There are several possible pathophysiological changes to the muscle as a result of CP including abnormal changes to muscle structure, mechanical properties and morphological structures of muscle [149, 150] (for more see Chap. 15).

Evidence: Current evidence suggests that lower limb resistance training programmes are effective at modifying strength in ambulatory children and adolescents with CP, as this is the group that has been studied [151].

There is emerging evidence that there is a relationship between upper limb function and strength [152, 153]. Level 2 evidence shows that resistance training improves strength (with variable effect sizes), and a smaller body of evidence shows improved outcomes in the activity domain [154]. Despite limited evidence, there is positive opinion that resistance training of the lower limb and upper limb has the potential to improve strength and activity in children with CP, and the lack of efficacy is due to study resistance training paradigms not meeting the US National Strength and Conditioning Association (NSCA) [155] training guidelines for training, type, intensity and time for inducing strength changes in children [151, 154].

How to, volume of therapy: Resistance training can be completed via home programmes or in community gym settings. The programme needs to be individualised based on starting strength for the muscle group being trained. Training intensity

and duration will depend on the desired type of strength related change, e.g. improved force or improved endurance. Based on the US NCSA for children, the following guidelines should be followed to induce strength related gains. Strength training must:

1. Be individualised so that each muscle group being exercised has baseline 1 repetition max determined.
2. Involve progressive resistance exercise, that is, progressive increase in intensity, thereby stimulating strength gains that are greater than those associated with normal growth and development.
3. Include 8–15 repetition maximum, which is the number of repetitions that can be completed before fatigue.
4. Incorporate an increase in amount of resistance as strength increases.
5. Be performed 2–3 times per week for a minimum of 12 weeks [155].

Who the intervention was designed for: The majority of evidence for positive strength gains in CP is for ambulatory children with spasticity (GMFCS Level I, II and II) [151]. There is limited evidence for upper limb training [154]. Resistance training requires cognitive capacity for learning and some selective muscle control to perform the exercises effectively. The US NSGS recommend children be at least 7 years of age [155].

How you know it is working: Change in strength are measured by dynamometry or by the maximum weight moved with one repetition. To determine if change in strength is associated with functional change, an appropriate functional measure should also be used pre- and post-training [62].

Therapist training required: Therapists who use resistance training with children with CP should know the US NCSA for children [155] and incorporate these recommendations with those provided by Verschuren et al. (2011) for resistance training in CP [151].

17.2.3.3 Management of Gait Deterioration

Definition: Gait deterioration is a change in gait impairments in children with CP that results in either a decrease in functional capacity for walking or higher energy cost of walking.

Theoretical rationale: Walking capacity has been found to be related to muscle strength, optimal muscle lengths and gross motor capacity [156]. In order to improve or prevent further deterioration in gait caused by spasticity and/or muscle contracture, and/or weakness, treatment should focus on restoring these impairments. This requires a comprehensive treatment approach including a gait rehabilitation program, orthoses and serial casting, augmented with botulinum toxin A if indicated. See also Sects. 17.2.7 and 17.2.5 and Chap. 22.

Deterioration of gait has been identified around the age of 12 years [157] and can progress to be pronounced problem in adolescents and adults with CP [131, 158]. The most common gait deviations are in-toeing, excessive knee flexion, stiff knee, hip flexion, internal rotation, adduction and equinus [159]. Strong predictors of deterioration are age at commencement of walking [131, 157] and increasing gait disability, with those GMFCS Level IV and V showing greater deterioration [131, 159]. Maintaining gait ability in children at GMFCS Levels III and IV can make a significant difference to independence or assisted transfers and ease of care. Other predictors of gait deterioration are pain, fatigue and general physical capacity [158]; therefore, interventions that are known to decrease pain and improve fatigue levels, physical activity and general aerobic capacity may minimise gait deterioration. When the gait does not respond sufficiently to rehabilitation, then surgical intervention to address muscle contractures and lever arm dysfunction to prevent further gait deterioration and drop in GMFCS level may be effective [20, 160].

Evidence: There is Level 1 evidence that endurance training is effective short term in improving aerobic capacity, anaerobic capacity, muscle strength, agility and oxygen uptake, but with limited information on effectiveness on activity and participation [161–163]. There are no long-term studies to show that improving gross motor capacity and fitness prevents deterioration in gait. Despite significant strength gains

with strength training, many studies fail to show a significant improvement in walking capacity [151, 164]. Reasons for poor translation of strength improvements to walking capacity may be due to strengthening exercises being prioritised for the knee extensors and flexors, despite their relatively minor role in human walking [165]. Further consideration of the specificity of strength training may provide greater translation of strength gains to improved walking outcomes.

The recently developed Hand Arm Bimanual Intensive Therapy Including Lower Extremities (HABIT-ILE) [166] is an intensive task-specific training of upper and the lower limbs that involves structured activities of increasing motor difficulty, involving bimanual tasks that also engage the trunk and lower limbs. This approach may offer an opportunity to improve gait and is currently being studied in an RCT.

For task-specific training of the lower extremity, locomotor training paradigms have been utilised with many studies incorporating partial body weight support systems in addition to motorised treadmills. Systematic reviews evaluating the effectiveness of treadmill training in CP found insufficient evidence for their effect [167]. Over-ground walking may be a better option than treadmill training as it is task specific and more easily applied [168].

Rehabilitation robotics and computer-assisted systems are being trialled to complement physiotherapy in CP. Well-designed randomised controlled studies in children are lacking. The theoretical rationale is based on repetitive practice, intensity and maintaining motivation [169]. Apart from intensity of practice, robotic-assisted therapy does not provide the other key factors involved in motor skill learning and that the task should be frequently challenged in contextually relevant environments.

Electrical stimulation is gaining popularity and acceptance, particularly as the devices become smaller and less costly. Functional electrical stimulation (FES) is defined as surface electrical stimulation to muscles and/or nerves that have impaired motor control for the purpose of overcoming an inability to contract and execute functionally useful movements. The evidence for effectiveness of FES in improving gait is difficult to interpret because different types of electrical stimulation have been studied (i.e. functional, neuromuscular and therapeutic) in varying CP populations, to address varied goals related to gait [170]. A recent RCT has shown that using FES can improve gait kinematics while the FES device is in use; however, the effects are not maintained once the device is off and long-term outcomes are unknown [171].

How to, volume of therapy: Rehabilitation strategies based on participation or activity-based models are likely to have a positive effect on locomotor ability (see Sect. 17.2.1). Rehabilitation paradigms to prevent gait deterioration should focus on participation and goal-directed interventions augmented where appropriate with impairment-based approaches of strength training, increasing physical capacity by improving fitness, plus management or prevention of lower limb contractures, particularly the plantar flexors.

Williams et al. (2014) suggests that if strength training is provided to improve walking capacity, then task specificity needs to be considered [165]. Task specificity relates to how well the exercises target the primary muscle groups responsible for propulsive strength during walking. These are the three important power events in the gait cycle that are responsible for forward propulsion during walking:

1. Ankle plantar flexor power generation at push off
2. Hip extensor power generation in early stance phase
3. Hip flexor power generation in terminal stance and early swing phase

As well as targeting these muscles, specificity of strength training considers the actions of the muscle groups being trained and the speed and range in which they act [172]. The muscle activity related to these power events occurs briefly at a specific phase of the gait cycle and in a defined range; therefore it is important that the timing and velocity of the trained contractions of the muscle are specific for walking. For intensity and duration of strength training, refer to the NCSA guidelines.

For training endurance the individual must have sufficient motor ability to undertake aerobic training. Motor skills training may be used before undertaking this approach, as has been conducted successfully in adults with acquired brain injury

[173]. Orthoses may also have a role to play in minimising gait deterioration. See Sect. 17.2.7.

Who the intervention is designed for: GMFCS Levels I, II, and particularly III and IV who are at greatest risk of deterioration of gait.

How do you know it is working: Assessments of any of the gait-related parameters pre- and post-intervention can include the 6 min Walk test [174], Timed Up and Go [53] and High-level Mobility Assessment Tool [71].

Therapist training required: No formal training is required, but knowledge and use of the NSCA guidelines [155] is recommended. For guidance in training endurance in CP, we recommend the protocol described by Verschuren et al. [162] and specificity of training published by Williams et al. [165].

17.2.3.4 Casting and Orthoses

Definition: Orthoses (or splints) are removable external devices designed to support a weak or ineffective joint or muscle [175]. Orthosis descriptions relate to its purpose: to mobilise, immobilise or restrict movement at the joint(s) it acts on. Mobilising orthoses are commonly used in the treatment of children with CP and are typically rigid, serially adjusted for fit or change in soft-tissue length, and are designed to improve muscle length and joint ROM. Dynamic orthoses improve outcomes in the activity and participation domain of the ICF-CY [176]. Rigid orthoses are therefore worn during rest, whereas dynamic orthoses are worn during activity to optimise performance (see also Chap. 22). Casting aims to mobilise soft tissues through the application of a rigid serially adjustable cast. Plaster or fibre-glass casts are applied to a limb to stretch soft tissues increase range of movement.

Theoretical rationale: The rationale underpinning rigid orthoses and casting is that the muscle fibres and other soft tissues in children with CP become short and that immobilisation of the muscle in a lengthened position will lead to an increase in muscle length through an increase in sarcomere numbers in series.

Evidence: There is no evidence available related to long-term outcomes following orthosis use with people with CP [177]. There is Level 3 evidence supporting functional orthosis use in the upper limb in children with CP. There is Level 3 evidence that orthosis improve body structure and function and some upper limb function and gait parameters when the orthoses are in use, but the effects are not maintained when the orthosis is removed and the long-term benefit in preventing deterioration is not clear [175, 178, 179].

There is Level 1 evidence [13] that casting is effective at improving ankle dorsiflexion but limited evidence that it prevents deterioration in muscle length or leads to a functional benefit in gait (see Chap. 22). There is limited information on the secondary consequences of repeated casting and best age for greatest effect. Gough (2007) suggests that repeated serial casting for equinus in children with CP may result in altered muscle morphology and function resulting in a potentially damaging increase in eccentric loading in an already weak muscle [180]. Further research is required.

How to, volume of therapy: Orthosis prescription is complex. Each child with CP has a different clinical presentation and goal of orthosis prescription, therefore the orthoses fabricated need to be individualised and goal directed. Although orthoses might improve some aspects of function, they may limit others. For example, a fixed ankle foot orthoses (AFOs) may improve foot pre-position at initial contact and maintain gastrocnemius length in gait but may limit the second and third rocker of gait movements needed to walk efficiently.

Removable, rigid, serially adjustable orthoses are typically fabricated using thermoplastic materials and designed to stretch soft tissues. They are prescribed for long-term wear as a contracture prevention measure. They may be worn at night or during periods of 'rest'. Typically, a 6 h period of wearing per night (or day if night is not possible) is prescribed.

Serial casts, designed to stretch soft tissues, are prescribed for short-term wear, and activity is usually encouraged in joints not immobilised to minimise unwanted weakness from immobilisation. When serial casting, successive removal, assessment and fabrication is repeated every 4–5 days for a minimum of 2 weeks and continues until muscle length goals are achieved to a maximum of 4 weeks. Contraindications and precautions when casting include, but are not limited to, skin breakdown, swelling or oedema at the extremity to be casted, history of non-union fracture or recent fracture or decreased bone density at the extremity to be casted and compromised

neurovascular circulation, including recent deep vein thrombosis or heterotopic ossification at the extremity to be cast. Serial casting should be coupled with botulinum neurotoxin (BoNT) when spasticity is also present with fixed muscle contracture, but the timing of commencement of casting after BoNT remains unclear (see Chap. 22).

The individual and family need to be educated (verbally and in writing) about the purpose of the orthoses or serial casting and its expected outcomes. They are shown how to conduct neurovascular checks, orthoses donning and doffing techniques, activities to be addressed at home or in therapy. When serial casting, education to support recognising emergent and non-emergent situations and identifying when to return for cast changes must also be provided.

Who the intervention is designed for: Serially adjusted rigid upper limb orthoses are typically provided to children with spasticity to prevent loss of, or maintain, range of movement. AFOs are indicated to improve function (usually of gait or upright standing, but also alignment of the foot in sitting) and to maintain and/or increase range of motion. AFO use is higher in younger children, and compliance may decrease with increasing age.

Serial casting can be utilised when there is a contracture of muscle and/or poor joint alignment, there is a risk of further deformity, the joint/extremity cannot be controlled with orthoses alone or other conservative efforts to restore joint mobility and muscle extensibility have failed. Several studies have outlined protocols for serial casting, and there are variations in joint application, length between reapplication of casts, number of cast applications, total length of time of the serial casting and casting material.

How you know it is working: Before and after orthotic prescription and at each serial casting application, the following should be assessed for managing potential negative outcomes and ensuring safety as well as assessing positive improvements because of the intervention:

Pain, skin integrity, active and passive range of motion, passive (R1/R2), muscle tone (modified Tardieu and/or ASAS), strength, posture and functional skills appropriate to the goal of the orthosis/serial casting

Therapist training required: It is recommended that therapists providing casting and orthosis prescription and fabrication should have appropriate education, training and competence in orthotic fabrication, casting and cast removal skills. This can either be done through formal professional development activities or mentoring with colleagues experienced in the area.

17.2.3.5 Therapy Following Botulinum Neurotoxin (See Detailed Chap. 22)

Botulinum toxin (BoNT) decreases spasticity in the injected muscle and reduces the muscle tone for approximately 8–12 weeks. BoNT may be used to augment therapies when it is felt spasticity is interfering with functional movement. To optimise the success of BoNT, a comprehensive rehabilitation programme is essential, and therapy is usually more intense during the pharmacologic period of BoNT (see Chap. 22).

17.3 Summary

There is positive evidence supporting occupational therapy and physiotherapy interventions to effectively improve outcomes for children with CP. Currently, the strength of evidence is in surveillance to minimise the effect of impairments, and intense delivery of goal focussed, activity-based interventions to promote activity performance. Surveillance of body structures and functions remain critical in the growing child with CP and adulthood. Future directions should focus on building strong evidence about how to improve participation outcomes.

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Early Intervention for Children with Cerebral Palsy

18

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Abstract

Whilst starting intervention early is a common goal of many clinicians and researchers, there is paucity of high-quality evidence to support early interventions in improving motor and other neurodevelopmental outcomes when commenced in the first 2 years of life. The evidence that does exist for early motor intervention for infants with cerebral palsy (CP) or high risk of CP recommends interventions based on motor learning principles with child-initiated movement that actively involves parents and focuses on environmental enrichment. Ideally diagnosis-specific intervention should occur as early as possible, during key periods of brain plasticity and prior to maladaptation of the musculoskeletal and central nervous system.

18.1 Starting Early

The first years of life involve rapid maturation and development of both the musculoskeletal and central nervous systems that set the foundations for a child's future function [1]. The lifelong ability of both the brain and the body is largely activity dependent, and there is increasing evidence that environment and experience shape development [2]. When an infant is born, they have to learn how to move outside the mother's womb in an antigravity environment. This involves intensive self-initiated practice that enables the fundamental characteristics of motor control in the upper and lower limbs which normally results in the infant learning to roll, sit, crawl and ultimately walk, usually within the first 18 months of life (see also Chaps. 9 and 11). However, when

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there is an injury to the brain during the prenatal or perinatal period, the infant's attempts to move are hampered by poor muscle activation, muscle weakness and disordered motor control. Repeated attempts at movements may result in learning inefficient and often stereotypical motor patterns [1]. Not only does the resultant maladaptive movement result in muscle disuse and changes to the muscle function but can also effect central nervous system organisation [3]. For infants who are identified early in life as being high risk for CP, it is essential that targeted motor training to stimulate and guide postnatal brain and corticospinal organisation is commenced early, before these maladaptive patterns of movement occur, with the aim to ultimately improve the child's function [4].

18.2 What Is Early Intervention?

The definition of early intervention is variable throughout the world but is generally defined as "multidisciplinary services provided to children from birth to 5 years of age to promote child health and well-being, enhance emerging competencies, minimized developmental delays, remediate existing or emerging disabilities, prevent functional deterioration and promote adaptive parenting and overall family function" [5]. In this chapter we will focus on early intervention from birth to 2 years, with an emphasis on the first 2 years of life. Traditionally, early intervention for children with CP commenced after a confirmed diagnosis around 18–24 months of age [6]. There has been a shift in practice in recent times to commence intervention early in development during key periods of brain and musculoskeletal development prior to impairment in developmental milestones, such as crawling and/or walking.

18.3 Early Detection

Early detection of CP is crucial to ensuring timely referral to early intervention. Clinical signs and symptoms of CP emerge and evolve during early infancy, with infants with CP showing signs of movement deviations as early as 1 month of age [7]. Many infants with CP are identified as "high risk" in early development, due to risk factors in the newborn period, such as brain injury along with neurological findings assessed with a combination of standardised tools [6]. Using standardised assessments, such as Prechtl's method of assessment of quality of general movements, the General Movements Assessment (GMA), clinicians can predict those children most at risk of CP within the first few months of life (see also Chaps. 9 and 11 and Panteliadis et al. 2015) [8, 9]. A recent systematic review established that the GMA was the best predictor of CP with summary estimates of sensitivity and specificity of 98% (95% confidence interval [CI] 74–100%) and 91% (95% CI 83–93%), respectively [9]. Magnetic resonance imaging (MRI) and neurological examination, such as the Hammersmith Infant Neurological Examination (HINE), can also be used within the first year of life to accurately predict CP [9]. Where possible, a trajectory of abnormal GMs and/or HINE in combination with MRI should be used to make an early diagnosis of CP [7, 10]. Early detection of infants at high risk of CP allows for CP-specific early intervention and should be the standard of care to optimise infant neuroplasticity, prevent complications and enhance parent well-being.

18.4 Using the International Classification Function (ICF) Model in Early Intervention

Early intervention has historically focused upon minimising impairments in body structures and functions with an expectation that improvements would enhance children's functional abilities in daily tasks. However, evidence that improvements in body functions and structures lead to enhanced activity and participation is weak.

The biopsychosocial model endorsed by the International Classification of Functioning, Disability and Health [11], which appreciates the impact of personal and environmental factors on the health experience of the individual, has facilitated a shift in focus away from a traditional

impairment-based approach. Current trends in early intervention are focused on ways to enhance children's participation in their preferred activities, despite emerging or persistent deficits. Further, the importance of the personal factors including the developing child within a family context and surrounding environmental factors that influence health is a key target of early intervention.

There is an increasing focus on participation, that is, "involvement in meaningful life situations", and should be an essential goal of paediatric rehabilitation [11, 12]. In children and youth, participation at home and school and in their communities involves taking part in a wide range of activities, such as playing sports, doing arts and crafts, shopping or going to the movies with friends. Evidence suggests that children with a variety of disabilities have fewer social engagements than their peers and are involved in fewer activities and that these activities tend to be home based and less physically active [13].

Many factors impact upon children's participation in activities including functional skills, activity preferences, attitudes and the environment. Participation for infants is not as well understood, but from an early intervention perspective, it seems prudent to focus on targeted play activities, the involvement of families and enrichment of the environment.

18.5 Environmental Enrichment

Neuroplasticity has been the subject of both basic science and clinical research for several decades. Demonstrable changes in structure, function and connections at the molecular and cellular level provide scientists and clinicians with confirmation that injuries to the brain are not static and that harnessing these mechanisms might be the solution to recovery [14]. The first 2 years of life is commonly regarded as the critical period for motor development due to the timing of corticospinal tract development and the plasticity mechanisms at work in the infant brain.

Activity-dependent plasticity is the basic mechanism that rehabilitation interventions try to harness in order to improve function. Early childhood experiences determine how the brain is wired; early and repeated experiences make synaptic connections.

Animal studies have demonstrated that early motor training post injury is required to establish connectivity, brain changes and functional skills [15]. In addition, recovery after brain injury has been shown to be significantly enhanced by an enriched environment (EE). Gains documented in animal studies of EE include improved memory and motor recovery [16]. Whilst animal studies use consistent animal housing set-ups, it is more difficult to describe the "essential ingredients" of an enriched environment in human settings with more data available about the negative effects of environmental deprivation on development. A recent systematic review and meta-analysis showed a small but favourable effect of EE interventions over standard care for improving motor outcomes in infants at high risk of CP [17]. In this review an EE was defined as one containing complexity and variability, and that includes cognitive, sensory, social and motor stimuli and challenges. These findings, along with the ICF inclusion of environmental factors as influential to child activity and participation, should lead clinicians to deliberately attend to environmental enrichment when planning early intervention.

18.6 Interventions in the NICU

Early intervention can commence from birth and in many cases whilst the infant is in the neonatal intensive care unit (NICU) [18]. Most early interventions that commence in the NICU will be targeted towards infants at risk of motor impairment, such as preterm infants rather than infants with a specific diagnosis of CP, due to most infants not having a specific diagnosis at such an early age. There is an increased focus in early detection of infants at high risk of CP earlier in the developmental course whilst the infant is in the NICU using a combination on neuroimaging and neurobehavioural assessments [19, 20]. However, the use of early detection in the NICU of infants

at high risk of CP for enrolment in research studies of early intervention is limited.

18.7 Early Motor Interventions in Cerebral Palsy

The evidence base for effectiveness of early motor interventions for cerebral palsy is modest at best and is in part a result of the historical late diagnosis of CP. A recent systematic review found only ten randomised controlled trials [21]. Of the studies that commenced intervention when "high risk of CP" was determined and prior to a confirmed diagnosis, only one study had more than 50% infants with CP officially diagnosed by the end of the study. The difficulties in early identification of CP have been discussed previously, and it is expected that implementation of international clinical guidelines for the early detection of CP will assist in recruiting the "right" babies to intervention studies for CP.

18.7.1 Traditional Approaches

Traditional approaches to motor interventions have followed two basic paths: firstly those that developed from the early work of the Bobaths and include Bobath therapy and neurodevelopmental therapy (NDT); see also Chap. 16. These approaches focus on the normalisation of movement patterns and strategic use of facilitation techniques as well as positioning and handling [22]. Earlier descriptions of these interventions were based on the then current thinking regarding cephalocaudal CNS maturation, and intervention included the treatment of postural control, abnormal muscle tone and stereotypical synergistic movement patterns. As understanding grew regarding motor control and neuroplasticity, so NDT evolved to also address a person's goals and functional capacity [23]. Core techniques and strategies however have remained the same particularly the central place of therapeutic handling including facilitation and inhibition. Similarly NDT therapists define their point of difference as the focus on impairments of CP [23]. Systematic reviews have repeatedly shown that NDT is no more effective than regular care when offered in infancy [21, 24, 25] and childhood [26].

NDT is now recognised as a very broad approach such that it is difficult to describe what is and isn't included under the Bobath/NDT banner. It has even recently been suggested that these names now engender so much confusion that it is time to abandon the use of the terms altogether [27].

The second widely used approach, the developmental skills approach, is largely focused on sequential milestone attainment across all developmental domains [28]. Children are typically engaged in curriculum-based programmes organised according to their level of ability. Intervention might be conducted in group settings with individualised support to assist parents to practise functional skills embedded in home-based routines. Whilst motor skills are included in the curricula, individual therapy sessions are often added on to focus on the specific impairments associated with cerebral palsy. Well-known programmes include Portage, Hawaii Early Learning Program, Peabody Developmental Motor Activities programme, the Carolina Curriculum and Learning Games (Creative Curriculum). Inherent in these approaches is the assumption that children will progress through these milestones, albeit at their own pace.

Studies examining the effectiveness of these two approaches in very young children with CP are few and far between. One quasi-controlled study [29] that compared the two approaches found no between-group differences in motor outcomes. In contrast the study by Palmer and colleagues in 1988 demonstrated significant between-group differences in favour of the *Learnin games* programme over NDT in a homogenous group of infants with spastic diplegia [30].

18.7.2 Functional Therapy Approaches

Effective interventions to improve motor activities in older children with CP tend to be goal oriented, involving practice of functional tasks that are meaningful to the child and family, delivered

in a natural environment and repeated at a sufficient intensity [24]. Interventions such as goal-directed training or functional training have been shown to produce improvements in gross motor function and performance of daily activities in young children and toddlers with CP [31–33] (Ketelaar, Law, Ostenjo). In many ways these approaches that emerged in the late 1980s were a reaction against the normalisation and largely child-passive interventions that had been in use for children with CP for decades. These changes were also influenced by increasing attention to the principles of family-centred practice that by definition involves organising therapy around family goals and preferences.

Early motor intervention prior to diagnosis, that is, in early infancy, did not undergo the same change and has tended to largely follow traditional approaches.

More recently new early motor protocols based on the principles of experience-dependent plasticity have been studied with some promising results:

- GAME (goals, activity, motor enrichment) is a goal-oriented therapy intervention delivered in a parent partnership model [34–36]. Therapists jointly set goals with parents and develop infant-friendly motor training activities at the "just right challenge". The infant learning environment is enriched via parent coaching and targeted parent education. The natural (home) environment is the site of all therapy visits, and the home environment is modified to provide learning opportunities. Motor training is scaffolded so that the infant is an active agent in all activities and passive interactions are avoided. The aim is self-generated motor activity, and trial and error in practice is encouraged. GAME has been tested in infants with CP in two small randomised trials resulting in improved motor and cognitive outcomes when compared with standard care.
- Infant-friendly constraint therapy is a modified version of the well-studied constraint-induced movement therapy (CIMT) used in children with hemiplegia. In this modified version, infants wear a soft constraint for short periods whilst engaging in play activities aimed at eliciting new motor behaviours. Emerging evidence indicates children with hemiplegia who had received mCIMT during infancy had better functional ability at 2 years [37]. It is not yet known whether early constraint is any more beneficial than early bimanual therapy for infants with hemiplegia, as in older children both approaches are effective [7].

18.8 The Application of Neuroplasticity and Motor Learning Principles

These newer approaches are informed from neuroscientific principles of activity or experience-dependent plasticity and motor learning [38]. These principles (Table 18.1) describe characteristics of experience-dependent neuroplasticity from which motor interventions can be devised and applied to infants and toddlers with CP.

18.9 Parental Involvement

Within the context of the ICF, an infant and young child are most often dependent on a parent or caregiver for activity and participation. Further, targeting the parent-infant relationship and parental well-being is essesntial for early intervention to be effective [39]. Warm and responsive parenting and a more optimal home environment have been shown to have a protective effect on child development, in children both with and without brain injury [40]. Parents play a critical role in early intervention for their child, and it's important to consider factors that may influence parent function both positively and negatively [39, 41]. Higher rates of anxiety, depression, grief and stress are reported in parents of children with CP for many reasons [42–44]. Compared with typically developing children, parents of children with CP need to be proactive, skilled and conscious in their parenting choices [41]. To optimize their child's development, they need skills including forward thinking, scaffolding abilities, a commit-

Table 18.1 Principles of motor learning in practice for infants

Principle	Application for therapy design
Use it or lose it	Motor skills will not be optimised if infants are deprived of early motor exploratory opportunities. All awake time is an opportunity for learning, and the infant's routine should help inform all opportunities for practice
Use it and improve it	Training specific motor functions, e.g. targeted reaching training, induces measurable cortical plasticity and improves the functional task of reaching
Specificity	Training ought to be task specific, not general, e.g. improving standing balance will not result from spending time in a supportive standing frame
Repetition	Specific tasks need to be repeated many times; one successful attempt is not enough to drive plasticity. Home programmes to continue tasks initially tried or learned during therapy are essential to skill acquisition
Intensity	Practice needs to occur at an adequate intensity. Daily practice will be more effective than weekly therapy sessions
Timing	Training ought to begin as soon after the injury as feasible; therefore early detection of CP is vital
Salience	Training should be fun and rewarding. Tasks that do not motivate the infant or are too difficult are less likely to result in skill acquisition
Age	Training-induced plasticity occurs more readily in younger brains. Match training to the age of the child but it is never too young to start
Transference	Plasticity in response to a training experience can enhance acquisition of similar behaviours. Practice tasks in a variety of ways, e.g. sitting on the floor, will, at some level, improve the ability to sit on a low chair
Interference	Plasticity can also be maladaptive. The formation of compensatory strategies might inhibit the development of preferred skills

ment to supervision, patience, compassion and behavioural management skills whilst also taking care of their own well-being [41]. To date there have been very few studies that have focused specifically on parenting interventions for parents of children with CP in infancy, which show benefits in child behaviour, but further high-quality studies are needed [44]. Nonetheless interventions that involve parents in early intervention are more effective than interventions that don't include the parent(s) in studies of both CP and infants at high risk of developmental impairments [18, 21]. Further, targeting parental well-being is essential for early intervention to be effective.

18.10 Future Research

Whilst there are many fundamental elements thought to be key in early intervention for children with CP, there are still many questions to be answered. Limitations of the research to date include a diversity of interventions trialled and heterogeneity of children with CP. With increasing accessibility to early detection of infants at high risk of CP, the effectiveness of early interventions can be assessed on a larger scale. It is most likely that early interventions will be most effective when targeted to the functional impairment, for example, CIMT for infants with hemiplegia. Further research to support parent well-being in early infancy of parenting a child with CP is also needed.

Learning to move is not only important for the development of muscle strength, postural control and independent mobility but also allows the infant to explore their environment to develop language, cognitive and behavioural regulation skills.

Although CP is by definition a motor disorder and targeting motor skills is a key component of early intervention, it is important to recognise that cognitive, language and behavioural development may also be impaired. Whilst these impairments may be related to a motor function,

they can also be a result of the underlying brain injury. There is still limited evidence for early intervention in infants with CP to improve cognitive, language and behavioural function, and further research is needed [45].

Conclusion

Early intervention for infants and children with CP aims to improve brain connections during key periods of brain development, rather than waiting for an impairment to occur once altered brain connections have developed. Early intervention focuses on coaching parents to use play to train motor, cognitive, language and behaviour skills. Importantly, training needs to be active, rather than passive, so that the infant is learning (i.e. development, alteration and/or selection of neural circuits) through their experiences [39].

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Suggested Reading

Panteliadis CP, Hagel C, Karch D, Heinemann KJ. Cerebral palsy: a life long asks for early intervention. Open Neurol J. 2015;9:45–52.

Hip Dysplasia in Children with Cerebral Palsy

19

M. Wade Shrader and Bopha Crea

Abstract

Neuromuscular hip dysplasia is common in children with cerebral palsy, especially those with GMFCS IV or V functional level. The pathophysiology of progressive hip subluxation and dislocation comes from abnormal muscle tone superimposed over growth and developmental delay. Proactive surgical care in the form of soft tissue releases and hip osteotomy is successful in stopping progressive subluxation and dislocation. Neglected hip dysplasia in CP leads to painful dislocations that can be treated with salvage surgical procedures but with lower success rates than preventive and reconstructive techniques.

19.1 Introduction

Hip dysplasia represents a common and debilitating orthopedic problem seen in children with neurodevelopmental disabilities such as cerebral palsy (CP).

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Neuromuscular hip dysplasia is different than developmental dysplasia in the hip, as most children with CP do not have hip dysplasia at birth. Children with CP are at increased risk of developing dysplasia and dislocations of the hip as they become dysplastic and unstable during childhood pursuant to progressive spasticity of the hip flexor and adductor musculature. The prevalence of hip dysplasia among children with CP is more common in advancing GMFCS levels and in patients without gait function, particularly in GMFCS IV and V children where the incidence is close to 90% [1].

Hip dysplasia has a significant impact on the quality of life in these children. Left untreated, hip dysplasia may eventually lead to neurogenic hip dislocation.

Dysplasia can be associated with pain, mobility problems, and decreased participation levels [2, 3]. Dislocation may result in severe problems

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with ambulation, sitting balance, and perineal nursing care and may increase the risk for developing decubitus ulceration.

19.1.1 Prognosis

A child's GMFCS level has a strong impact on subluxation risk, and the risk continues to the end of growth [4]. Children at functional level GMFCS V are at significantly higher risk of displacement vs GMFCS III–IV. This risk is highest at 2–3 years of age [5]. Mean migration percentage (MP) increases with decreasing functional level, from 0.2% per year at GMFCS level I to 9.5% per year at GMFCS V [3].

Head-shaft angle is a risk factor for hip displacement in children with CP. When comparing two children with the same age, GMFCS level, and MP, a 10° difference in HSA results in a 1.6 times higher risk of hip displacement in the child with higher HSA [6].

Recent literature supports the use of hip surveillance programs in improving hip morphology as well as decreasing pain [7]. In Sweden, the CPUP program is a national hip surveillance program designed for early detection and treatment of children with CP or suspected CP who are at risk of developing significant contractures or dislocations of the hip. The Australian CP Registry also has demonstrated improved outcomes with an intentional hip screening program for patients with CP.

19.2 Pathophysiology

Cerebral palsy is a static encephalopathy that can result in myostatic contractures in the knee and hip. Progressive spasticity creates a set of muscular imbalances that loads the acetabulum eccentrically as the center of rotation shifts from the femoral head to the lesser trochanter. This results in superior and lateral migration of the head. If left unrecognized and unbalanced, it can lead to silent hip dislocations or progressive subluxation of the femoral head and subsequent femoral head deformity as it impinges on the acetabulum.

Normal anteversion at birth is approximately 40° and decreases progressively over time to an average of 15° at adulthood. Children with spastic hip disease have a persistence of fetal anteversion, which may progressively increase over time and contribute to eccentric loading at the hip joint. Children with CP are also at increased risk for lateral displacement of the femoral head. The overall incidence of lateral displacement and dislocation varies between 7% in children who are ambulatory and 60% in children who are nonambulatory [8, 9]. Population-based studies show a marked trend toward hip displacement in nonambulatory children and recommend close surveillance beginning from age 1 to 2 [3].

19.3 Physical and Radiographic Evaluation

Physical examination should include a comprehensive exam of the spine, hips, and bilateral lower extremities. This exam should evaluate the child in their wheelchair and on the examination table. The spine should be evaluated for scoliosis and include a thorough exam of the skin over the spine and the pelvis with flexibility and location recorded. Sagittal balance and pelvic obliquity should be documented. There is a strong correlation between hip morphology and the presence of pelvic obliquity; as such it deserves close scrutiny in children and adolescents with CP [10]. This is especially true in nonambulatory adolescents (GMFCS IV and V, [10]). Assessment of hip flexion deformity can be made using the Thomas test. Hip abduction as well as rotation, popliteal angles, and the degree of spasticity should be noted.

The initial assessment should include an anterior-posterior radiograph of the pelvis (AP pelvis). A *standard* technique should be used to obtain plain radiographs in monitoring dysplasia of the hip. The patient can be imaged supine with hips held in neutral adduction-abduction. Significant flexion contractures may make it difficult to interpret, as the pelvis will tilt forward as the hips are extended producing more of an inlet view as opposed to a true AP radiograph.

19.4 Radiographic Evaluation

Migration percentage (MP) is the percentage of the femoral head lateral to Perkin's line divided by the total width of the femoral head, effectively measuring the proportion of uncoverage. Using this calculation, hips can be classified as normal (MP under 33%), subluxation (MP 33–89%), and dislocation (MP 90% or greater) [3]. Migration percentage per year can be calculated and followed by an orthopedic surgeon based on initial and last radiographs. A migration change of greater than 10% has been felt to represent a true change [11, 12].

Acetabular index (AI) refers to the angle formed by a line drawn along the acetabular roof and *Hilgenreiner*'s line. Normal AI is 30° within 1 year of age, 25° from 1 to 5 years of age, and 20° in adulthood. Until approximately 30 months of age, children with CP are often normal. Over time, however, the AI of children with CP becomes progressively higher where the index is generally in the range of 40° when the MP is 50% or greater.

19.5 Early Treatment

The use of physical therapy, standing frames, and abduction devices is somewhat controversial in this patient population. There is some evidence that bracing in conjunction with botulinum toxin injections may help in delaying the need for surgical intervention, however do not prevent the need for surgery [13]. Boyd and Hays [14] showed the rate of surgical intervention at the 3-year follow-up point in patients who received botulinum toxin A in addition to bracing was significantly less with 27% needing surgery compared to 47% in the non-Botox group.

Picciolini et al. [15, 16] followed 51 children with CP enrolled in a 2-year combined treatment program of neurodevelopment treatment (NDT) two times a week in addition to a 5-h daily siège moulé postural exercises and a control group undergoing only NDT. At 2 years, there was marked worsening in the MP of the control group from 23.0 to 37.7% compared to stability (28.8–26.8%) in the group receiving postural treatment. This study provides supporting evidence that postural management may provide a useful tool in helping prevent the natural progression of hip dislocation. Similar to *Picciolini*'s findings, Macias-Merlo et al. [17] demonstrated that children with spastic diplegia CP who underwent a daily standing program with hip abduction may enhance acetabular development where hip migration percentage remained stable in the standing group in comparison to those who did not participate [17].

19.6 Surgical Planning and Treatment

Surgery for hip dysplasia in the setting of CP is broadly split into three categories: preventative, reconstructive, and salvage. Orthopedic surgeons employ several clinical algorithms for preventative surgery; the majority are based on migration percentages reaching >30–40% or a migration percentage progression of greater than 10% in 1 year [2].

During the preoperative planning phase, careful attention should be paid to the initial ambulatory status of the patient. When the decision is made to proceed with surgical intervention, careful and thorough preoperative evaluation should be completed with the patient's dedicated specialists.

19.7 Preventive Surgery

Soft tissue procedures offer a prophylactic measure against osseous procedures in at-risk children, better defined as those with passive abduction less than 30–45° and MP greater than 25% or when mild subluxation is present without osseous deformity. It can also be considered in children who present with mild subluxation and are under the age of 4 as they have a high risk of recurrence following femoral/pelvic osteotomies.

Soft tissue procedures include open myotomies, including lengthening of the adductor longus, adductor brevis, gracilis, sartorius, and iliopsoas, a proximal or distal hamstring

release, and neurectomy of the anterior branch of the obturator nerve, as indicated. These procedures are aimed at preventing or slowing down the progression of dysplastic transformation of the hip. The goal is to achieve at least 30° of passive abduction. Adductor and psoas tenotomies are preferably completed between 2 and 3 years of age prior to the development of more severe hip dysplasia. In some studies, soft tissue releases before the age of 4 have been shown effective in preventing lateral migration of the hip [18].

Bilateral procedures should be considered to decrease the risk of recurrence or imbalance. Unilateral procedures may result in unequal limb lengths and asymmetrical appearance in the proximal thigh. Recent literature, however, has tried to address when bilateral procedures should be completed. Abdo and Forlin [19] studied the progression of the contralateral hip after unilateral reconstruction (adductor release, femoral varus osteotomy, and acetabuloplasty) of hip dislocation in patients with GMFCS IV–V [20].

19.8 Reconstructive Surgery

Reconstruction should be considered in patients with progressive subluxation and/or dislocation (MI greater than 40–60%) or those who have failed soft tissue procedures. Procedures are tailored to the pathologic findings and typically include soft tissue releases, proximal femoral varus derotational osteotomy in conjunction with a peri-acetabular osteotomy of the pelvis, and, occasionally, open reduction with capsulorrhaphy, when deemed necessary.

Osteotomies of the proximal femur are used to correct a valgus neck-shaft angle in addition to correction of femoral torsion, as the common proximal femoral deformity is an increase in anteversion and valgus. This osteotomy is frequently called a varus derotational osteotomy or *VDRO*. This can be completed in conjunction with shortening of the femur. An osteotomy may inadvertently decrease passive abduction; as such, a soft tissue procedure may be performed when passive abduction is less than 45°. When possible, femoral osteotomies should be delayed until at least 4 years of age [21, 22]. Care should also be taken so as not to overcorrect as retroversion may increase the risk of posterior subluxation or dislocation.

When done at a young age, femoral osteotomies are performed with the intent of promoting a more normal development of the acetabulum. The decision to proceed with a pelvic procedure may be based on suboptimal head coverage under fluoroscope after the completion of a VDRO. Patients with higher preoperative migration percentages are more likely to be treated with the use of a pelvic procedure in addition to VDRO as opposed to VDRO alone. It is also recommended that patients with coexisting acetabular dysplasia (AI >25°) and a type II sourcil, in which the lateral corner of the sourcil is turned upward and lies above the weight-bearing dome, also receive a pelvic osteotomy.

In most cases of subluxation, acetabular dysplasia is posterolateral or global. The most common pelvic procedures in patients with neuromuscular hip dysplasia are volume-reducing procedures as opposed to redirectional procedures. Most orthopedic surgeons perform a pericapsular pelvic osteotomy 5 mm above the insertion of the joint capsule. A curved osteotomy is extended down to the triradiate cartilage, which serves as a hinge, and the lateral margin of the acetabulum is levered downward and bone graft is inserted. The addition of an open reduction may be considered in cases of severe dysplasia, i.e., when the MI exceeds 80%.

Concomitant procedures such as pelvic osteotomy should be considered for patients of GMFCS IV and V, as these patients are at risk for recurrent subluxation [23]. Combined femoral and pelvic osteotomies in this group demonstrate the lowest failure rates, so the decision to proceed with the addition of a peri-acetabular osteotomy should take into consideration the child's GMFCS level.

19.9 Salvage Procedures

The treatment of chronically dislocated hips in adolescents and adults with cerebral palsy presents a challenge to both families and treating physicians. Both the femoral head and acetabulum are often severely dysplastic and require salvage options to adequately treat the pain and deformity. Surgical options include proximal femoral resection (PFR), hip arthrodesis, total hip replacement, and the McHale et al. [24] procedure (a valgus osteotomy and femoral head resection). Girdlestone initially described resection of the femoral head alone; however this is troubled with proximal migration of the shaft. This can be combatted with a resection of the proximal femur below the level of the lesser trochanter combined with a soft tissue interposition. The McHale et al. [24] procedure utilizes a lateral exposure to the hip to resect the femoral head at the base of the neck, and a lateral closing wedge osteotomy is performed at the level of the lesser trochanter and stabilized with a plate construct (to achieve 45° abduction). The ligamentum teres is then attached to the lesser trochanter by suturing it to the psoas tendon, and a capsulorrhaphy is performed, thereby stabilizing the lesser trochanter to the acetabulum.

Wright et al. [25] evaluation of outcomes following surgical procedures for a painfully dislocated hip found good or excellent results in 67% with PFR, 67% in subtrochanteric valgus osteotomy, and 73% in proximal femur prosthetic interposition arthroplasty using a humeral prosthesis after a mean follow-up of 4.1 years.

Recent systematic review of salvage options (proximal femoral resection, valgus osteotomy, or total hip arthroplasty) in severe hip dysplasia in patients with CP [26] shows that among patients with functional levels of GMFCS IV or V, all the typical salvage procedures relive pain better than arthrodesis, which has a significantly higher rate of complications. The proximal femoral resection had the lowest absolute percentage of complications. Among salvage options, [27] also recommended the utilization of a proximal femoral resection as it has the best complication profile. Arthrodesis in nonambulators is associated with a >100% complication rate and inferior pain relief [26].

19.10 Postoperative Care

In the past, most surgeons recommended spica casting in wide hip abduction. Concerns over cast skin issues have caused a shift in postoperative immobilization. Today, most patients are immobilized in a removable hip abduction pillow. Knee immobilizers are frequently used to prevent hip flexion.

If other orthopedic procedures, such as lower extremity tendon lengthenings, foot reconstructions, or other parts of a single-event multilevel surgery or SEMLS, are performed concurrently with the hip reconstruction, a short stay in the PICU may be prudent. Otherwise, patients are cared for on the pediatric surgical floor. Postoperative care pathways and patient education programs are crucial to help improve postoperative outcomes.

Postoperative pain control is extremely important to minimize patient and parent anxiety [28]. Typical pain control modalities include a postoperative epidural, regular dosing of benzodiazepines and nonsteroidal anti-inflammatory agents, including ketorolac.

Length of stay is typically 3–4 days and is primarily determined by the effectiveness of pain control and bowel management. Patients are maintained non-weight-bearing for 6–8 weeks until the osteotomy is healed. Gentle ROM is encouraged to minimize scar formation. After weight-bearing has been cleared, the patient is encouraged to resume normal physical and occupational therapy (PT and OT) to regain their preoperative functional status.

19.11 Complications

Patients with CP experience almost twice as many complications after surgery for neuromuscular hip dysplasia as those patients with

developmental dysplasia of the hip (*DDH*). Most of the complications however are medical, as opposed to patients with DDH who experienced predominantly orthopedic complications [29].

It is important to outline preoperative expectations and goals, especially among GMFCS IV and V patients who are at greater risk of failure after soft tissue release in the prevention of hip displacement [30]. A retrospective review of 330 children with CP and an MP of greater than 30% showed that GMFCS II patients had a failure rate of 6% compared to GMFCS III, IV, and V that showed failure rates of 51%, 73%, and 86%, respectively. Failure was defined as a MP >50% or the requirement of subsequent surgeries.

Shore et al. [31] demonstrated that independent risk factors for surgical revision include younger age at surgery, increased GMFCS level, and lower annual surgical hip volume. Soft tissue release at the time of a hip osteotomy was protective against revision. The 5-year survivorship showed a 92% success rate for GMFCS I and II vs 76% for GMFCS level V. 5 years following a varus derotational osteotomy for hip subluxation or dislocation, children show a re-dislocation rate of 16% [20] (Figs. 19.1 and 19.2).

A retrospective review of 330 children with CP with a migration percentage of >30% on at least one hip found that the risk of failure after soft tissue release in the prevention of hip displacement was associated with increasing GMFCS level.

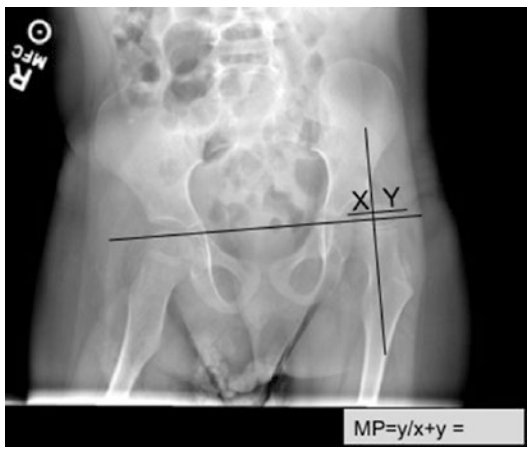

Fig. 19.1 Preoperative radiograph of a 5-year-old child with CP (GMFCS level V); migration percentage of the left hip 80%

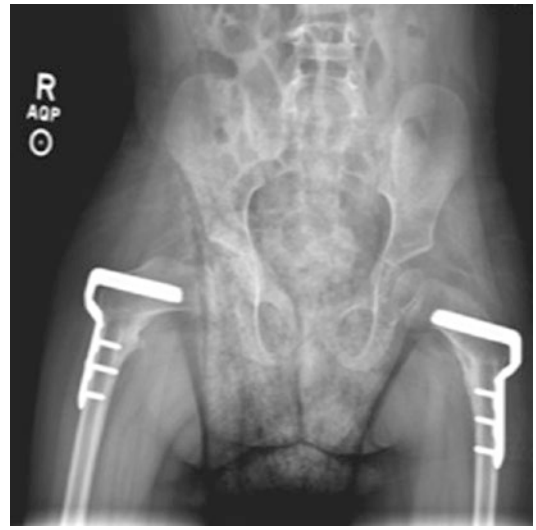

Fig. 19.2 1-year postoperative radiograph demonstrates bilateral varus derotational osteotomies with improved coverage of both hips

A systematic review of 399 articles demonstrated that the frequency of avascular necrosis (AVN) ranges from 0 to 46% with an overall rate across studies of 7.5% [32]. On the basis of the current literature, no significant association has been found between age at surgery, severity of subluxation, length of follow-up, and type of surgery with the risk of AVN. Most surgeons feel that mild AVN is primarily a radiographic finding and unlikely to be of much clinical significance.

Independent risk factors for blood transfusion in the treatment of hip dysplasia include longer operation time, preoperative hematocrit, female sex, developmental delay, pulmonary comorbidity, and older age [33]. Relative to non-neuromuscular patients with or without comorbidities, children with neuromuscular disease experience higher rates of transfusion as well as higher volumes [34].

19.12 Outcomes

Recent midterm results at a mean follow-up of 13–71 months demonstrate a nearly 90% success rate in achieving and maintaining adequate hip

reduction at [34]. Buxbom et al. [35] evaluated stability and migration across VDRO in children with neuromuscular disorders at 5, 3, 6, and 12 months after surgery using radiostereometric analysis (RSA) demonstrated that migration stagnates within the first 5 weeks postoperatively. Even in severe spastic quadriplegia, VDRO in combination with pelvic osteotomies leads to good mid-term results with stable, pain-free hips [36].

The Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) is a commonly used measure for health-related QOL. Patients as well as caregivers/parents can complete the questionnaire, allowing patients who may be nonverbal or cognitively impaired to participate. Using this questionnaire, DiFazio et al. [28] have demonstrated that reconstructive hip surgery is effective in improving health-related quality of life of nonambulatory children with CP [28]. Each additional 1% correction in migration percentage is correlated with an increase by 0.2 points.

Long-term outcome data is also promising. At a mean follow-up of 7 years after reconstruction, pain intensity and frequency are significantly reduced with an overall complication rate of 10.5% [37]. Braatz et al. [38] demonstrated improvement in pain and function in children with CP and severe hip dislocations, even if the hip joint was incongruent after reconstruction.

Conclusions

Neuromuscular hip dysplasia in cerebral palsy can have a significant impact on the lives of our patients and their families. Hip surveillance and early, proactive treatment strategies are important to maximize the quality of life in these patients. Preventative and reconstructive hip surgery is preferred and usually can be very successful to treat the hip dysplasia. Salvage surgery should be considered only as a last resort but can also provide pain relief in those patients with severe pain from severe, neglected hip dislocations. Future work on improving care pathways, pain control, and studies on maximizing quality of life will continue to improve the care we deliver to patients with CP and hip dysplasia.

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Scoliosis in Children with Cerebral Palsy

20

M. Wade Shrader and Bopha Crea

Abstract

Scoliosis commonly occurs in children with cerebral palsy. This spine deformity is much more common in non-ambulators (GMFCS Levels IV and V) and can be progressive with negative consequences on quality of life, including increased pain, difficulty seating, progressive restrictive lung disease, and a potential shortened lifespan. Spine fusion is a reliable method of treating progressive scoliosis in these children, but the complication and infection rate is high. However, spine fusion has been demonstrated to improve the quality of life of these patients and their family or caretakers.

20.1 Introduction

Children and adolescents with neurodevelopmental disabilities, such as cerebral palsy (CP), frequently complain of spine deformity. Although patients with CP may have a variety of different types of spine deformities, scoliosis is the most common. The prevalence of scoliosis is much higher in patients with GMFCS functional Levels IV and V, affecting as many as 90% of those children [1]. However, it is important to note that scoliosis can affect a patient with any functional level, although the approach to an ambulatory patient with scoliosis is somewhat different.

20.1.1 Impact

Scoliosis has a significant impact on the quality of life in these children. It primarily affects those patients in wheelchairs, so positioning and seating become more difficult with progressive deformity. As the curve progresses, patients frequently have more trouble with head control, as a significant amount of energy is expended trying to keep the trunk straight. Severe deformity is often accompanied with

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significant pelvic obliquity, and this often causes pain from pelvic impingement on the ribs. This pelvic obliquity often can cause pressure ulcers from pelvic-rib impingement and ischial tuberosity decubiti [2].

Severe curves can cause systemic organ dysfunction. Many of these children already have restrictive lung disease. The *deformity* of the spine and chest wall impairs the function of the lungs and causes worsening and progression of their lung disease. Also, the curve can affect gastrointestinal (GI) motility. Similarly, these patients have issues with constipation, which is made worse from the spine deformity. Reflux or gastro-oesophageal reflux disease (GERD) can also be made worse with scoliosis [3]; for more see Chap. 30.

20.1.2 Prognosis

Differentiating which patients will have a progressive spinal deformity is difficult. Those patients with a worsening curve will likely have a decrease in quality of life (QoL), although that is not as well documented. The consensus is that QoL worsens with curve progression and complications due to the spine deformity increased with curve magnitude [4, 5].

The prognosis of progressive scoliosis in a child with CP is also difficult to determine, due to limited data. Severe curves with worsening restrictive lung disease likely would lead to a shortened lifespan. Our current literature on spine deformity is unclear if posterior spinal fusion (PSF) improves life expectancy. The idea of life expectancy and scoliosis in these patients is very hard to tease out, since life expectancy is decreased in patients with CP and GMFCS functional Levels IV and V. One article documents increased longevity in Rett syndrome, whose spine deformities are very similar to CP [6].

Parents should be educated about the likelihood of spine deformity, and the spine should be discussed at early visits. It is important for that family struggling with the diagnosis of scoliosis to see other families who have had spine surgery.

20.2 Pathophysiology

The overall pathophysiology of why the spine curves is unclear. As it mostly happens in patients with GMFCS Levels IV and V, it may be due to lack of weight bearing, standing, and walking (for more see Chap. 23). Scoliosis occurs in all types of CP, including hypotonia and spastic subtypes of CP, although it seems to be more common in patients with more dominant spasticity. *Hypotonia* often leads to truncal weakness, which can lead to structural spine deformity. *Paraspinal* spasticity can lead to asymmetry muscle forces acting across the spinal column which can lead to structural curve, as well [1].

The curves tend to be very flexible in the younger child. However, once the curve progresses past 50° and once the child reaches the onset of adolescence, the magnitude and stiffness of the curves seem to increase rapidly, sometimes exponentially [7].

20.3 Physical and Radiographic Evaluation

Most children with cerebral palsy need at least annual evaluation by a paediatric orthopaedic centre with CP experience. Patients with GMFCS functional Levels IV and V need a spine examination as part of a thorough physical exam every 6 months in paediatric orthopaedics. This exam should evaluate the child in a seated or standing position and should also include a bending exam to detect subtle rotational deformities that are the prelude to true structural scoliosis [1].

The spine exam should include a thorough exam of the skin over the spine and the pelvis, including the ischium looking for possible skin at risk or decubiti. The flexibility of the curve should be assessed using the "Miller Flexibility Test" where the child is placed over the examiner's knees. If the spine deformity corrects, then the curve is still quite flexible. If the curve is more rigid, then the deformity will be quite rigid, even using the knee as a fulcrum. A complete distal neurological exam should be done in front of the family. Oftentimes, the patient's ability to use

synergistic full-body motion will be diminished after a spine fusion; with that loss of truncal motion, there may be an apparent loss of lower extremity distal function. Therefore, it's important both for the family and the provider to know exactly what distal lower extremity function the child has preoperatively [8].

Once a curve is suspected, radiographic evaluation is necessary. The technical details of the radiograph are critical. The patients should be allowed to sit so that a true, functional position of the spinal curve is assessed. Supine films are not clinically useful. A special radiographic chair that is radiolucent but allows for free sitting can be extremely useful so that reproducible films are done every time. That is very important as surgical decisions are made on serial radiographs over time. Newer technology allows for biplanar radiograph measurement, which includes a seat in the imaging chamber. If special chairs are not available, then parents/radiology techs should try to support the patient in a consistent manner with minimal lateral forces and support, but while maintaining a safe seated position for appropriate radiographs.

The initial *radiographical* assessment includes both posterior-anterior (PA) and lateral full spine radiographs. Follow-up evaluations usually involve just a PA radiograph, unless there is significant concurrent kyphosis or if kyphosis is the primary deformity. If that's the case, then lateral radiographs should also be included.

Most scoliosis curves in patients with CP are long, sweeping curves that are very representative of neuromuscular scoliosis. These curves usually involve both the thoracic and lumbar curve, with the apex of the deformity in the lower to middle part of the spine. Frequently, significant pelvic obliquity coexists with the spinal deformity, especially with the long-sweeping C-shaped curves. However, other types of scoliosis may be present, including typical and atypical upper and main thoracic curves. Cobb angle measurements are the standard method of measuring the magnitude of the curve.

The sagittal profile is also very important. Severe thoracic and upper thoracic kyphosis is often present and can impact the patients by making it difficult to keep their head erect so that they can see and interact with their environment. Occasionally, that kyphosis is the major spinal deformity, rather than scoliosis. Lumbar lordosis is also a very frequently seen deformity in non-ambulatory children with CP. This lumbar lordosis occurs with severe rotation of a lower lumbar curve. But it can also occur iatrogenically after a selective dorsal rhizotomy (SDR); for more see Chap. 25. This lumbar lordosis can be quite rigid and is a very important deformity to address during surgical correction [9].

20.4 Early Treatment

The early treatment of spine deformity in children with CP centres mostly on seating support. Wheelchair evaluation with a specialized rehab seating expert is necessary. Custom wheelchairs with scoliosis pads with offset chest laterals to correct the deformity often are enough for early treatment.

The use of bracing is somewhat controversial in this patient population. Bracing can be helpful for positioning, seating, and comfort. There is some thought that it may slow progression, but most evidence demonstrates that bracing produces no real change in the natural history of the curve progression [10, 11].

In *addition*, bracing can create negative impacts on the child's overall health. Bracing can make breathing difficult, can cause pressure sores, and can increase abdominal pressure, which can make constipation worse. Finally, most of these children have restrictive lung disease at baseline; bracing can negatively affect chest wall growth, which could worsen their restrictive lung disease. Bracing should be used to help support the child and with seating support, and parents should not be counselled that the brace will help stop or slow curve progression.

20.5 Surgical Planning

Once the curve reaches 40°, the paediatric orthopaedic surgeon should begin in earnest surgical discussions with the family. It is common that

many families are hesitant to put their child through such a major operation. It may take some time and more than one visit for them to be able to make an appropriate decision. The best time to perform the spinal fusion is when the curve is 40–50° and flexible. Some families prefer to defer the decision until the curve becomes much larger and stiffer; that spinal deformity is much more difficult to treat surgically and carries a much higher risk of complications. Extensive counselling and a shared decision-making approach are important to help families make the appropriate decisions for their children (Fig. 20.1) [9].

If a family is having difficulty making a decision, a consultation with the special needs/medically complex paediatric service or the paediatric palliative care service can be helpful. A medical conference with all the medical subspecialists can also help the family understand the risks of spinal fusion and weigh that against the potential benefits of improved seating and stopping curve progression. It is important that the family understands what the future holds if the spine deformity progresses significantly in the future, and that future state needs to be acceptable if the family decides against surgery.

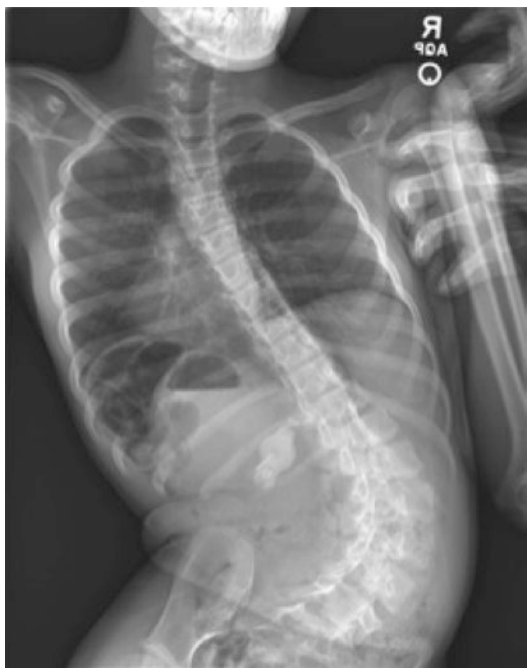

Fig. 20.1 A 12- year-old boy with cerebral palsy and a 75° curve

Once the family has decided to pursue the spine fusion, a thorough multidisciplinary preoperative assessment must take place. The child should be assessed for proper nutrition, which typically involves a nutrition consult (for more see Chap. 31). Children that are gastric-tube fed must be assessed to make sure they are getting appropriate caloric intake. Laboratory values such as complete blood count, total lymphocyte count, total protein, and albumin may be obtained, but these are not reliable indicators of adequate nutrition.

If the patient has a shunt, it needs to be evaluated by neurosurgery prior to the spine fusion. Many patients with CP will have baclofen pumps (for more see Chap. 24); that should not impact the surgical decision, but a plan for a possible catheter repair/replacement should be in place if it is damaged during the dissection.

All patients with CP who are GMFCS Level IV or V should be assessed by paediatric pulmonology prior to posterior spine fusion (PSF); for more see Chap. 29. Many of these children have restrictive lung disease and some may have sleep apnea. One of the major difficulties of a prolonged ICU stay with ventilator support is the weaning of the ventilator. Although most patients are taken off the ventilator immediately postoperatively or within the first 24 h in contemporary ICUs, the potential for a respiratory complication is high in these children. Preoperative assessment and possible preoperative non-invasive pressure-supported ventilation (BiPAP) education can be critical to help these children better adapt and cope with possible postoperative BiPAP. Furthermore, sleep studies are becoming more and more commonplace for preoperative assessment.

If the patient has other medical comorbidities, they must be seen by those particular specialists for preoperative evaluation. Also, the patient should see their primary care physician to discuss the overall care of the patient and the family prior to proceeding with such a large surgery. Finally, the patient and family should see the paediatric orthopaedic surgeon as often as is necessary to make sure all of their questions are answered and everyone feels comfortable proceeding with the surgery.

20.6 Surgical Treatment

The specific surgical treatment of scoliosis in a child with CP differs somewhat to the treatment of idiopathic scoliosis. The child with CP will be more medically fragile, will have larger blood loss, will need a longer stay in the paediatric intensive care unit (PICU) and the hospital, and will be at risk for higher complications [12].

The goals of the surgery are fourfold: the most important goal is to cause spinal fusion and prevent deformity progression. The pelvic obliquity should be corrected, and the overall spine should be balanced with the head over the pelvis, which will allow for improved positioning and seating. Finally, the outcomes of the surgery should allow for improved quality of the life for both the patient and their family or caretakers [5] (Fig. 20.2).

Adequate intravenous access is mandatory, usually through a central line, multiple large-bore peripheral IVs, and an arterial line. Pulmonary artery catheterization is not typically needed. The child is placed prone on a standard spine table, with care taken to properly pad all bony prominences. Prophylactic antibiotics need to cover for both gram-positive and gram-negative bacteria in this patient population; typically cefazolin and gentamicin are utilized. *Antibiotics* are re-dosed if the procedure lasts longer than 4 h. *Antifibrinolytics* (Amicar or tranexamic acid) are now considered standard treatment to minimize blood loss.

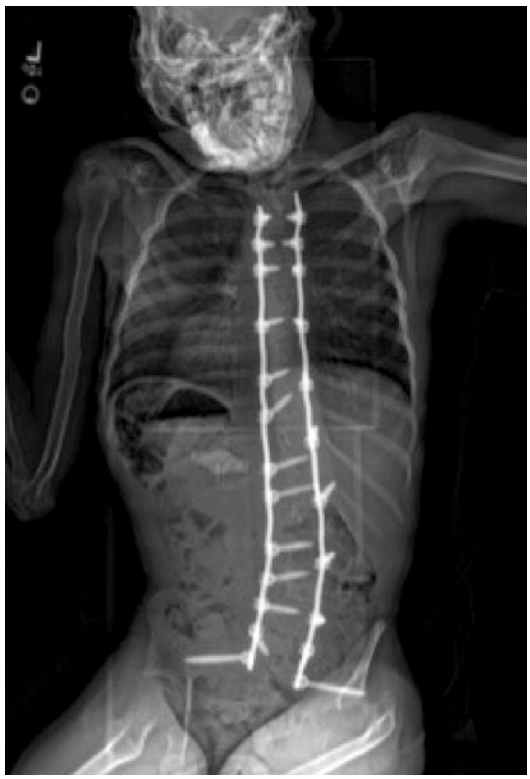

Fig. 20.2 One-year postoperative radiograph after posterior spinal fusion with excellent improvement in deformity and improved seating balance

The surgical team should consist of experienced paediatric anaesthesiologists, attending paediatric orthopaedic surgeons, and orthopaedic-specific scrub technicians with spine experience. There have been some suggestions that the surgical time, blood loss, and complications are lower when two experienced attending surgeons assist one another during this complex surgical procedure. Our institution treats these cases like "paediatric cardiac surgical cases" with extra circulating nurses and an extra scrub tech during instrumentation.

The exposure is standard and should typically extend from the upper thoracic spine (typically T1, T2, or T3) down to the sacrum and pelvis. Frequent packing assists haemostasis, and the use of Gelfoam and thrombin is not unusual.

The choice of implants is largely up to the preference of the surgeon and typically includes either sublaminar wires or pedicle screws. Both have been shown to be appropriate in patients with CP. Sublaminar wires require small laminotomies which may increase blood loss; the use of pedicle screws in poor-quality bone in non-ambulatory patients may provide less fixation. Also the severe deformities may make screw placement more difficult in some surgeons' hands and require more radiation from fluoroscopic guidance [13].

Pelvic fixation can be accomplished through Galveston fixation with smooth rods or a unit rod construct. Alternatively, iliac bolts through a standard approach or more contemporary S2-alar screws can be used. These S2Al screws can be placed from the sacrum outwards through the inner and outer tables of the pelvis which can

cause the rods to be placed in line with the lumbar and thoracic rods without additional offset connectors and rods.

The deformity correction should concentrate on the pelvic obliquity and overall deformity balance. It is not necessary to make the spine perfectly straight and correct the Cobb angles to zero. However, more stiff curves may require supplemental techniques to achieve appropriate surgical goals. These may include posterior spine osteotomies, vertebral column resections, intraoperative traction, intraoperative temporary rib-pelvis distractions, or even an open anterior approach. The specific indications for when these additional techniques are necessary have not been clearly delineated in the literature.

Meticulous sterile technique with frequent irrigation is imperative to decrease the risk of infection. Our institution uses cancellous allograft for fusion mass; large volumes (typically 90–120 cc) are used with vancomycin and tobramycin antibiotic power. A water-tight closure is important in layers over a superficial drain. Nylon skin sutures should be used if the child is incontinent to prevent stool wound contamination. An impervious dressing also is used during the hospitalization.

20.7 Postoperative Care

Essentially every patient with CP should be monitored in the PICU postoperatively. The PICU stay is primarily focused on pulmonary management with the goal to wean them from the ventilator quickly and to return them to their preoperative oxygen requirements. Critical care management of blood pressure balanced with pain control is also important in those first postoperative days. Patients should be transfused as needed for symptomatic postoperative anaemia.

Once transferred to a regular nursing unit, the goals then shift to getting the patients and families back to their baseline in terms of transfers out of bed to their wheelchair and returning to their normal feeding, whether through the g-tube or with oral feeds. Special caution should be given towards the risk of pancreatitis, a postoperative ileus, and, more rarely, superior mesenteric artery syndrome.

The patients should be set up with a wheelchair evaluation soon in the postoperative period, since their sitting height and overall seating posture will be markedly different following a spine fusion. At home, patients have to build up their endurance to preoperative levels by slowly getting in their wheelchair more and more and slowly resuming their normal daily lifestyle.

20.8 Complications

Neuromuscular scoliosis is a known risk factor for postoperative complications following corrective spine surgery. Comparatively, neuromuscular scoliosis results in higher postoperative morbidity and mortality rates [14]. Children with CP more often have significantly lower body weight, pulmonary reserves, and larger curves preoperatively compared to patients with idiopathic scoliosis. Complication rates occur in 40–80% [15–17] with the overall complication rate averaging around 25% [3, 18]. Common complications include severe bleeding, pulmonary compromise (pneumonia, effusions, pneumothorax), deep wound infection, spinal cord dysfunction (including paraplegia), gastrointestinal complications (ileus, gastritis, pancreatitis), and urinary tract infection (UTI).

Excessive bleeding and disseminated intravascular coagulation (DIC) is the biggest risk of the intraoperative period. The use of antifibrinolytics, meticulous surgical technique, and every effort to decrease surgical time are all effective means to minimize excessive blood loss. Excessive blood loss leads to the necessity of extensive fluid resuscitation, which often produces significant pulmonary oedema which can place the child at significant pulmonary risk. Surgical blood loss in patients with CP undergoing scoliosis correction is greater when compared to adolescent idiopathic scoliosis [12, 19]. Increased estimated blood volume loss is independently associated with experiencing a major perioperative complication [20]. Brenn et al. [19] performed a prospective analysis of clotting parameters at

baseline and at an estimated intraoperative blood loss of 15% of total blood volume in children undergoing PSF. When compared with children with idiopathic scoliosis undergoing PSF, those with CP demonstrate significant differences in coagulation profiles at 15% total blood volume loss. As a result, children with CP who undergo PSF have increased bleeding that starts earlier in the procedure than it does for patients with idiopathic scoliosis. The use of unit rod constructs compared with pedicle screw-rod constructs in this cohort is associated with a 12.6-fold higher odds of blood volume loss. Additionally, each 1° increase in coronal curve magnitude correction increases the odds of loss of blood volume by 1.03-fold [12].

Pulmonary complications are frequently seen in this population. The severity of these complications ranges from minor increases in oxygen requirements to pulmonary oedema or effusion to the need for prolonged ventilator support. Children with CP undergoing scoliosis surgery have a higher rate of delayed extubation. As many as 25% develop postoperative respiratory issues, with prolonged mechanical ventilation (>3d) required in 5% [2]. Preoperative pulmonary consultation will often make the management of postoperative pulmonary complications much easier for the patient and family.

Gastrointestinal difficulties are also frequently encountered. A postoperative ileus is not unusual and usually responds to a slow resolution of normal feeding once bowel sounds are heard and flatus resumes. Patients who are g-tube fed usually will start with continuous feeds and transition to more bolus-type feeds prior to discharge. Pancreatitis can occur and should be vigilantly monitored. Finally, superior mesenteric artery syndrome can be caused after spinal fusion, especially in patients who are malnourished and have very little abdominal fat.

One of the biggest complications in this procedure for children with cerebral palsy is postoperative wound infection. The rate of significant infection ranges in the literature from 10 to 30% [21, 22]. Aggressive wound management and excellent patient care in terms of hygiene can help lower the risk of infection. The overall risk of surgical site infection ranges from 4 to 10%; however the risk is about threefold higher in neuromuscular scoliosis than it is in idiopathic [14]. Infections are more often polymicrobial and caused by gram-negative organisms than is typical for elective orthopaedic procedures. This suggests an enteric source. Sponseller et al. [21] support the notion that infection rate in scoliosis for patients with CP is higher than that for most elective spine surgeries and note that two study factors predicted infection: higher preoperative WBC count and the use of a unit rod. Final curve correction was lower for patients with deep infections than those without, and a trend towards greater percentages of pain was also seen in the infection group. For those unfortunate patients who do get a deep infection, a thorough surgical debridement followed by intravenous antibiotics followed by long-term (at least 1 year) oral suppressive antibiotics is required.

Hardware failure can occur, especially when considering the osteopenic nature of most of these children's bones. Radiographical evidence of screw loosening, especially in the pelvis, without clinical loss of deformity correction is not significant and should just be monitored radiographically. Wire breakage in the setting of sublaminar wires is not unusual and also should not be treated routinely. However, a significant hardware failure in terms of rod breakage, screw pullout, in the clinical setting of a loss of deformity correction mandates the serious consideration of revision spine fusion.

Finally, the mortality risk of these procedures should not be underestimated. In surveys of paediatric orthopaedic surgeons who care for these patients and an excellent long-term review of over 300 cases at DuPont, the perioperative mortality was about 1%.

Recent studies have evaluated the factors predicting postoperative complications in spinal fusions for children with CP in efforts to minimize their occurrences. Samdani et al. [20] conducted a prospective multicentre longitudinal cohort analysis revealing that risk factors for experiencing a major perioperative complication (pulmonary, gastrointestinal, other medical, wound infection, neurological, instrumentation

related, and unplanned staged surgery) include greater preoperative kyphosis, staged procedures, a lack of antifibrinolytic use, and increased estimated blood loss.

Bendon et al. [23] retrospective review of a cohort of CP patients undergoing spine surgery from 2008 to 2014 demonstrates that the presence of two or more comorbidities and previous thoracotomy represent risk factors for having perioperative complications in children with CP undergoing scoliosis surgery. The most common comorbidities seen include reflux and seizure disorder.

Nishniandize et al. [24] review of 303 CP children undergoing PSF between 2004 and 2013 found that dependence of a g-tube is a predictive factor of complications in PSF in CP children. More specifically, postoperative pancreatitis and deep wound complications are more common in these patients. [8] showed that patients with CP who had a g-tube were 61% more likely to develop postoperative pancreatitis and reflux 52% and those with reactive airway disease were 54%. There was also a clinically relevant, though nonstatistically significant, association with seizure disorder and postoperative pancreatitis [25].

20.9 Satisfaction and Short-/Long-Term Outcomes

Improved operative techniques and implants have led to successful correction of scoliosis in children with CP with predictable curve correction and improvement in patient and caregiver quality of life. Surgery presents an effective technique for correcting deformity and restoring sitting posture. Beckman et al. [13] have shown that the use of posterior-only instrumentation compared to combined anterior-posterior instrumentation obtains comparable radiological results as measured by Cobb angles at immediate discharge and final follow-up with a median follow-up period of 4.1 years in GMFCS IV and V CP patients. Posterior-only instrumentation was associated with shorter operating times and shorter ICU and hospital stays than combined surgery. As the duration of surgery is a relevant predictor for postoperative complications, posterior-only instrumentation may reduce the overall complication burden.

Short-term follow-up at 3 years as evaluated by Modi et al. [25] demonstrates improved functional ability grades and sitting balance and maintained coronal and sagittal correction when compared to immediate postoperative measurements at a mean follow-up of 36.1 months. Long-term clinical outcomes in this population however are limited to overall disease burden and mortality. *Recently*, Sitoula et al. [7] retrospective review of 33 CP patients who underwent spine fusion with unit rod instrumentation between 1989 and 2006 showed that there was minimal short-term and long-term morbidity associated with early-onset neuromuscular scoliosis and spine fusion and maintenance of postoperative Cobb and pelvic obliquity measurements. Definitive fusion in juveniles (skeletally immature with open triradiate cartilage) with progressive curves approaching 90° results in significant radiographic and QoL improvements.

The overall satisfaction rate by parents and caregivers as reported in the literature is over 90% (91.7%, [4]) (92%, [3]). Despite limited overall functional improvements, 8–40% of patients still perceive the results as improved following surgical correction [3] and report a high degree of satisfaction [5, 9]. Improved healthy quality of life as measured by the "Caregiver Priorities and Child Health Index of Life with Disabilities" over a 2-year follow-up in CP children with scoliosis undergoing spinal fusion has been demonstrated in the literature [4]. Interestingly, in this study the overall subjective improvement of HRQL (health-related quality of life) did not statistically correlate with degree of objective radiographic changes postoperatively. The occurrence of a complication also did not correlate with the satisfaction rate of the overall outcome of the operation or HRQL.

Conclusion

Although spinal deformity can be a significant impact on the quality of life of children and adolescents with CP, spine fusion can successfully treat the majority of these patients and help them immensely. This *procedure* should be performed by paediatric orthopae-

dic surgeons with experience in cerebral palsy and spinal deformity. The perioperative care should also be multidisciplinary in nature to make every effort to improve outcomes and minimize the risk of complications. Although the procedure carries a significant risk of complications, modern surgical care results in a lasting improvement in seating and positioning and improves the QoL of these children [26].

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Management of the Upper Limb in Cerebral Palsy

21

Erich Rutz and H. Kerr Graham

Abstract

The management of the upper limb in children with cerebral palsy (*CP*) is complex and challenging, requiring a co-ordinated, multidisciplinary approach. The management team may include developmental paediatricians, occupational therapists, physiotherapists, orthotists and upper extremity surgeons from an orthopaedic or plastic surgery background. Interventions are generally aimed at improving function and cosmesis by various combinations of motor training, strengthening, spasticity management, movement disorder management and the prevention of contractures and other fixed deformities by effective splinting and positioning. Movement disorders may respond to oral medications but when severe, may require neurosurgical approaches such as intrathecal baclofen (*ITB*) or deep brain stimulation (*DBS*). The correction of fixed musculoskeletal deformities requires various combinations of muscle-tendon lengthenings, tendon transfers, osteotomies, arthrodeses and joint stabilizing procedures. These can be performed as individual surgical procedures or as multiple procedures, in a single session of upper limb surgery, single-event multilevel surgery (*SEMLS*).

Occupational therapy and physiotherapy have small treatment effects in isolation but are essential adjuncts to medical and surgical management. The therapy with botulinum toxin A has small effects and short-lived. Surgery is also effective but requires careful patient selection, as many children with CP are not candidates for upper limb surgery. Surgery management varies according to the needs and goals of each child and family.

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Children with severe involvement (*MACS* IV and V) may benefit from simple surgery to relieve pain and to make care and activities of daily living easier. Procedures include correction of severe fixed deformities around the shoulder, elbow and wrist by soft tissue releases or in the case of the severely flexed wrist, by arthrodesis. Children with higher levels of function (*MACS* I-III) may benefit from various combinations of muscle-tendon lengthenings, for flexion deformities and tendon transfers and for muscle imbalance, joint stabilization and correction of "thumb-in-palm" deformity. SEMLS for the upper limb can improve both cosmesis and function. The outcomes of surgical management are greater than those obtained from therapy or botulinum toxin A injections in the domains of joint range of motion, function and quality of life.

21.1 Introduction

The management of the upper limb problems in children and adolescents with cerebral palsy (CP) is complex and demanding [1]. Effective treatment requires a multidisciplinary approach involving neuro-paediatricians, occupational therapists, physiotherapists, orthotists and orthopaedic or plastic surgeons. The aim of treatment is at improving function and cosmesis by spasticity management, preventing contractures and correcting established bony or soft tissue deformities [1, 2].

Treatment objectives vary according to each child and need to be tailored to improve the function of upper limb. They range from static correction of deformities to ease nursing care, to improvements in dynamic muscle balance to augment hand function. Botulinum toxin A therapy in combination with occupational therapy is a standard treatment and has been shown to relieve spasticity and improve function in the short term [3]. Occupational therapy and physiotherapy have small treatment effects alone but are essential adjuncts to orthotic and surgical treatment. Surgery is also effective but requires careful patient selection, as many children with CP are not candidates for surgery and may not achieve functional improvements [1].

Biomechanical factors include a limited passive range of motion (*ROM*) due to joint instability or contractures. Muscle function is impaired by weakness, spasticity, dystonia and poor selective motor control, resulting in abnormal posturing and joint positions [4]. Upper limb dysfunction affects children with unilateral CP (spastic hemiplegia) and children with more severe involvement and bilateral CP (quadriplegia/spastic bilateral, GMFCS levels IV and V). Individuals with unilateral CP (spastic hemiplegia/unilateral) are often physically high functioning (*GMFCS* levels I or II). Despite the mildness of the impairment, abnormal upper limb posturing during walking can be pronounced resulting in a significant cosmetic issue. Riad et al. concluded that movement deviations in teenagers and young adults with mild, unilateral CP were correlated with lower self-esteem [5]. This is more pronounced with increased arm posturing, and the functional and cosmetic effects must be considered when evaluating children and adolescents [1, 5].

21.2 Clinical Assessment

It is important to commence assessment by classification of the overall level of bimanual function. In the lower limb, the Gross Motor Function Classification System (*GMFCS*) is the starting point to classify the level of function and the long-term, gross motor prognosis. Similarly, in the upper limb, bimanual function should be classified according to the Manual Ability Classification System (*MACS*) [6]. Accurate classification of bimanual function in children with CP is essential to guide prognosis and goal setting, as well as the choice of operative and

Table 21.1 The Manual Ability Classification System (MACS [6], http://www.macs.nu)

Level	Description
I	Handles objects easily
II	Handles objects with reduced quality and speed
III	Handles objects with difficulty requiring modification
IV	Handles objects only in adapted situations
V	Does not handle objects

nonoperative therapies. The MACS is used to classify the child's abilities to handle objects during daily activities (Table 21.1).

Following classification by the MACS, detailed, systematic clinical evaluation is important and starts with an analysis of the child's arm and hand function. *Physical* examination and analysis of the postural deformities are essential. Plain radiographs in an anteroposterior view are required to assess for bony and joint deformities/instabilities [1]. The active and passive ROM, presence of contractures, selective motor control, manual muscle strength and sensory deficits should be recorded systematically and meticulously. The Modified Ashworth Scale (*MAS*) [7] and the Modified Tardieu Scale (*MTS*) [8] are useful clinical tools to assess spasticity and evaluate longitudinal changes over time and following intervention.

Most clinicians are familiar with three-dimensional gait analysis (3-DGA) to assess gait and function in ambulant children. Summary statistics of gait, gait such as the Gait Profile Score (*GPS*) described by Baker et al., are increasingly used as outcome measures [9]. For the upper extremity, the Arm Posturing Score (*APS*) first described by Riad and colleagues [5] may be equally useful for objective assessment of upper limb function. However, there is no substitute for dynamic electromyography to determine the timing of muscle activity and to identify important issues such as co-contraction [1].

Both the GMFCS and MACS are expected to remain stable over time. There is therefore a need for more assessment tools which may be responsive to interventions and serve as outcome measures. The best known example in the surgical field is the House classification of upper extremity functional use (Table 21.2) [10]. This nine-level classification is useful for establishing baseline function, to communicate functional levels and goals to parents and other clinicians and to monitor progress of treatment [1]. This classification is useful to classify function in each upper limb, seperately, whereas the MACS is a classification of bimanual function. Most children with spastic hemiplegia function at MACS level I or II, but the involved upper limb may function from House 0 to 8 [1, 6, 10].

Table 21.2 House classification of upper extremity functional use [10]

Class	Designation	Activity level
0	Does not use	Does not use
1	Poor passive assist	Uses as stabilizing weight only
2	Fair passive assist	Can hold an object placed in hand
3	Good passive assist	Can hold onto object placed in hand and stabilize it for use by other hand
4	Poor active assist	Can actively grasp object and hold it weakly
5	Fair active assist	Can actively grasp object and stabilize it well
6	Good active assist	Can actively grasp object and then manipulate it against other hand
7	Partial spontaneous use	Can perform bimanual skills easily and occasionally uses the hand spontaneously
8	Full spontaneous use	Uses hand completely and independently without reference to the other hand

In *addition*, cognitive function, sensation and stereognosis may influence upper limb functional profile in children with CP [1]. Following clinical evaluation, management plans are developed with realistic, achievable treatment goals identified, taking into account the child's cognitive, motor and sensory limitations. By definition, CP is a movement disorder, but the type of movement impairment may be manifested as spasticity, dyskinesia or mixed movement disorders [1, 4, 11]. In addition the manifestations vary in different segments of the upper limb: shoulder, elbow, forearm, wrist, fingers and thumb [1, 3].

21.3 Management Options for Upper Limb Problems in CP

There are three main treatment options [1, 2]:

1. *Non-surgical treatment*: Occupational therapy and physiotherapy. These include neurodevelopmental treatment, motor learning, conductive education, strength training and constraint-induced movement therapy (CIMT; see Chap. 17), splinting and casting.
2. *Spasticity management*: Treatment of focal spasticity includes phenol neurolysis and botulinum toxin A (BoNT-A) or regional management (intrathecal baclofen), ITB and selective dorsal rhizotomy (SDR; see Chaps. 25 and 26).
3. *Surgical treatment*: Soft tissue procedures include muscle-tendon recession or lengthening and tendon transfers to restore muscle balance and bony procedures including corrective osteotomies and joint stabilization or fusion.

21.3.1 Non-surgical Treatment

Motor training is goal directed, and measurable goals are identifiable by children, parents and caregivers. Recent innovations include the use of electronic games, virtual reality and Internet-based programmes [12, 13]. Children can be engaged and motivated by motor training because it is focussed on activities rather than individual movements. Constraint-induced movement therapy (*CIMT*) is popular for the management of learned non-use, which is very common in children with hemiplegia [1, 11, 14]. CIMT involves encouraging the use of the most affected upper limb by restricting the use of the less involved hand in a cast, splint or glove for defined periods of activity during the day. The evidence for CIMT has been reviewed by the Cochrane Movement Disorders Group [15] (see Chap. 17).

In a *systematic* meta-analysis, Jackman and colleagues (2014) evaluated the effectiveness of hand orthoses in children with CP [16]. Although they found that the use of hand orthoses in addition to therapy may offer a small benefit for manual skill development, this effect diminishes 2–3 months after discontinuation of orthosis use. Orthoses can create discomfort and cosmetic problems, and this may be an important problem for adolescents. There are positioning orthoses to stretch soft tissue which should be used 1–2 h per day or functional orthoses to improve the child's function of the affected upper limb. These orthoses may be used during the whole day (see Chaps. 17 and 22).

21.3.2 Spasticity Management

The primary aim in the management of spasticity is to prevent the development of fixed muscle contractures as well as secondary bone and joint deformities [1, 3, 4, 11]. With all spastic deformities, there is an initial dynamic phase with gradual development to fixed contractures [1, 11]. As a consequence, younger children will tend to have mostly dynamic deformities, which are amenable to treatment aimed at reducing spasticity [3]. In contrast, older children may have a greater degree of fixed deformity, which can only be adequately treated with surgery [3].

The choice of spasticity intervention is usually determined by the topographical distribution of the CP. In hemiplegia (spastic unilateral), botulinum toxin A (BoNT-A) can be injected into selected target muscles in the upper and lower extremity. This can be combined with splinting or casting, followed by a period of intensive occupational therapy or physiotherapy to stretch weakened spastic muscles, strengthen antagonist muscles and retrain more functional patterns of movement [3]. Injection of specific upper limb target muscles requires accurate targeting. Electrical stimulation and ultrasound are essential adjuncts to upper limb injection protocols. Specific indications, dose per muscle and recommendations regarding dilution have been previously published [1, 3, 17, 18]. Injections of BoNT-A may improve joint ROM, permit more functional movements, reduce painful spasms and may delay the onset of fixed contractures. However, the effects are generally small and short-lived [1, 3, 11, 17–19].

SDR in the lumbosacral segments is used in selected children with spastic diplegia for lower limb spasticity (see Chap. 26). It is not used specifically for upper extremity spasticity, but incidental improvements in upper limb function have been reported [20]. In severe spastic quadriplegia, continuous intrathecal baclofen may be administered by an implantable pump (ITB) to effect a more generalized reduction of spasticity (see Chap. 25). A reduction in upper limb spasticity and improvements in function using intrathecal baclofen can be achieved by placing the catheter tip at the level of the cervical nerve roots [21]. Injections of phenol to the musculocutaneous nerve and the deep branch of the ulnar nerve have a useful role for spasticity of elbow flexors and the intrinsic muscles of the hand, respectively [1, 21].

21.4 Surgical Treatment

21.4.1 Upper Limb Surgery in Children with Cerebral Palsy

Surgery can improve both function and cosmesis in the upper limb of a child with CP, but patient selection is paramount, as many children with cerebral palsy are not candidates for upper limb surgery [1]. Occupational therapy, physiotherapy and targeted rehabilitation are essential adjuncts to surgical management [1, 11] (see Chap. 17). As with lower limb surgery for children with CP, there is a need for detailed preoperative analysis, the identification of segmental component deformities and muscle imbalances and the development of a detailed single-event multilevel surgical plan which is followed by casting, splinting and rehabilitation [11].

The typical upper limb deformities in the spastic type CP include adduction and internal rotation of the shoulder, pronation of the forearm, wrist flexion and ulnar deviation, finger flexion and "thumb in palm" [1]. The deformities associated with both mixed tone and dystonia are more variable, less predictable and less amenable to surgical correction [11].

21.4.1.1 Functional Impairment

Functional deficits include problems with reaching, grasping, releasing and manipulation and should be carefully evaluated in each child. The appearance of the involved upper limb may be of great concern to children and caregivers [1, 5].

21.4.1.2 Principles of Surgical Management

Children with spastic hemiplegia function at a high level and may require interventions aimed at developing sophisticated fine motor control for bimanual hand activities [22]. Improving cosmesis by reducing flexion posturing of the elbow during running and flexion of the wrist with grasping activities are important goals for children functioning at House 5–8 [1, 5]. Simpler hand activities such as grasping and releasing assistive walking devices and using the controls for an electric wheelchair or communication device are the main objectives of treatment in children with more severe involvement, House 2–4. In those still more severely involved, ease of dressing and hygiene are the primary reasons for correcting upper limb deformities, House 0–1 [22].

21.4.2 Assessment of the Upper Limb in CP

Detailed history, standardized physical examination and radiographs are the cornerstones of upper limb assessment [1, 3]. The active and passive range of motion, presence of spasticity, dystonia, contractures, selective motor control, muscle strength and sensory deficits should be recorded. The child's functional use of the affected hand may be quantified according to the House classification of upper extremity functional use. This nine-level classification is useful for establishing baseline function, to communicate functional levels and goals to parents and to monitor progress of treatment [10].

Objective evaluation of upper limb function using standardized, validated instruments such as the Melbourne Unilateral Upper Limb Assessment (Melbourne Assessment) or Quality

of Upper Extremity Skills Test (*QUEST*) is strongly recommended to document baseline function and also to assess changes following treatment [23, 24]. Both scales have established reliability and validity. Video recordings of postural and functional assessments are very useful, especially when combined with an objective scoring system such as the Shriner's Hospital for Children Upper Extremity Evaluation (SHUEE) [25]. Kinematic analysis is developing rapidly but is not yet as standardized or as widely available as 3D motion analysis of walking [26]. Compared to the extensive repertoire of upper limb function, walking is simple and stereotypical, and the parameters for typically developing children are easily established and agreed [9, 11]. Markerless systems such as the Microsoft Kinect are showing promise in the analysis of upper limb motion, especially in the context of rehabilitation [27].

21.4.3 Principles of Surgical Management

Most fixed contractures of muscle-tendon units may benefit from lengthening, but which procedures to use and when requires experience and judgment [1, 22]. Tendon transfers can be utilized to improve hand or wrist function. BoNT-A may be used with surgery as a spasticity reducing measure, to protect the integrity of tendon transfers and as an aid to pain relief [1, 3]. Surgical results are most predictable in spastic movement disorders and are unpredictable in dystonia. Realistic expectations are vital because surgery cannot restore normal hand function or appearance [1, 3, 22].

Elbow: Dynamic flexion contracture of the elbow is the most common deformity in children with spastic hemiplegia and is particularly marked as an associated movement during running. Phenolisation of the musculocutaneous nerve is useful in younger children when the problem is purely dynamic, i.e., before the onset of a fixed contracture [21]. When there is a fixed flexion deformity at the elbow, a transverse incision across the elbow crease can provide adequate access to perform a 2–3 cm Z lengthening of the biceps tendon, as well as a fractional lengthening of the brachialis. If no other distal surgery is performed, the elbow is splinted in extension for 4 weeks before passive flexion, and the use of a sling is introduced to regain active flexion whilst maintaining passive extension [28].

Forearm Pronation: The pronator teres is the first muscle-tendon unit to develop a contracture in the hemiplegic upper limb [1]. A contracted, fibrotic pronator teres can be simply released, but if it has a reasonable excursion, it can be rerouted to act as a supinator [29]. The forearm is immobilized in maximum passive supination with the elbow flexed to 90 degrees. Forearm pronation can also be improved by transferring FCU to ECRB (Green transfer). By virtue of the dorso-ulnar course of the transferred tendon, FCU becomes a secondary supinator in addition to its new role as a wrist extensor [29, 30].

Wrist: The majority of children with hemiplegic CP have wrist flexion deformities [1]. The two most useful procedures for wrist flexion deformities are the Green transfer and arthrodesis but for different indications [22, 30]. Children who have a functional hand, with a good range of wrist motion, but constant posturing into the flexion range secondary to out of phase activity in FCU, may be candidates for the Green transfer [29, 30]. This can be assessed clinically by palpating the FCU tendon as patients open and close their fingers and confirmed using dynamic electromyography. Some children have poor finger extension and an FCU working in phase with finger extensors. These children may benefit from transfer of the FCU to the extensor digitorum communis (EDC). Contractures of FCR, palmaris longus and the long finger flexors must be addressed at the same time.

Adolescents with severe wrist flexion contractures and limited function may appreciate the cosmetic gains and improvements in palmar hygiene from arthrodesis of the wrist, combined with soft tissue releases [22]. A dorsal wrist fusion plate provides stable fixation, permits early mobilization and has excellent outcomes in terms of fusion rates and deformity correction.

The soft tissues should be rebalanced by an extensive release of all contracted muscle-tendon units and plication of the redundant wrist and finger extensors. Improvements in cosmesis are substantial because the atrophic limb appears to be longer following correction of the severe wrist flexion deformity as well as partial correction of the digital contractures [22]. There may be minor improvements in "helper hand" functions. In appropriately selected cases, satisfaction with the procedure is very high.

Fingers: When wrist flexion is corrected, as described above, occult spastic contractures in the fingers and thumb may be unmasked. There are three main options. Mild spastic contractures in the long flexors may respond to Botox, combined with casting. Fractional lengthening at the musculotendinous junctions of FDS and FDP, especially when combined with injections of BoNT-A and splinting, is effective and preserves function. In severe contractures, when functional goals are more limited, FDS to FDP transfer may be performed [22, 29]. The FDS tendons are divided distally, close to the wrist. The FDP tendons are exposed and are divided more proximally towards the musculotendinous junction. The proximal FDS muscle-tendon units are then repaired en masse to the distal FDP tendons to provide a degree of tension. This works well in conjunction with wrist arthrodesis [22].

Release of the finger flexors may unmask swan neck deformities, particularly when the intrinsic muscles of the hand are spastic. An uncorrected wrist flexion posture has a tenodesis effect on the extensors, which is expressed by deformities at the PIP joint. In addition to rebalancing the flexor and extensor tension across the PIP joints, correction of unstable swan neck deformities is performed where there is incompetence of the volar plates [22, 29, 31].

Thumb in Palm: The "thumb-in-palm" deformity is variable and may include adduction of the first metacarpal, flexion at the metacarpophalangeal (MP) joint and either flexion or extension at the IP joint. Many children have hyper-extendable MP joints, and, with adduction of the metacarpal, this leads to a swan neck-type deformity of the thumb [22, 31]. This is managed with a release of adductor pollicis and the flexor pollicis brevis (FPB) from the flexor retinaculum. Release of the first dorsal interosseous and the overlying fascia is also frequently required. A contracted first web space may be corrected by Z-plasty or "square flap". Instability of the thumb MP joint can be corrected by arthrodesis of the radial sesamoid of the thumb to the underlying metacarpal [22]. Re-routing the EPL to the volar side of the wrist makes it an abductor, rather than an adductor of the thumb. EPL function can be augmented by transferring palmaris longus. An opponensplasty using the FDS to the ring or middle fingers can provide functional correction of a thumb-in-palm deformity [22, 29].

Surgical Results: The efficacy of surgery is supported by multiple studies, including improvements in House scale, grasp and release, self-care, grip strength and dexterity. Satisfaction with both functional and cosmetic outcomes by both children and caregivers is generally high [28–32]. The literature has generally reported the outcomes of specific therapeutic approaches such as CIMT, motor training or injections of botulinum toxin A compared to a control group or placebo [12–15, 17, 18]. The first high-quality, comparative study to compare therapy, botulinum toxin injections and upper limb surgery was by Van Heest and colleagues in 2015 [33]. This was a study of 39 children with CP and upper limb involvement, who met standard criteria for soft tissue surgery to the upper limb. Children were allocated to treatment group randomly (n = 29) or by patient/family preference (n = 10). Assessment measures included active ROM, pinch and grip strength, stereognosis and a total of eight functional or patient-orientated outcome measures. For the primary outcome of the Shriner's Hospital Upper Extremity Evaluation (*SHUEE*), significantly greater improvement was seen in the surgical group, compared to therapy or injections of Botox ($p < 0.001$). Improvements in the PedsQL, COPM and pinch strength were also greater in the surgical group. This study is of great importance to patients, parents, caregivers and clinicians responsible for counselling and referring children for appropriate management [33].

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22 Integrated Management in Cerebral Palsy: Musculoskeletal Surgery and Rehabilitation in Ambulatory Patients

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Abstract

In this chapter, current treatment concepts for ambulatory children with cerebral palsy (CP) will be introduced and discussed. The Gross Motor Function Classification System (GMFCS) was the first of the family of classification systems, which have given clinicians a common language with which to communicate about cerebral palsy.

In 1987 Winters et al. classified the sagittal gait patterns in unilateral spastic CP (USCP or spastic hemiplegia) in a cross-sectional study, based on three-dimensional kinematics. Rodda and Graham extended the Winters, Gage and Hicks classification to include the coronal and transverse planes. Classification of sagittal gait patterns in bilateral spastic CP (BSCP) is also useful to guide integrated management including the selection of target muscles for injection of botulinum toxin A, the choice of ankle-foot orthoses and surgical procedures in single-event multilevel surgery (SEMLS). In the SEMLS approach, the gait pattern is identified and evaluated by instrumented gait analysis (IGA) as part of the diagnostic matrix. A comprehensive plan is then developed for the correction of all muscle-tendon contractures, torsional malalignments and joint instabilities in one operative session. Rehabilitation requires at least 1

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year, and improvements continue into the second year postoperatively. In non-ambulatory children with CP, spine problems such as scoliosis and hip dislocation are the most important problems to deal with.

22.1 Introduction

The 2006 definition of cerebral palsy (CP) emphasises a number of issues, which are critical to integrated management [1]. Although the cerebral lesion is a *static encephalopathy*, the *secondary musculoskeletal problems* are progressive. The purpose of this chapter is therefore to provide an integrated view of the musculoskeletal management of children with CP from soon after diagnosis until skeletal maturity. In the early part of this timeframe, there is a *dynamic phase* characterised by spastic hypertonia, without fixed contractures. Later, this gradually changes to a *fixed stage* characterised by progressive musculoskeletal pathology, including contractures, bony torsion and joint instability (Fig. 22.1). This stage is often accompanied by musculoskeletal pain and decreased quality of life [2]. During the early, dynamic phase, gross motor function is increasing, and during the later fixed stage, gross motor function has reached a plateau or is decreasing ([3, 4], Fig. 22.2).

22.2 Classification System

The Gross Motor Function Classification System (*GMFCS*) was the first of the family of classification systems, which have given clinicians a common language with which to communicate about CP [5, 6]. As a classification system for gross motor function in children with CP, the GMFCS can be used alongside the classification of bimanual upper limb function (the Manual Ability Classification System, *MACS*) and communication function (Communication Function Classification System, *CFCS*) [7]. The popular illustrations, which we developed to illustrate the GMFCS, have become controversial. Parents of children with severe CP have expressed justifiable concern about the negative connotations of the GMFCS V illustrations due to their focus on activity limitations. Following a consultation process involving parents of children with CP, young adults with cerebral palsy and clinicians from a wide range of backgrounds, revised illustrations have been developed for children aged 6–12 years (Fig. 22.3) and for children aged 12–18 years

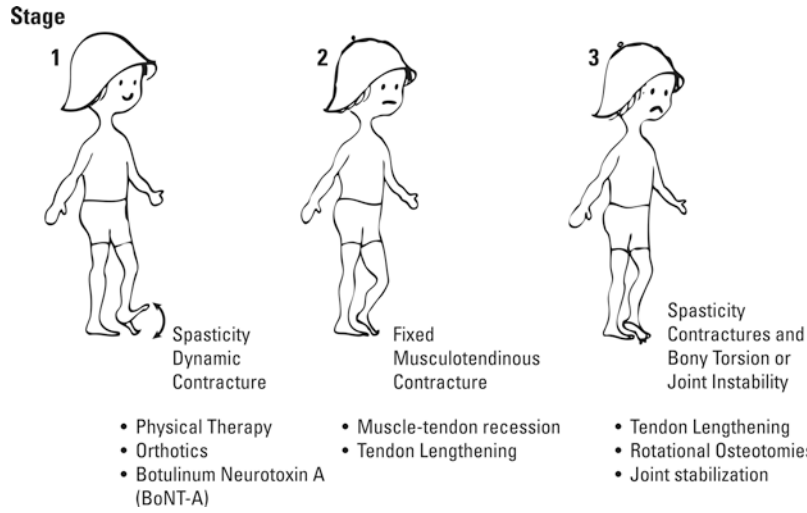

Fig. 22.1 Musculoskeletal pathology in children with cerebral palsy is progressive. At stage 1, children have spasticity but no fixed contractures and should be managed nonoperatively. At stage 2, there are fixed contractures and at stage 3 contractures and bony deformities which usually require corrective orthopaedic surgery

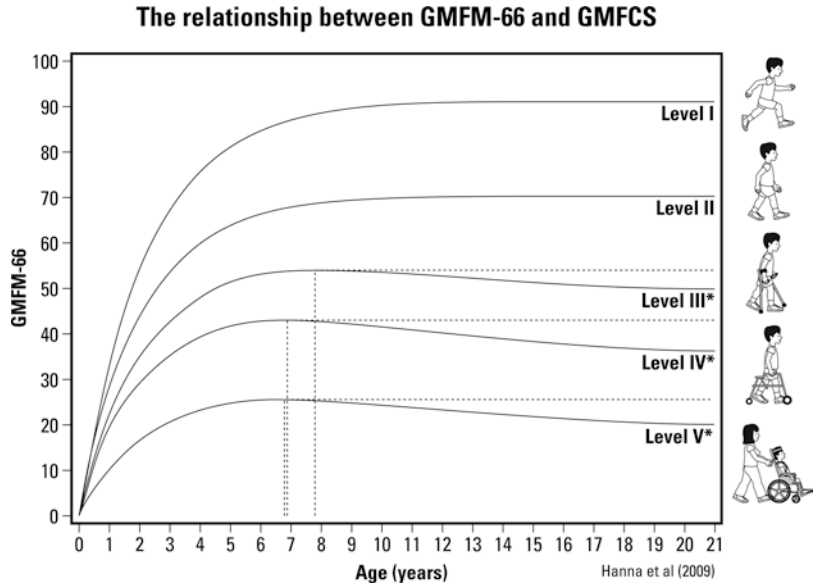

Fig. 22.2 Gross motor curves in children with cerebral palsy and the five levels of the Gross Motor Function Classification System (*GMFCS*) modified from Hanna et al. [3]. Note that gross motor function deteriorates with age at GMFCS levels III, IV and V

(Fig. 22.4). The revised illustrations emphasise the gross motor abilities of children who function at GMFCS levels IV and V, and we recommend replacement of the original illustrations with the revised versions which are available from the CanChild website (https://www.canchild.ca/en/resources/42-gross-motor-function-classification-system-expanded-revised-gmfcs-e-r).

The combination of motor growth curves [4] and GMFCS provides a framework for understanding long-term prognosis, goal setting and clinical management strategies. For example, a child who is functioning at GMFCS level II, aged 18 months, is pulling to stand but not walking independently. Progress may be hindered by dynamic equinus. Injections of botulinum toxin A (*BoNT*-A) are administered to the gastrocnemius muscles. Foot-flat position is achieved, and soon afterwards the child commences independent walking [8, 9]. Whilst the injections may have been of benefit, the child is on the upswing of their gross motor curve, and major gains could have been anticipated as part of the natural history of spastic diplegia (see Fig. 22.2). In another example, a child classified at GMFCS level IV, aged 6 years, may perform some standing and walking with an adapted walker under the supervision of a parent or physiotherapist (see Fig. 22.3). However, following the pubertal growth spurt, functional walking is rarely sustained. It would therefore usually be inappropriate to offer invasive surgical management to improve or prolong walking because such interventions are unlikely to be successful in the long term. More appropriate functional goals would be to prevent hip dislocation, ensure comfortable sitting and, when possible, preserve standing transfers [10].

The GMFCS has strong predictive values in other areas of musculoskeletal management, including the prediction of the risk of hip displacement and the shape of the proximal femur [11, 12]. The GMFCS also is a strong predictor of the success (or failure) of interventions for hip displacement such as injection of the adductor muscles with botulinum toxin A, adductor release surgery and bony reconstructive surgery [13–16].

The GMFCS is a categorical system and generally remains stable throughout childhood. However, changes in GMFCS level sometimes happen, and these may occur in either direction, i.e. improvement or deterioration. After a major intervention such as selective dorsal rhizotomy (*SDR*) or single-event multilevel surgery (*SEMLS*), a small number of children move up a level. This is uncommon and should not be expected in more than 5–10% of children [17].

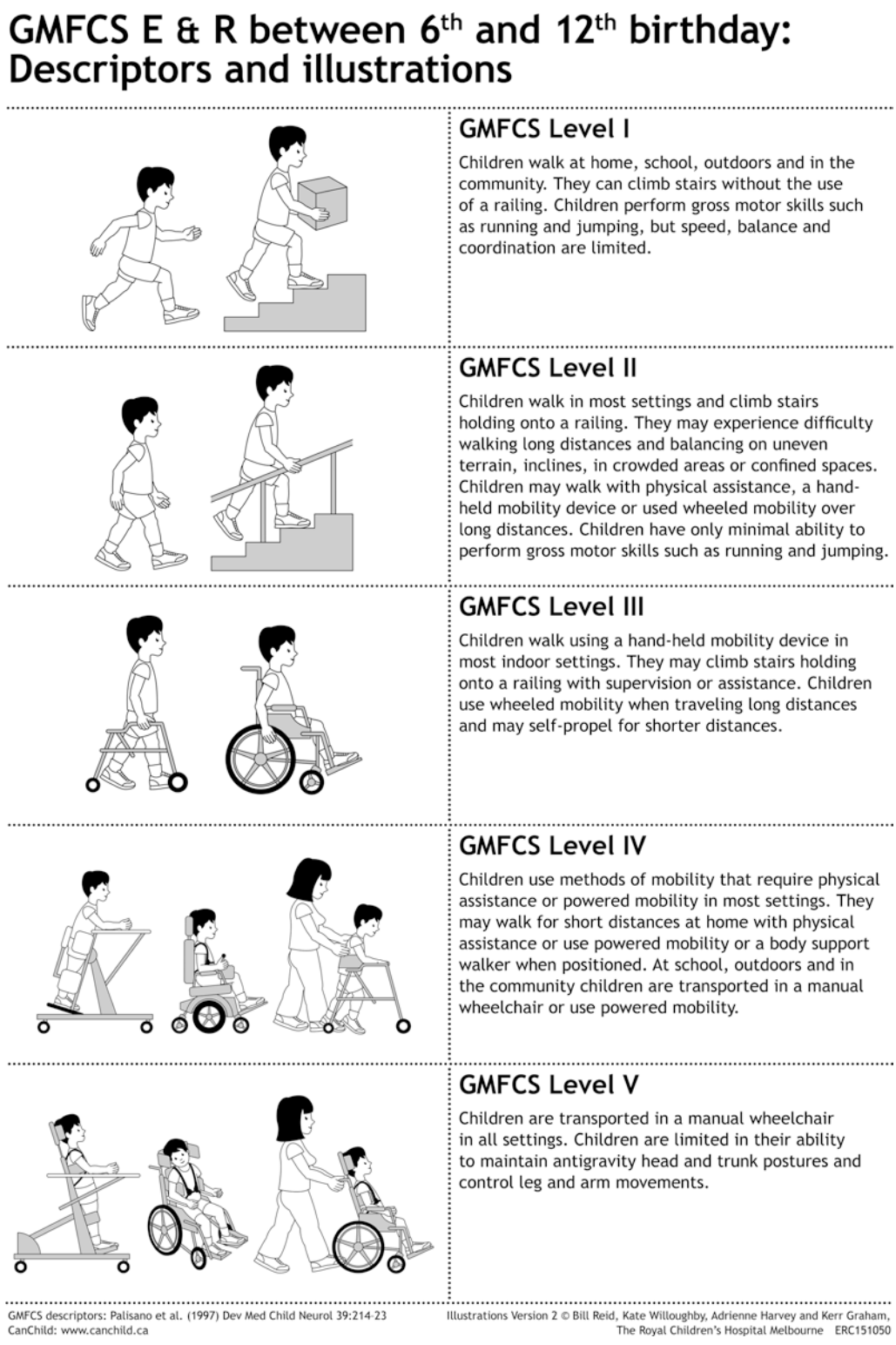

Fig. 22.3 GMFCS age 6–12 years: GMFCS E & R (expanded and revised) between 6th and 12th birthdays. Descriptors and illustrations. These are the new, preferred version (© Reid, Willoughby, Harvey and Graham, The Royal Children's Hospital, Melbourne)

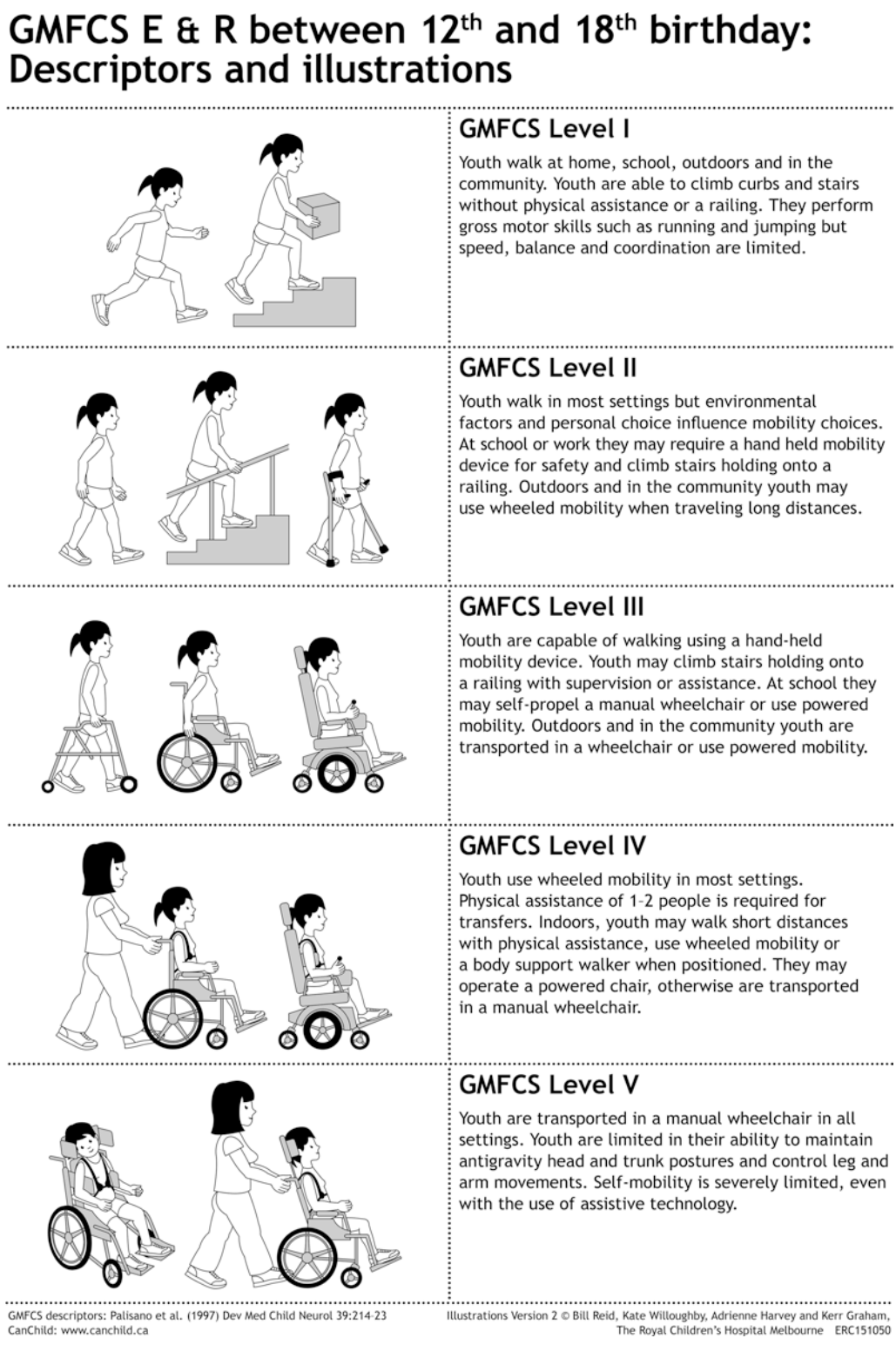

Fig. 22.4 GMFCS age 12–18 years: GMFCS E & R (expanded and revised) between 12th and 18th birthdays. Descriptors and illustrations. These are the new, preferred version (© Reid, Willoughby, Harvey and Graham, The Royal Children's Hospital, Melbourne)

Deterioration in GMFCS level is more common. For example, isolated lengthening of the *Achilles* tendons for toe walking in children at GMFCS level II can result in progressive crouch gait and the need for assistive devices, i.e. a change from GMFCS II to GMFCS III [18].

22.3 Sagittal Gait Patterns in Unilateral Spastic Cerebral Palsy (USCP, Spastic Hemiplegia)

In 1987 Winters, Gage and Hicks classified the sagittal gait patterns in unilateral spastic CP (*USCP* or spastic hemiplegia) in a cross-sectional study, based on three-dimensional kinematics [19]. Rodda and Graham extended the Winters, Gage and Hicks classification to include the coronal and transverse planes ([20], Fig. 22.5). The Winters, Gage and Hicks classification is a useful guide for the integrated management of children with USCP including the use of botulinum toxin injections (which muscles to target) and the type of ankle-foot orthoses (*AFOs*) to guide surgery when children develop fixed deformities (see Figs. 22.1 and 22.5).

22.3.1 Type I Hemiplegia

In type I hemiplegia, there is a foot drop in the swing phase of gait on the affected side. This is due to loss of selective motor control or weakness in tibialis anterior. There is no contracture of the gastrocsoleus, and second rocker in gait is relatively normal.

22.3.2 Type II Hemiplegia

In type II hemiplegia, there is foot drop in swing phase but there is also equinus during stance phase. There is spasticity in the gastrocsoleus, which gradually becomes fixed resulting in an equinus contracture. There can also be equinovarus or less commonly, equinovalgus.

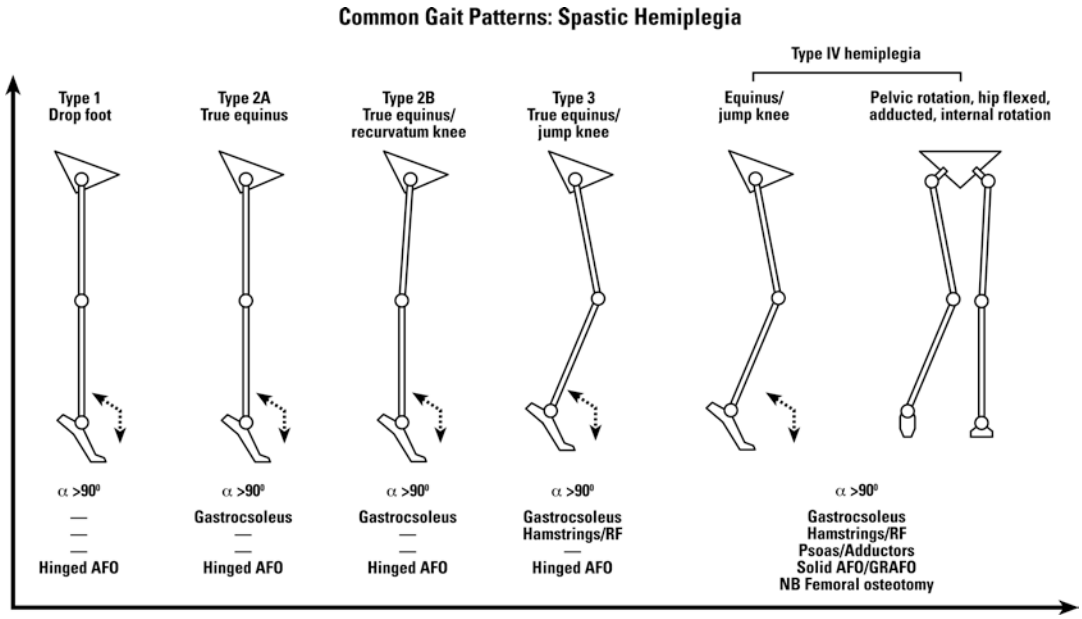

Fig. 22.5 Common gait patterns: spastic hemiplegia (unilateral spastic cerebral palsy (USCP)). Gait patterns and management algorithm spastic hemiplegia. ©Rodda and Graham, Royal Children's Hospital, Melbourne, Australia (2001). Modified after Winters, Gage and Hicks (1987)

22.3.3 Type III Hemiplegia

In type III hemiplegia, involvement moves proximally to include the knee as well as the ankle level. There is equinus at the ankle and a reduced range of motion at the knee with co-contraction of the hamstrings and rectus femoris. This subtype is not common.

22.3.4 Type IV Hemiplegia

In type IV hemiplegia, involvement moves proximally to include the hip, as well as the knee and ankle. It also extends from the sagittal plane into the coronal and transverse planes. There is equinus at the ankle, a flexed, stiff knee and involvement at the hip, with incomplete hip extension. In the coronal plane, there is excessive hip adduction and, in the transverse plane, excessive internal rotation and ipsilateral pelvic retraction. Contractures are present at the ankle (*equinus*), knee (*flexion deformity*) and hip (*adduction and flexion*). There is usually an increased femoral neck anteversion (*FNA*) on the affected side, which contributes to hip dysplasia [21]; see Fig. 22.5.

22.4 Sagittal Gait Patterns: Bilateral Spastic CP (BSCP, Spastic Diplegia)

Classification of sagittal gait patterns in BSCP is also useful to guide integrated management including the selection of target muscles for injection of botulinum toxin A, the choice of ankle-foot orthoses and the surgical procedures in single-event multilevel surgery (*SEMLS*) ([20], Fig. 22.6).

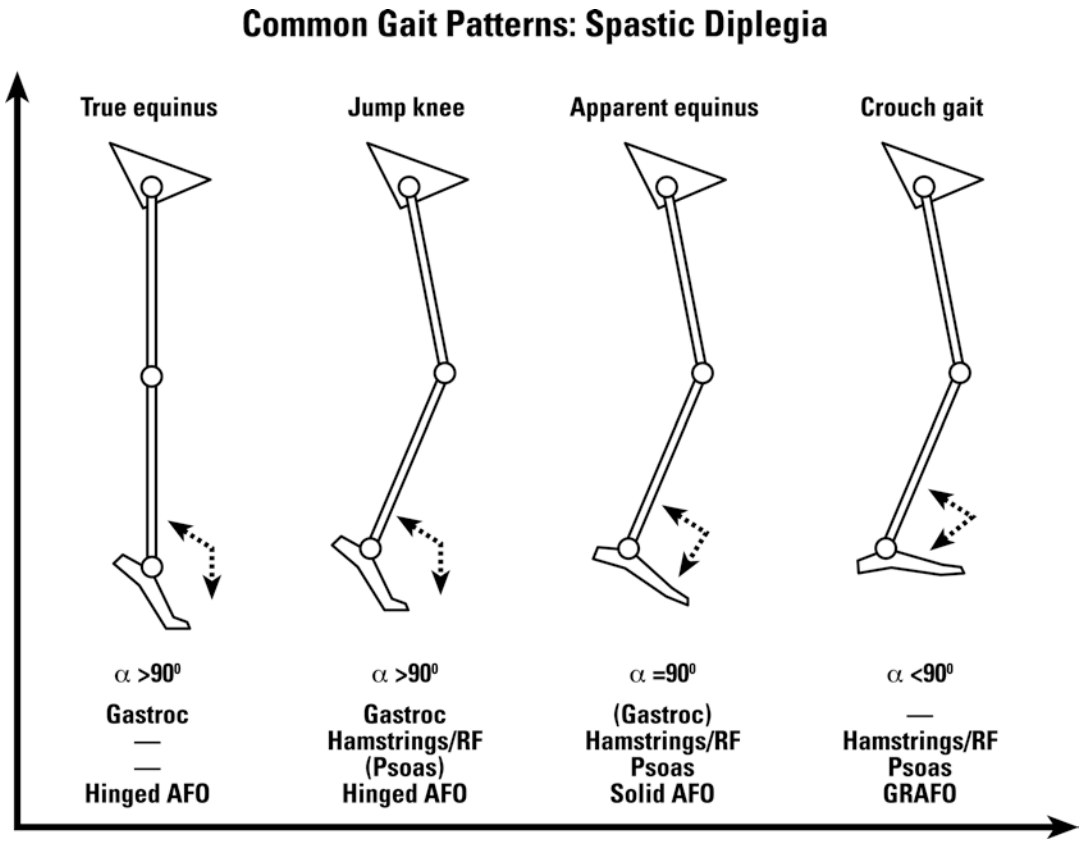

Fig. 22.6 Common gait patterns: spastic diplegia (bilateral spastic cerebral palsy (*BSCP*)). Gait patterns and management algorithm spastic diplegia (©Rodda and Graham, Royal Children's Hospital, Melbourne, Australia (2001))

22.4.1 True Equinus

True equinus is characterised by the child walking on tiptoes with the knees and hips extended. It is commonly seen in younger children with BSCP when they first learn to walk. The plantar flexion-knee extension couple is overactive, and the ground reaction force (*GRF*) is in front of the knee throughout the stance phase of gait.

22.4.2 Jump Gait

Jump gait is characterised by equinus associated with incomplete extension at the knee and hip in late stance. There is usually excessive knee flexion at initial contact with rapid extension in later stance to a near-normal range. In other children, there is more severe knee flexion throughout stance, combined with incomplete hip extension. This is the most common pattern in the preadolescent.

22.4.3 Apparent Equinus

Apparent equinus is characterised by the toe walking but with near-normal ankle range of motion. There is flexion present at the knees and hips. The recognition of *apparent equinus* in contradistinction to *true equinus* is very important to avoid inappropriate lengthening and weakening of the gastrocsoleus. Apparent equinus is due to spasticity and contractures at the knee and hip levels. Instrumented gait analysis (*IGA*) is very helpful in differentiating "apparent equinus" from *true equinus*. The "apparent equinus" pattern is often transitional. With further growth and progression of lever arm deformities, the majority of children will develop *crouch gait* [20].

22.4.4 Crouch Gait

Crouch gait is characterised by excessive knee flexion in stance phase, increased flexion at the hip and excessive ankle dorsiflexion (*calcaneus*). Knee stiffness in swing is common. The soleus is excessively long and usually weak. This is a very common gait pattern in adolescence and may be part of the natural history of bilateral spastic CP but is more often caused by isolated tendon Achilles lengthening (TAL) [18, 22–24]. A key feature of crouch gait is that the majority of muscle-tendon units (*MTU*) are excessively long. This is by definition true for all of the one-joint muscles such as the soleus, vasti and gluteus maximus and often for the two-joint hamstrings. The only consistent contractures are of the iliopsoas. In crouch gait, the hamstrings are short only in patients with a posterior pelvic tilt. When the pelvis is in the neutral range, the hamstrings are of normal length, and when the pelvis is anteriorly tilted, the hamstrings are excessively long. Without the use of IGA and the modelling of muscle lengths, it is very difficult to appreciate these findings. The popliteal angle is decreased; the hamstrings feel tight and are often incorrectly assumed to be short [18].

22.5 Functional Assessment of Children with CP During Childhood

Systematic, longitudinal assessment of children with CP has shown to be effective in preventing progression of contractures, preventing hip displacement and optimising management. The best known example of this approach is the Swedish CPUP programme. It is beyond the scope of this chapter to deal with assessment in detail, and the reader is referred to appropriate sources [25].

The World Health Organization (*WHO*) describes health conditions in several domains, including body structure and function, activities and participation ([26], ICF, International Classification of Functioning). These domains are influenced by both environmental and personal factors. Some of the important tools which we employ routinely in both clinical and research settings include the GMFM, measures of joint range of motion and muscle strength, along with measures of hypertonia including the Modified

Ashworth Scale (*MAS*) and the Barry-Albright Dystonia (*BAD*) Scale. Functional scales include the Functional Mobility Scale (*FMS*) and the Functional Assessment Questionnaire (*FAQ*). Generic scales such as the Child Health Questionnaire (*CHQ*) and the CP-specific scales such as the Cerebral Palsy Quality of Life (*CPQOL*) questionnaire and the Pediatric Quality of Life Inventory (*PedsQL*) are also very useful [27, 28]; for more see Chap. 34. Some CP-specific scales have been designed for ambulant children (*GOAL*™) and others for non-ambulant children (*CPCHILD*™) [29]. Serial radiological monitoring of hip displacement (*hip surveillance*) using plain radiology has now been well established and accepted in many parts of the world. For ambulant children, a comprehensive biomechanical assessment using all components of the diagnostic matrix, as described by Davids and colleagues [30] (Fig. 22.7), is utilised. These include three-dimensional gait analysis (3DGA) including kinematics, dynamic EMG and energy cost of walking.

22.6 Botulinum Toxin A (BoNT-A), Musculoskeletal Surgery, Orthoses and Rehabilitation

Children with CP have fixed deformities at birth, but with time, and despite optimal nonoperative management, the majority of children develop a complex mixture of hypertonia, weakness, impaired selective motor control, contractures of muscle-tendon units, bony torsion and joint subluxation (especially the hip and midfoot) [2]. This process occurs slowly and continuously throughout childhood although it may speed up during periods of rapid growth, e.g. the pubertal growth spurt. For these reasons, we propose a musculoskeletal management algorithm for children and adolescents with cerebral palsy. In the early phase, the emphasis is on the management of spastic hypertonia or dystonia by nonoperative methods (see Fig. 22.1). During this phase, the only surgery is for the prevention of hip displacement. Equally, it is not logical or effective to continue with injections of BoNT-A throughout childhood once the musculoskeletal pathology becomes fixed. Age 6–12 years is the optimal period for single-event multilevel surgery for the one-stage correction of all fixed deformities and contractures to stabilise or improve gait and functioning for the second decade and beyond (Fig. 22.8 [27, 28]).

Although there are many other methods for the management of both spasticity and dystonia, the injection of BoNT-A, *Botox*, followed by orthopaedic surgery is the most frequently used combination. Methods of treating generalised hypertonia include selective dorsal rhizotomy (SDR) and intrathecal baclofen (*ITB*); for more see Chaps. 24 and 25. These interventions are used for carefully selected groups of children, and this has been discussed in detail elsewhere [7, 25].

22.6.1 BoNT-A in the Management of the Lower Limb in Younger Children with CP

Injection of the skeletal muscle with BoNT-A results in a dose-dependent, reversible chemodenervation by blocking presynaptic release of acetylcholine at the neuromuscular junction. The binding of BoNT-A to receptors at the neuromuscular junctions of the target muscle is rapid, and little systemic spread of neurotoxin occurs. Neurotransmission is restored by sprouting of new nerve endings, and these are eliminated at about 3 months when the original nerve endings regain their ability to release acetylcholine [31]. BoNT-A may be useful in children with CP to manage dynamic gait problems and to delay the need for orthopaedic surgery until the child is older [7]. The most common indication for BoNT-A therapy in ambulatory children with CP is the injection of the gastrocsoleus for spastic equinus [9]. Before the widespread use of BoNT-A for spastic equinus, the majority of children with CP who walked on their toes had a lengthening of their Achilles tendons when they were very young. This resulted in progressive crouch gait, which was much more disabling than the original equinus gait [24]. A nonoperative

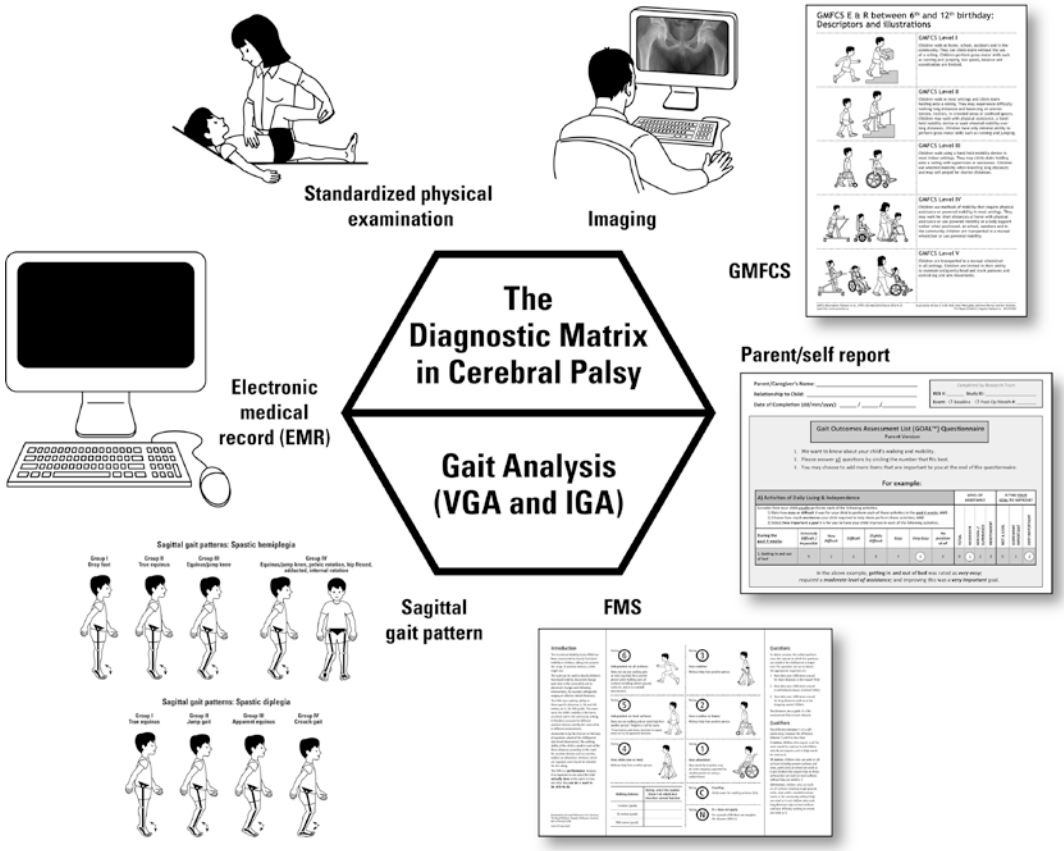

Fig. 22.7 Diagnostic matrix: The diagnostic matrix consists of a standardised approach to clinical history, physical examination, radiology, functional scales (*FMS* and *FAQ*) and sagittal gait pattern identification. These components can be used in conjunction with either video gait analysis (VGA) or instrumented gait analysis (*IGA*)

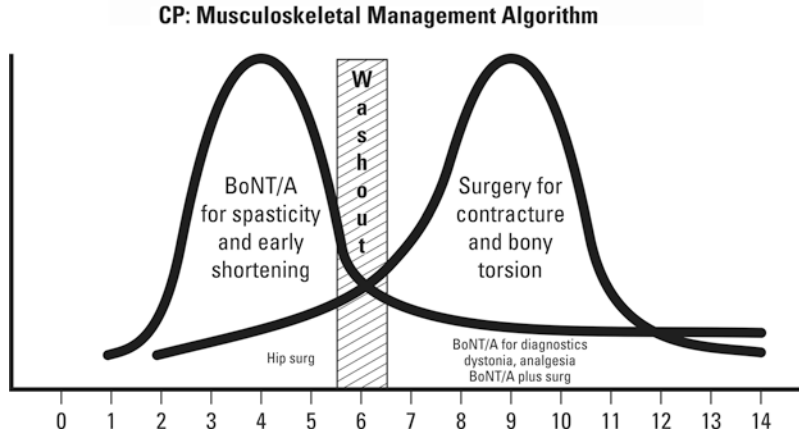

Fig. 22.8 CP: musculoskeletal management algorithm, neurolytic blocks, botulinum neurotoxin A (*BoNT*-A) and phenol are used in younger children with spasticity. Under the age of 6 years, the only surgery required is preventive hip surgery. Surgery for contracture and bony torsion is most often required between the ages of 6 and 12 years by which stage the role of botulinum toxin is very limited

programme of care utilising BoNT-A should be viewed as complementary to orthopaedic surgical reconstruction and not as an alternative. Information about dosing, dilution, muscle targeting and safety have been published elsewhere [8, 9, 32].

Injection of BoNT-A for spastic equinus increases the dynamic length of the gastrocsoleus with improvements in ankle dorsiflexion during gait, as determined by the Physician's *Rating* Scale (PRS, [8, 33, 34]). Improvements have been reported in studies using instrumented gait analysis, including kinematics and electromyography [35]. This may lead to minor, temporary improvements in gait but not in gross motor function. The evidence base supporting the use of BoNT-A in CP is quite good as confirmed in several randomised controlled trials and systematic reviews. However, the treatment effect size is very small and temporary [35–37].

In non-ambulant children with CP, BoNT-A can reduce adductor and hamstring spasticity but does not increase gross motor function nor prevent hip displacement [13, 16]. Given that parents and therapists can reliably recognise the effects of BoNT-A injection, randomised clinical trials (*RCT*s) of BoNT-A cannot be double-blinded and are therefore confounded by placebo effects [38]. Improvements in pain and ease of care in non-ambulant children are equivalent to placebo [39].

22.6.2 BoNT-A and Adverse Events in Children with CP

BoNT-A is generally safe in ambulant children with CP. Most adverse events are localised, minor and self-limiting [9]. Systemic side effects including temporary incontinence and weakness have been reported. In non-ambulant children, BoNT-A carries significant risks, leading to the requirement for a "black box warning" from the Food and Drug Administration (FDA). Dysphagia, aspiration and respiratory infections are the most serious complications after injection of BoNT-A in children at GMFCS IV and V. If unrecognised or inadequately treated, death from aspiration and asphyxia may occur [7, 32]. Recent concerns from studies in animal models and from clinical studies in children have also raised concerns about denervation atrophy [40]. The *mechanism* of action of BoNT-A dictates that a clinically successful injection will be followed by a period of muscle weakness and muscle atrophy. The duration of atrophy and the long-term implications for muscle growth and function have not been fully studied. In adolescents, the management of weakness is a much greater challenge than the management of spasticity, in GMFCS levels II and III [41]. Until the long-term implications of denervation atrophy are more clearly understood, it is prudent to limit the use of BoNT-A in the antigravity muscles of ambulant children with CP. Both the dose and frequency of injections should be reduced to the absolute minimum required to achieve the desired functional goals. Two recently published RCTs have shown that injection once in any 12-month period is as effective as injection three times per year [42, 43]. Injection once every 12 months is associated with reduced costs, improved safety and reduced denervation atrophy.

22.6.3 BoNT-A as an Analgesic Agent in CP

BoNT-A can be used to treat muscle spasm following operative procedures, such as adductor release surgery. Injection of BoNT-A can be useful for short-term relief of pain associated with hip displacement. Target muscles include the hip adductors, medial hamstrings and hip flexors. Pain relief is associated with a decrease in spastic adduction and scissoring postures [44]. Some children with neglected hip displacement have limited life expectancy and may not survive salvage surgery. BoNT-A may provide useful palliation in such circumstances. Better still is to prevent painful hip displacement [45].

22.6.4 BoNT-A as a Preoperative Test Before Muscle-Tendon Lengthening in CP

In 2010, Rutz et al. [46] described a preoperative BoNT-A test before muscle lengthening in children with CP. Muscle weakening is a well-known side effect of muscle-tendon lengthening. Hence, application of the drug is a logical step to test whether weakness deteriorates function prior to an operation. Functional deterioration, e.g. increased dorsiflexion at the level of the ankle and increased anterior pelvic tilt, was detected with 3DGA before surgery. In cases with deterioration (20.9% out of 110 children), the lengthening was not performed.

22.7 Principles of Surgical Management for Children with CP

Orthopaedic management of the lower limb for children with bilateral spastic CP used to start at the ankles with TALs for equinus gait and then moves up to the knee and then to the hip. Mercer Rang [22] caricatured this approach as the "birthday syndrome" (Fig. 22.9). Children spent most of their birthdays in hospital, in casts or in rehabilitation. The current concept for the management of musculoskeletal deformities is single-event multilevel surgery (*SEMLS*). A recent systematic review of SEMLS found evidence for large improvements in gait function, moderate improvements in health-related quality of life and small gains in gross motor function [47]. Since then, the evidence base has rapidly increased, and the first randomised clinical trial (*RCT*) of SEMLS reported a 50% improvement in gait function (*Gillette Gait Index*, GGI) and a 4.9% improvement in gross motor function measure (GMFM-66) [27]. The 5-year results of this clinical trial show that these improvements were largely maintained at 5 years post-SEMLS [28].

In the SEMLS approach, the gait pattern is identified and evaluated by IGA as part of the diagnostic matrix. It is necessary to consider all components of the matrix so that surgical planning is optimised for the individual child [30].

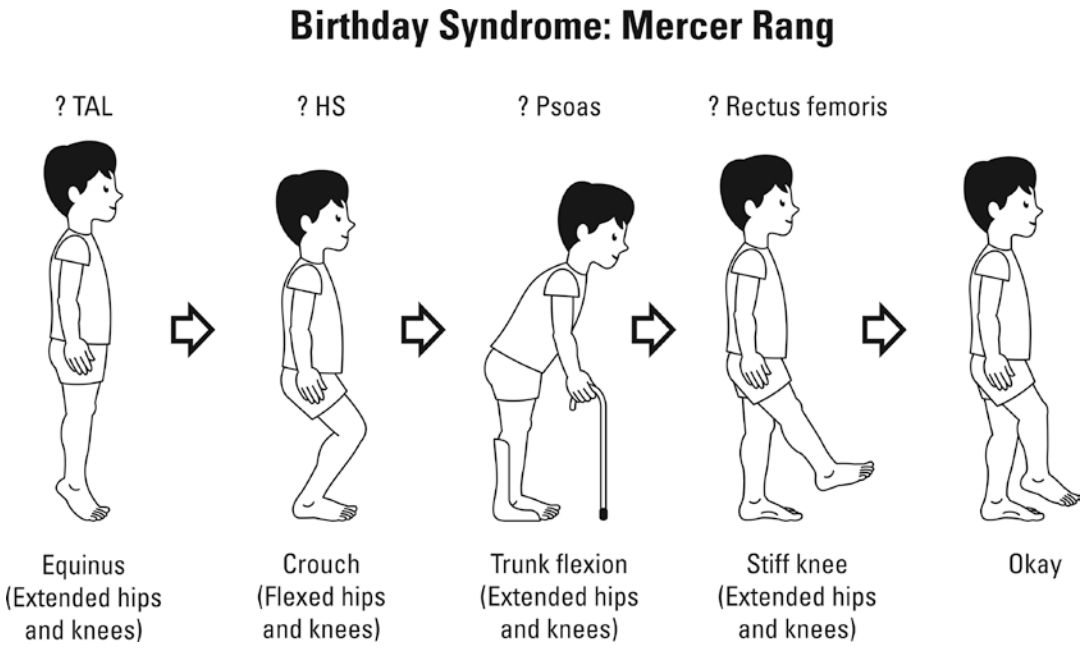

Fig. 22.9 Birthday syndrome: Mercer Rang. The birthday syndrome as described by Mercer Rang. In the younger child walking on tiptoe, surgery starts with bilateral lengthening of the Achilles tendons. This results in a combination of *foot flat* and crouch (increased knee flexion); lengthening of the hamstrings followed by the hip flexors is required. Finally rectus femoris transfer is performed for stiff-knee gait

For example, muscle weakness is an impairment which is easily overlooked and which may have a greater impact on energy cost of walking and function in the community than musculoskeletal deformities. It is also essential to consider the child in the context of the family, participation and psychological and environmental factors, which may have a major influence on surgical outcomes. It is important to have a frank discussion about the family and child's goals and aspirations. This requires a multidisciplinary approach with the involvement of the family and child, the rehabilitation team as well as community therapists. For a child at GMFCS level III, independent ambulation is rarely achievable, and it is essential to have these discussions before surgery and rehabilitation. A detailed examination of the child's level of activity and participation, using measures such as the Canadian Occupational Performance Measure, the Children's Assessment of Participation and Enjoyment or the Activities Scale for Kids [48, 49], may be useful.

It is crucial to distinguish between the needs of children and adolescents. The decision to proceed with SEMLS for younger children is largely made by their parents. However, adolescents must be given the freedom to make their own informed decisions regarding surgery and rehabilitation. Adolescents who feel that they have been forced into SEMLS against their will or without their full consent are likely to be resentful and may develop depression and struggle with rehabilitation. Careful preoperative discussions about setting realistic goals help to ensure that patient's, parents" and surgeon's goals are consistent and achievable [25]. The Gait Outcomes Assessment List (*GOAL*™) can be invaluable at this stage of surgical planning [50].

A comprehensive plan is then developed for the correction of all muscle-tendon contractures, torsional malalignments and joint instabilities in one operative session. Rehabilitation requires at least 1 year, and improvements continue into the second year postoperatively [25, 28].

The principal components of a successful SEMLS programme are as follows:

1. Planning based on the diagnostic matrix, including instrumented gait analysis
2. Preparation and education of the child and family
3. Optimal perioperative care, including epidural analgesia
4. Carefully planned and supervised rehabilitation
5. Appropriate orthotic prescription
6. Close monitoring of functional recovery
7. Follow-up gait analysis at 12–24 months after the SEMLS
8. Removal of fixation plates and other implants
9. Follow-up until skeletal maturity, for new or recurrent deformities [25, 51]

The surgical team should consist of two experienced surgeons and two experienced assistants. Expert anaesthesia and pain management are essential. Postoperative nursing care must be vigilant. The use of epidural analgesia carries risks of masking the signs of compartment syndromes and nerve stretch palsies. The surgery is a series of steps which correct deformity (Figs. 22.10 and 22.11). However, for 6–9 months after surgery, children are more dependent and less functional than they were prior to surgery. A child who walks into hospital with a typical CP gait pattern leaves hospital in a wheelchair with straighter legs but may be unable to walk independently for weeks or even months [28]. Only a carefully tailored and carefully monitored rehabilitation programme can ensure that the child will reach a higher level of function [27, 28].

The child may commence full weight bearing once they are comfortable a day or two after soft tissue surgery. Weight bearing can commence after 2–3 days if the child has had a femoral osteotomy with stable internal fixation such as stable, blade plates for femoral osteotomies ([52]; [53]) or after a maximum of 1–2 weeks if there has been more extensive reconstructive surgery at the foot-ankle level. Casts are only required after foot and ankle surgery. Removable extension splints may be used at the knee level after hamstring-rectus surgery. The goal is to achieve full extension of the knee, combined with regaining full flexion, so that the transferred rectus

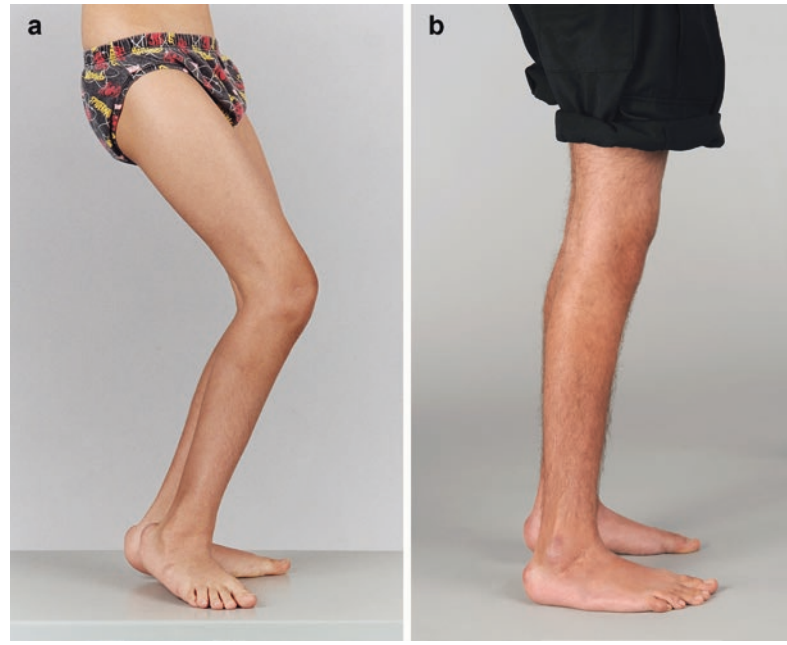

Fig. 22.10 Musculoskeletal pathology in a 10-year-old boy with bilateral spastic CP, GMFCS level III in the sagittal plane, includes contractures of the two joint muscles, psoas, hamstrings and gastrocnemius [2]. (A) Before and (B) after single-event multilevel surgery (*SEMLS*), which included lengthening of the iliopsoas, lengthening of the medial hamstrings and gastrocnemius recession

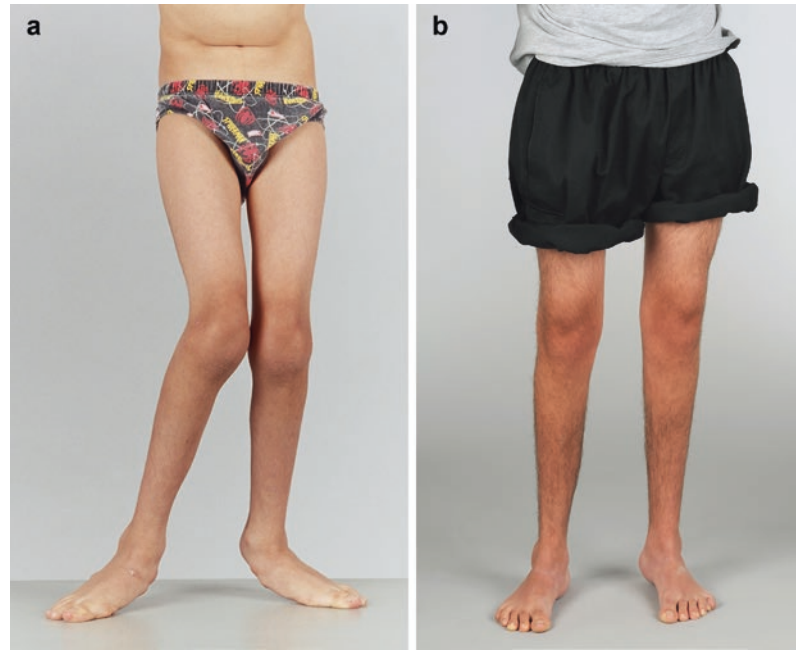

Fig. 22.11 In the same 10-year-old boy, there are bilateral pes valgus, external tibial torsion and increased femoral neck anteversion. (A) Before and (B) after bilateral foot stabilisation and bilateral femoral derotation osteotomy

femoris does not become scarred and adherent in its new site. New ankle-foot orthoses (*AFO*s) must be prepared for immediate fitting after cast removal, usually 6 weeks after surgery. The initial postoperative brace is usually a solid AFO. The orthotic prescription must be carefully monitored throughout the first year after surgery. A less supportive AFO, such as a hinged or posterior leaf spring, may be introduced when the sagittal plane balance has been restored and the plantar flexion-knee extension couple is competent. Functional recovery and orthotic

prescription can be monitored by a gait laboratory visit every 3 months for the first year after surgery and yearly thereafter. Our approach to SEMLS rehabilitation has been described in more detail elsewhere [25].

Surgical techniques continue to evolve with time including innovations such as shortening of antagonist at the same time as lengthening of the agonist. For example, Rutz and colleagues have reported improved results for the correction of equinus gait by shortening the tibialis anterior at the time of gastrocsoleus lengthening [54]. This is similar to the approach to crouch gait surgery in which the knee flexion deformity is corrected by supracondylar extension osteotomy (SEO) and the knee extensor lag is corrected by patellar tendon shortening (PTS) [23, 55]. Improved correction of pes valgus by osteotomies and fusions, which permit early mobilisation, is also critical to the long-term success of SEMLS in BSCP [56].

22.8 Management of Lower Limb in Unilateral Spastic CP (USCP) by Sagittal Gait Pattern

22.8.1 USCP Type I Hemiplegia

The principal impairment is a drop foot in the swing phase of gait. There is no contracture of the gastrocsoleus. Neither spasticity management nor musculoskeletal surgery is necessary. Gait and function can be improved by the use of an AFO, usually a leaf spring or a hinged AFO. The majority of teenagers prefer a less obtrusive in-shoe orthosis, which may not be biomechanically very effective. Extensive research is underway to develop an effective means to deliver phasic electrical stimulation to the ankle dorsiflexors during gait to obviate the need for an orthosis to correct foot drop [57].

A *systematic* review of the effect of functional electrical stimulation (*FES*) on activity in children with CP identified five randomised trials, three reported statistically significant between-group differences in favour of FES compared with no FES. The authors concluded that the evidence suggests that FES is more effective than no FES but that it has a similar effect as activity training alone in CP [58].

22.8.2 USCP Type II Hemiplegia

In type II hemiplegia, there is spasticity in the gastrocsoleus which gradually becomes fixed resulting in a contracture and equinus gait. During early childhood, injection of the gastrocsoleus with BoNT-A can be effective especially when combined with occasional use of serial casting, physiotherapy and the use of a hinged ankle-foot orthoses (*HAFOs*). Injection of tibialis posterior can be helpful for spastic equinovarus. Tibialis anterior often contributes to spastic equinovarus, but injection of this muscle increases foot drop and is not advised [9].

Contractures develop insidiously in both gastrocnemius and soleus, and the majority of children with USCP show reduced response to BoNT-A injection by age 4 years. By age 6 years, the majority are completely unresponsive to BoNT-A injection. Persisting with injections, in the presence of a fixed contracture, serves only to increase muscle atrophy and is not advised [59].

Management requires correction of fixed contracture in the gastrocsoleus (to *correct second rocker*) and provision of an AFO (to provide heel strike, swing-phase clearance and appropriate prepositioning of the foot during pre-swing). With good nonoperative management, the degree of fixed contracture is often small and can be easily managed by a conservative Zone 2 lengthening of the gastrocsoleus conjoined tendon [60]. In recent years, studies have shown that shortening of the antagonist muscle may augment the benefits of lengthening of the agonist. Rutz et al. [54] have reported good outcomes from combined lengthening of the gastrocsoleus and shortening of the tibialis anterior.

The definitive surgical management of spastic equinovarus requires a combination of muscle-tendon lengthening procedures and tendon transfers. The most useful combination is the Rancho triad, gastrocsoleus recession, intramuscular lengthening of tibialis posterior and split transfer

to tibialis anterior [45, 59]. In younger children, pes valgus can be managed with an orthosis. In older children, os calcis lengthening may be required [56]. Surgical decision-making should be guided by three-dimensional gait analysis.

22.8.3 USCP Type III Hemiplegia

In type III hemiplegia, there is a contracture of the gastrocsoleus at the ankle plus knee involvement with co-contraction of the hamstrings and rectus femoris. In younger children with dynamic gait problems, the most appropriate target muscles for BoNT-A therapy are the gastrocsoleus and medial hamstrings. Injection of the rectus femoris, even when apparently indicated on clinical and kinematic grounds, is not successful [9]. When deformities become fixed at about age 6 years, children in this transitional group may benefit from lengthening of the medial hamstrings and rectus femoris transfer, in addition to gastrocsoleus lengthening and a hinged AFO.

22.8.4 USCP Type IV Hemiplegia

In type IV hemiplegia, all levels of the lower limb are involved, and there is involvement in the sagittal, coronal and transverse planes at the hip. Hip dysplasia is common and often presents late (see Fig. 22.5). During the dynamic phase, the appropriate target muscles for BoNT-A therapy may include the gastrocsoleus, the medial hamstrings, the hip flexors and the hip adductors. The response to BoNT-A injections is limited when there is excessive in-toeing, secondary to increased FNA.

Gait correction surgery in type IV hemiplegia requires unilateral SEMLS. Procedures include gastrocsoleus recession for equinus, medial hamstring lengthening and rectus femoris transfer for flexed, stiff knee gait and lengthening of the adductor longus and the psoas over the brim of the pelvis as well as a proximal femoral derotation osteotomy [19, 61].

Equinovarus deformities are variable in severity and more resistant to surgical correction than in bilateral spastic CP. In younger children with documented overactivity in the tibialis posterior, both intramuscular recession and split posterior tibial tendon (*SPOTT*) transfer are good options [59]. Ideally, this should be undertaken before deformities become fixed, thus avoiding the need for bony surgery. In children with documented overactivity in both the tibialis anterior and tibialis posterior, a combination of split anterior tibial tendon (*SPLATT*) transfer and intramuscular recession of the tibialis posterior gives good long-term results [59].

Early identification of hip displacement affords the best opportunity for correction during unilateral SEMLS [21]. However, a few teenagers with USCP present with symptomatic hip dysplasia during the second or third decade and require a pelvic osteotomy such as the Bernese periacetabular osteotomy (*PAO*).

22.9 Management of Bilateral Spastic CP (BSCP) According to Sagittal Gait Patterns (Fig. 22.6)

22.9.1 1. True Equinus

22.9.1.1 Sagittal Plane: Ankle Equinus, Knees and Hips Extended

True equinus can be managed in the younger child by injections of BoNT-A to the gastrocnemius, physiotherapy and the provision of hinged AFOs. Injection once every 12 months is as effective as injection every 4 months, with lower costs, fewer side effects and less denervation atrophy.

By the time children develop fixed contractures and require surgery, true equinus is rare. When it persists, there are usually occult contractures of the hamstrings and iliopsoas. Single level surgery (*gastrocsoleus lengthening*) is almost never the correct strategy in bilateral spastic CP, no matter how tempting it may appear on observational gait analysis. The correct strategy is a full biomechanical assessment, based on the diagnostic matrix and 3DGA [30, 62].

22.9.2 2. Jump Gait

22.9.2.1 Sagittal Plane: Ankle Equinus, Knees and Hips Incomplete Extension in Late Stance

During the early dynamic phase, the most frequent target muscles for BoNT-A therapy are the gastrocnemius, medial hamstrings and hip flexors. When the knees appear to be rubbing together, it is usually secondary to excessive internal hip rotation (*increased FNA*) and not adductor spasticity. There may be too many target muscles for safe BoNT-A management, and combined neurolytic therapy with 6% phenol and BoNT-A may be appropriate. A small number of children with BSCP and generalised spasticity may benefit from SDR rather than multilevel BoNT-A therapy. These are children who are between 3 and 6 years old, with generalised lower limb spasticity, good underlying strength and selective motor control, and who do not have fixed contractures or bony torsion. Selective dorsal rhizotomy (for more see Chap. 25) is a better option when the spasticity is severe, generalised and adversely affecting gait and function [7, 63].

Older child: This is the ideal time (6–12 years) for SEMLS. SEMLS is rarely needed before age 6 years. All surgery and rehabilitation should be completed before the child leaves primary school as teenagers do not cope well with SEMLS and rehabilitation [25].

Musculoskeletal pathology in bilateral spastic CP, GMFCS level II, includes increased femoral neck anteversion and contractures of the two joint muscles, psoas, hamstrings and gastrocnemius [2] (see Figs. 22.9 and 22.10)**.** There is usually pes valgus and in adolescents hallux valgus. There is sometimes excessive external tibial torsion resulting in lower limb malalignment. In asymmetric bilateral spastic CP, pelvic retraction may make clinical estimation of rotational malalignment during gait very difficult. *Occasionally* in bilateral spastic CP, varus may be present but is more apparent than real because of excessive FNA and *rollover varus*. If present, varus is usually mild and flexible.

22.9.3 3. Apparent Equinus

22.9.3.1 Sagittal Plane: Ankle Plantargrade, Knees and Hips Flexed

Many children with bilateral spastic CP who walk on their toes, never achieving heel contact, have an ankle range of motion close to the normal range [20]. Such children are at risk of inappropriate management with injections of BoNT-A to the gastrocsoleus or even worse, lengthening of the gastrocsoleus. The important contractures are more proximal, at the level of the knee and hip. The recognition of "apparent equinus" in contradistinction to "true equinus" is very important to avoid inappropriate injection or lengthening and weakening of the gastrocsoleus with further deterioration in gait and functioning. These children may require SEMLS at proximal levels, and 3DGA is essential for planning the appropriate surgical interventions.

22.9.4 4. Crouch Gait

22.9.4.1 Sagittal Plane: Excessive Ankle Dorsiflexion and Knee Flexion, Incomplete Hip Extension

Crouch gait is uncommon in younger children with BSCP, and the only consistent target muscle for BoNT-A therapy is the iliopsoas and occasionally the hamstrings. The provision of solid or ground reaction AFOs and a physiotherapy/strengthening programme is more important than interventions which may further weaken muscles.

In crouch gait, the iliopsoas is usually contracted. The hamstrings are short only in patients with a posterior pelvic tilt. When the pelvis is in the neutral range, the hamstrings are of normal length, and when the pelvis is anteriorly tilted, the hamstrings are excessively long. Without the use of motion analysis and the plotting of muscle lengths, it is very difficult to appreciate these findings [64]. Consequently the majority of children with crouch gait are managed by excessive hamstring lengthening to improve knee extension when in fact the hamstrings are of normal length

or excessively long. Such surgery results in increased anterior pelvic tilt which may lead to recurrent crouch, back pain and spinal instability (spondylolysis and spondylolisthesis) [18].

Severe crouch gait can be defined as knee flexion >30° throughout stance, with excessive ankle dorsiflexion and incomplete hip extension [20]. It can be part of the natural history of gait in bilateral spastic CP, but the majority of affected individuals have had lengthening of the *Achilles tendons* [23, 24]. There is often a delay between lengthening of the gastrocsoleus and the development of crouch gait. The *Achilles tendons* are often lengthened in children with bilateral spastic CP between the age of 3 and 6 years. It may take another 3–6 years before crouch gait becomes a significant functional problem, and it is often not until the adolescent growth spurt when the maximum deterioration in gait and functioning occurs. Instead of "growing up", the adolescent with progressive crouch gait "sinks down", with an inability to maintain an extension posture at the hip and knee during the stance phase of gait [24]. Contributing factors seem to be a progressive mismatch between the strength of the one-joint muscles contributing to the body support moment (gluteals, vasti and soleus) and increased demand because of rapid increases in height and weight at the pubertal growth spurt. This typically occurs in conjunction with progressive bony deformities known as *lever arm disease*. Around the time of the pubertal growth spurt, increasing patella alta (sometimes with fractures of the patella or avulsions of the inferior pole), increasing external tibial torsion and breakdown of the midfoot with severe pes valgus all contribute to increasing crouch, fatigue and decreasing ability to walk [2, 45]. Understanding the biomechanics of severe crouch gait has led to improved surgical management in recent years with the development of more effective techniques to achieve lasting correction [23, 65].

Management should be based on the findings of IGA, and the hamstrings should only be lengthened when found to be short. Surgery may include iliopsoas lengthening, semitendinosus transfer, distal femoral extension osteotomy, patellar tendon shortening and correction of pes valgus and external tibial torsion. Before skeletal maturity, growth plate surgery is an option to correct small, residual knee flexion deformities [49].

Flexed knee gait is another example of when agonist lengthening and antagonist shortening may be very effective. Knee extension may be regained by a combination of hamstring lengthening, semitendinosus transfer to the adductor tubercle and supracondylar extension osteotomy (*SEO*). The extensor lag may then be corrected by shortening of the knee extensor mechanism by patellar tendon shortening [55]. Correction of soft tissue contractures in the sagittal plane will most likely be accompanied by external rotation osteotomy of the femur and internal rotation osteotomy at the supramalleolar level of the tibia and fibula to correct malalignment (see Fig. 22.11).

22.10 Integrated Management of the Non-ambulant Child: GMFCS IV and V

Children with more severe brain injuries may have *hypotonia* in the first year of life, but this is often followed by severe, generalised *hypertonia*. The most common form of hypertonia may be spasticity, but dystonia is also common as is mixed tone or "spastic dystonia" [7]. Interventions for severe, generalised hypertonia include oral medications and ITB (for more see Chap. 24). The majority of children at GMFCS IV and V have medical comorbidities such as epilepsy, feeding difficulties, aspiration, respiratory disease, poor nutrition, constipation and poor bone health. Optimum management of such complex children requires an experienced multidisciplinary team [7].

Non-ambulant children spend less time in weight bearing and standing and more time in seated postures. Flexion deformities at the hip, knee and ankle frequently develop [2, 22]. In the early, dynamic phase, focal tone management with BoNT-A has a very small role, in combination with the use of orthoses, standing frames, good seating and a physiotherapy programme. Botulinum toxin A is not suitable for the

management of severe, generalised hypertonia, because the number of affected muscles is too great, the effects are very short lived and the risks of high doses of BoNT-A in children with aspiration and respiratory disease are high [32]. *Managing* ankle and foot deformities is important to allow bracing, to enable the child to wear typical footwear and to have their feet rest comfortably on the footplate of a wheelchair. Correction of severe external tibial torsion by supramalleolar osteotomy of the tibia may be necessary [66]. Where children are able to participate actively in standing transfers, achieving stable and pain-free feet and ankles can be important. Stabilisation of the foot for pes valgus is more reliably achieved by a subtalar fusion than by os calcis lengthening [56]. Correction of hallux valgus and dorsal bunion by soft tissue balancing and fusion of the first metatarsophalangeal joint are effective for deformity correction, pain relief and comfortable shoe wear [67].

22.11 Hip Problems in Children with CP (See Chap. 19)

Children with CP rarely have dislocated hips at birth. Hip displacement progresses slowly in the first few years of life until the migration percentage reaches about 50% (see Chap. 19). Thereafter, displacement proceeds more rapidly, and the majority of the hips become painful [68–70], and the risk of developing progressive hip problems is very high for non-ambulant children. Even small increases in hip displacement, as determined by serial measurement of the migration percentage of Reimers, is associated with measurable decreases in Health Related Quality of Life (HRQol) [71]. Hip *displacement* may be managed by preventive or reconstructive surgery or, for many children, a combination of both (see Fig. 22.12, [72, 73]). *Preventive* surgery aims to facilitate proximal femoral and acetabular development by correcting adduction and flexion contractures.

Postoperatively, analgesia and muscle relaxants can assist in managing pain. A *broomstick* or "A" frame cast is often used to maintain the child's legs in abduction and can complement pain management strategies. Children can, and should, be encouraged to continue with many daily activities whilst wearing the plaster, including prone lying, long sitting and supported standing. The *majority* of these children will need bony reconstructive surgery, 2–10 years after preventive surgery.

The *most* common indication for reconstructive surgery is a persistently high migration percentage after adductor surgery. If the migration percentage remains >40%, at >12 months after adequate adductor releases, and the child is >4 years with little or no degenerative changes, reconstructive surgery is indicated [73, 74]. Nutrition and respiratory (see Chaps. 30 and 32) status should be optimised before embarking on any major surgery, especially bilateral hip surgery. It is also important to optimise tone management prior to salvage surgery as the surgery is much easier to perform when global tone is reduced.

Reconstructive surgery consists of three main components: adductor release, femoral osteotomy and pelvic osteotomy ([69], see Fig. 22.12). Firstly, abduction range is restored by a revision adductor release. Correction of the shape of the femur is achieved by varus derotation osteotomy of the proximal femur. Stable internal fixation is achieved by using a fixed-angle blade plate, avoiding the need for a hip spica in most children. Significant acetabular dysplasia should be corrected by a San Diego pelvic osteotomy, and older children and teenagers may benefit from a periacetabular osteotomy [69, 75].

After reconstructive surgery, there are no restrictions to weight bearing or movements of the hips, apart from consideration of the child's level of comfort. Blade plates are usually removed about 12 months after surgery. Pain is prevented or relieved and sitting tolerance is usually dramatically improved. Radiological monitoring of hip development should continue at least until skeletal maturity.

Pain following neglected hip displacement is reported to occur in between 10 and 90% of adolescents and young adults [70]. Fixed deformity,

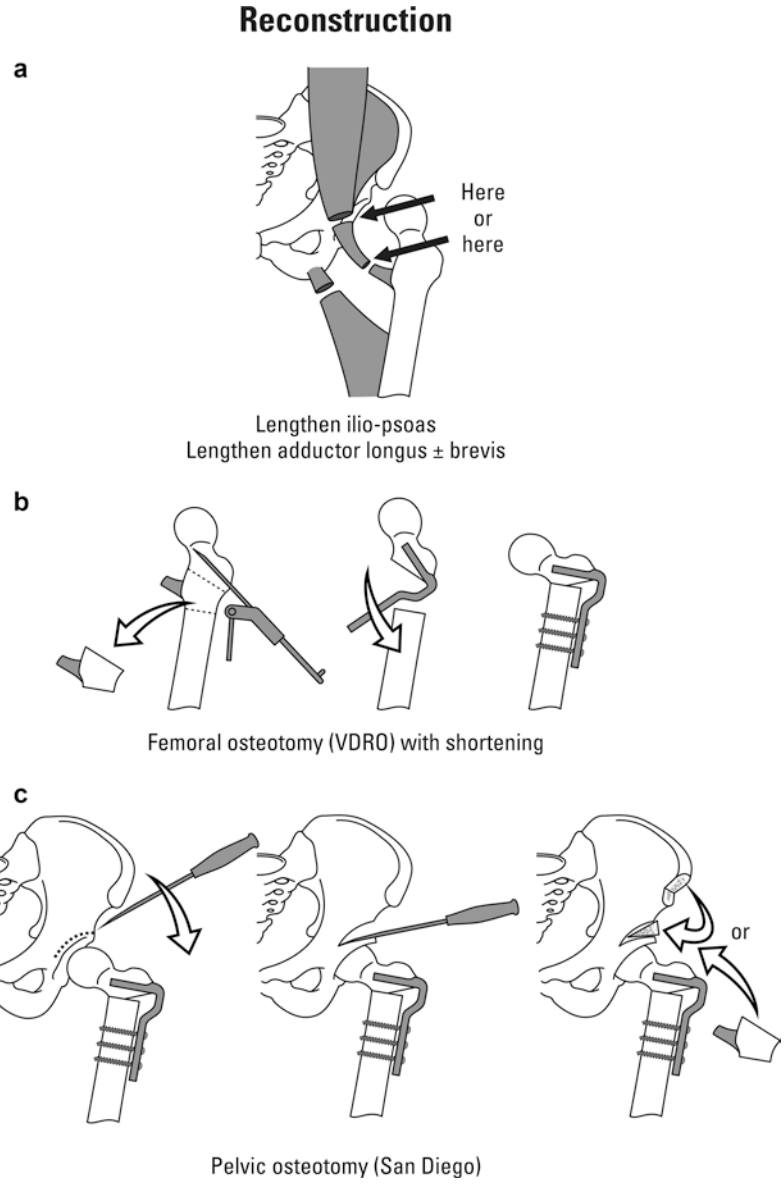

Fig. 22.12 Hip displacement may be managed by preventive or reconstructive surgery or, for many children, a combination of both. In this figure, the three classic stages are illustrated which include (**a**) lengthening of the hip flexors and adductors. (**b**) proximal femoral varus derotation osteotomy with shortening and (**c**) peri-ileal acetabuloplasty (San Diego or Dega)

especially the windswept deformity, is also a major impediment to comfortable sitting and care [76]. *Excision* of the proximal femur is widely used but has unreliable outcomes and a high complication rate [77, 78].

Referral to a pain management service is important as a number of adolescents can be managed nonoperatively, in the short term. ITB may also be considered for optimising tone management prior to salvage surgery [79].

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Bone Status in Cerebral Palsy

23

Sandra Mergler

Abstract

Children and adults with cerebral palsy (CP) are at risk for developing low bone quality and low-impact fractures. Important risk factors compromising bone health in this group are immobility, malnutrition, sex steroid deficiency and medication use (e.g. antiepileptic drugs). Dual-energy X-ray absorptiometry is most commonly used as diagnostic method for assessing bone quality. Suppletion of vitamin D and calcium and promoting weight-bearing activity are preventive measures that require attention in the care for children and adults with CP. Bisphosphonate therapy may be used to improve bone density in case of multiple or fragility fractures.

23.1 Introduction

Health problems concerning the musculoskeletal system are common in cerebral palsy (CP). Next to spasticity, paresis and contractures, there is increasing evidence of compromised bone health and low bone mass in children and adults with CP [1–3]. Fracture risk is therefore increased in this group, and fractures may even occur after minimal trauma (Fig. 23.1) [4].

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23.2 Pathophysiology

There are many factors known to influence bone mass (Fig. 23.2). Risk factors for compromised bone health in people with CP include malnutrition, immobility, sex steroid deficiency and medication use, e.g. antiepileptic drugs [1, 5]. Children with moderate or severe CP are also known to have poor growth compared with healthy children [6]. Low body mass index (BMI) and need for transfer assistance have a negative impact on bone mineral density (BMD) in people with CP [2, 7].

To adapt to stress and to maintain calcium homeostasis, the bone undergoes a constant process of remodelling. Bones will adjust their strength in proportion to the amount of stress placed upon them. Normal bones can detect and

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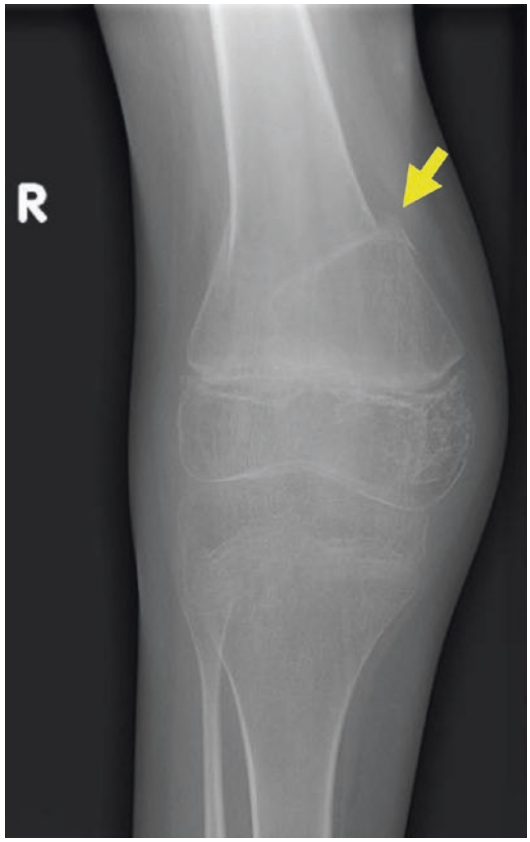

Fig. 23.1 Radiograph of the right knee of a 16-year-old boy with severe osteopenia. The *yellow arrow* indicates a fracture of the femur

repair small amounts of microdamage. In this process 'remodelling units' remove and replace bone in a coordinated manner. *Osteoclasts* are responsible for the absorption of bone tissue, while osteoblasts replace bone tissue. Low bone density arises when a longer existing mismatch occurs between the rates of bone resorption and bone formation [8].

Foundation for skeletal health is established early in life. In healthy children, in spite of constant remodelling of bone tissue, there is an accrual of bone mass throughout childhood and early adulthood (*peak bone mass*). However, in children with CP, suboptimal accrual is present, and a lower peak bone mass is reached [1, 6, 9].

While with increasing age bone mass further declines [7, 10], lower borders of fracture risk and bone density are reached at an earlier age in people with CP and can even occur in childhood [1, 11].

23.3 Fracture Incidence and Prevalence of Low Bone Density

Fracture incidence of children with moderate-to-severe CP is estimated to be 4.0%. This percentage is comparable to incidence in children without dis-

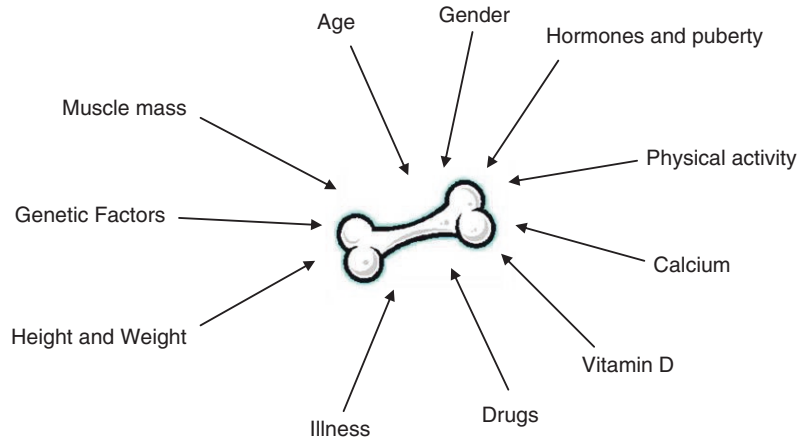

Fig. 23.2 Determinants for bone health

abilities [6]. Fracture incidence in adults with CP is assumed to be even higher. Most fractures occur at the lower extremities (*femur and tibia*) [2, 12].

In children with moderate-to-severe CP, the prevalence of low bone density varies from 27% to 77% depending on diagnostic method and measurement site. The mean bone density in children with moderate-to-severe CP measured at the distal femur lies 3.4 SD below the mean reference value for healthy children [13].

In a recent study in adults with CP, prevalence of low bone density is around 45% in the lumbar spine and 30% in the hip region [2].

23.4 Diagnostic Measures

23.4.1 Radiological Imaging

Different methods are used to assess bone status. Advantages and disadvantages of these methods are described in Table 23.1 [14, 15].

To determine bone mass and to diagnose osteoporosis, dual-energy X-ray absorptiometry (*DXA*) is generally accepted as the method of choice. However, it is known that in children the accuracy of *DXA* outcome is diminished by variability in skeletal size and body composition [16, 17].

Additionally, disrupting factors like movement during measurement, scoliosis, contractures and metallic implants are frequently present in people with CP [18]. The distal femur has been shown to have more reliable *BMD* outcome in children and adolescents with impaired mobility in comparison to the lumbar spine *BMD* [19]. The distal femoral site in adults has not been extensively investigated, and in adults total hip BMD and femoral neck are frequently used regions of interest [2].

23.4.2 Blood Tests

In order to detect disturbances in calcium metabolism or vitamin D deficiency, assessment of serum calcium, serum phosphatase, 25-OH vitamin D and parathyroid hormone is recommended in CP patients at risk for low bone density.

Table 23.1 Advantages and disadvantages of individual diagnostic methods for determining bone health

Diagnostic method	Advantages	Disadvantages
DXA	Short scanning time Low radiation	Special software for children necessary Distorting factors (e.g. scoliosis, osteosynthesis materials in situ, movement during examination or low height) No consensus on measure site (total body, lumbar spine, (distal) femur))
QUS	No radiation Low costs Mobile apparatus	Reference values for children not for every apparatus available Limited correlation with DXA
QCT	Measures volumetric bone density (takes into account bone shape) Differentiation between cortical and trabecular bone	High radiation Special software needed Not applicable in bones with smaller than 2 mm cortical thickness
MRI	No radiation	
DXR	Only hand radiograph needed Low radiation Simultaneous bone age determination possible	Good-quality hand radiography can be hard to make (e.g. contractures)

DXA dual-energy X-ray absorptiometry, *DXR* digital X-ray radiogrammetry, *MRI* magnetic resonance imaging, *QCT* quantitative computed tomography, *QUS* quantitative ultrasound

23.5 Treatment and Prevention

Interventions aimed at increasing bone density during childhood and adolescence may improve bone density and decrease the risk of fracture later in life [20, 21].

23.5.1 Nutrition, Calcium and Vitamin D

To optimize bone formation and to prevent excessive bone loss, the nutritional status of people with CP should be optimized. Malnutrition and deficiencies in calcium and *vitamin D* should be prevented, and supplementation should be given when necessary. Vitamin D status can also be optimized by regular sunlight exposure.

There is some evidence that addition of vitamin D and calcium increases bone density in children with CP [21, 22].

23.5.2 Activity and Weight Bearing

Physical activity can influence bone health by increasing or maintaining bone mass, especially with weight-bearing or impact activities. Additionally, improved balance, coordination and muscle mass may also decrease falls.

There is very limited evidence that passive standing devices and low amplitude mechanical loading may be effective in the treatment and prevention of osteopenia [21, 23, 24].

23.5.3 Bisphosphonates

Bisphosphonates inhibit osteoclast activity [15]. Although generally used in women with postmenopausal osteoporosis, only small studies are present concerning children with CP. These studies have shown that intravenous bisphosphonate therapy increases bone density [25, 26] and reduces fracture occurrence [27]. One small treatment study concerning adults is currently present showing an increase in the lumbar spine BMD [28]. A restrictive policy on oral bisphosphonates seems appropriate because of the *side effects*, e.g. gastritis and esophagitis. The duration of treatment is at present unclear.

23.5.4 Growth Hormone

In a small study, growth hormone has been shown to improve linear growth and bone density in children with CP [29].

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Oral Medication Use in Cerebral Palsy

24

James Rice

Abstract

The treatment of generalised hypertonia in cerebral palsy (CP) with the use of oral medications can be challenging in terms of improvement in patient function and quality of life. Despite the duration of published experience in the use of oral medications in CP, evidence for effect is generally limited. Spasticity, which is characterised by a velocity-dependent increase in muscle tone, can be treated with medications including baclofen and diazepam with complementary effects at the GABA spinal receptor level. Gabapentin also has a GABA agonistic effect and has gained use in the treatment of both spasticity and dystonia. Experience in the treatment of dyskinetic CP, which includes dystonia, chorea and athetosis, has largely focused on dystonia management. Anticholinergic medications including trihexyphenidyl have shown promise with evidence for improvement in upper limb function. Levodopa is commonly used for dystonia despite a lack of evidence for effect. Effective treatment of chorea and athetosis in CP remains elusive.

24.1 Introduction

The treatment of hypertonia, or increased muscle tone, in children with cerebral palsy (CP) with the goal of improving function, is a key challenge for the physician [1]. For over 50 years, there have been descriptions on the use of oral medication in the treatment of hypertonia. The questions of how and when to treat the child with significant hypertonia are often encountered in the paediatric rehabilitation clinic. Such children may receive a number of therapeutic treatments, including physical therapy, use of orthoses, mobility aids and other assistive devices, to improve their care and function. A child's family and therapists may inquire as to whether a pharmacological treatment approach will provide additional benefit. It is important that any decision on medication use for hypertonia is made in conjunction with the child's treating clinicians,

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including physical and occupational therapists, and ideally this should occur in a multidisciplinary clinical setting.

Increased muscle tone is commonly associated with activity limitation and participation restriction, as described within functional domains of the World Health Organisation's [2] International Classification of Function (Fig. 24.1). This model represents an important framework by which to describe an individual's functional limitations and to evaluate rehabilitation interventions in terms of their effect on body structure and function, activities of daily living and ultimately participation in society. Furthermore, outcome measures employed in clinical practice allows us to describe specific aspects of function. This is important in the evaluation of any medical intervention, including the use of oral medication. Examples of outcome measurement include the use of goal setting to identify specific activities which are relevant to the child's life, which can then be scored in a standardised fashion to measure the effect of an intervention. Goal setting allows the use of individualised measurements in evaluation, particularly where more standardised measurements may not be applicable to a particular child. They have an established use in the evaluation of treatment of hypertonia with oral medication in CP [3, 4].

24.2 Classifying Hypertonia

Spasticity is a form of muscle hypertonia in which there is a velocity-dependent resistance to passive movement due to heightened stretch reflexes. The specific characteristics of spasticity have been described elsewhere in this book (see Chaps. 10 and 15). Differing forms of hypertonia observed in cerebral palsy, including dystonia, have been classified according to experts' consensus [5]. Whilst lesions in the corticospinal tract may result in spasticity, dystonia usually results from lesions within the basal ganglia—cortical circuits. Dystonia in childhood is defined as "a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both" [5]. In contrast to spasticity, dystonia is inherently more difficult to observe and measure, particularly when spasticity co-exists.

Whereas spasticity is identified in approximately 80–90% of children with CP, the prevalence of dystonia may vary considerably, and it has been suggested that this reflects a clinical under-recognition of the components of the motor pattern [6]. Less frequently observed movement patterns in CP include chorea and athetosis. Chorea is considered "an ongoing random-appearing sequence of one or more discrete

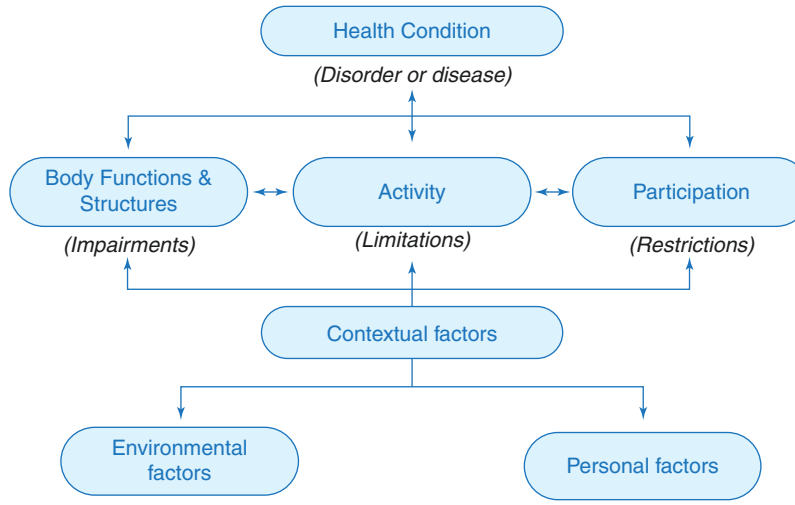

Fig. 24.1 International classification of function model

involuntary movements or movement fragments, and athetosis is "a slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture". There are few descriptions of their prevalence in CP populations and are likely to be under-recognised. In population-based study, the prevalence of abnormal dyskinetic movements including dystonia, chorea and athetosis is between 5% and 20% [7, 8].

24.3 General Considerations

In considering whether to use oral medication for the treatment of hypertonia, it is firstly important to establish whether the child's tone pattern fits with spasticity, dystonia, a combination of the two, or perhaps includes other components such as chorea and athetosis. Increasingly an overlap in movement patterns is recognised when such specific terms are operationalised (Fig. 24.2). Generally, the dominant form of hypertonia is targeted for treatment using an appropriate medication. The distribution of abnormal tone can be classified as focal, such as involving the hand; segmental, such as involving a whole limb; or generalised, where the majority of limbs and head/neck/trunk are included. Oral medications are considered most relevant in use when hypertonia is generalised and of a moderate to severe nature.

Prior to commencing medication, the clinician should determine whether potentially reversible factors have exacerbated the child's hypertonia. These can include painful conditions including constipation, pressure sores and even occult fracture. In many cases medication can be administered via gastrostomy. Alternate treatments, such as Botulinum toxin type A intramuscular injections or orthopaedic surgery, generally offer benefit for focal or segmental problems. Another treatment for generalised hypertonia, intrathecal baclofen, is described in the chapter on intrathecal baclofen therapy.

24.4 Treatment of Spasticity

24.4.1 Baclofen

Baclofen, a gamma amino butyric acid (GABA) agonist, acts selectively on GABA-B receptors in the brain and layers II and III of the dorsal grey matter of the spinal cord [9]. This action produces an inhibitory effect on presynaptic transmitter release via the restriction of calcium influx into presynaptic terminals, as well as an effect at postsynaptic terminals to decrease neuronal activity by increasing potassium conductance [10]. In addition, baclofen may have an effect by reducing the release of excitatory transmitters

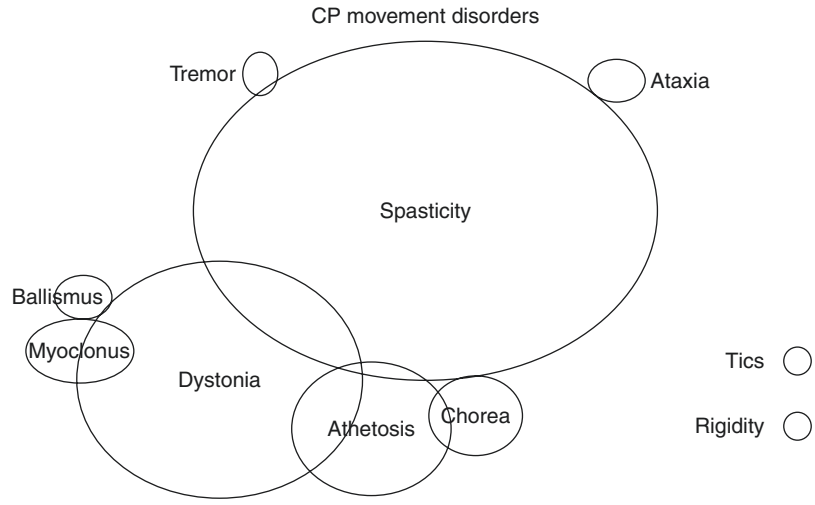

Fig. 24.2 Overlap of movement disorders seen in CP

Table 24.1 Summary of medication and dose ranges

Treatment spasticity	Initial dose	Maximal dose	Side effects
Baclofen	0.2 mg/kg/day	1–2 mg/kg/day	Sedation, constipation
Diazepam	0.05 mg/kg/day	0.5–1.0 mg/kg/day	Sedation, ataxia
Dantrolene	1 mg/kg/day	4–12 mg/kg/day	Excess weakness, hepatotoxicity
Tizanidine	1–2 mg/day	Up to 36 mg/day	Sedation
Clonidine	1 μg/kg/day	10 μg/kg/day	Sedation, hypotension
Gabapentin	5 mg/kg/day	40 mg/kg/day	Sedation, dizziness
Treatment dystonia/chorea/athetosis			
Trihexyphenidyl	0.1 mg/kg/day	1–2 mg/kg/day	Sleep disturbance, dry mouth, constipation
Levodopa	1 mg/kg/day	10 mg/kg/day	Nausea, sleep disturbance
Levetiracetam		5–10 mg/kg/day	N/A
Tetrabenazine		100 mg/day	Drowsiness

such as substance P which play a role in producing spasms (see Chaps. 10, 15, and 25) (Table 24.1).

Oral baclofen has been in wide clinical usage for the past three decades. Despite this, there have been few studies which have assessed its effectiveness in treating spasticity in children with cerebral palsy. Whilst one study [11] showed baclofen to be clearly superior to placebo in reducing spasticity in children, most studies of these have failed to demonstrate a significant reduction in spasticity with its use with sedation being a commonly reported side effect with oral baclofen use [4, 12, 13]. This lack of effect is likely to be related to a relative inability of the drug to cross the blood-brain barrier and the need for high-dose levels to achieve substantial clinical effect [14].

Baclofen has also been assessed in terms of its effect on voluntary muscle activation [15]. In a group of ten children with calf spasticity treated with oral baclofen for 4 weeks, electrophysiological testing indicated an increased voluntary ability to activate plantar flexor muscles. The use of baclofen in children with spastic quadriplegia has also been shown to be superior to the use of placebo in achieving goal-oriented tasks such as seating and transfers and positioning [4].

A common baclofen dose schedule consists of commencing with 5 mg once/day, slowly grading up over several weeks to a dose of 1–2 mg/kg/day, usually given two to three times per day. Side effects are relatively infrequent and more likely to occur as the dose increases. These include excess drowsiness, deterioration in posture with loss of muscle tone and constipation. The association between the use of oral baclofen and potentiation of seizures in children with a pre-existing seizure disorder is unclear, and many physicians will avoid the introduction of baclofen in children with unstable or frequent seizures. When baclofen is withdrawn, it must be done so gradually, as abrupt cessation can lead to complications including rebound hypertonia, altered conscious state, seizures and rhabdomyolysis.

In summary there is modest evidence for the efficacy of oral baclofen in treating severe spasticity in cerebral palsy. Whilst a key limitation is a relative inability to cross the blood-brain barrier, it offers the ability to treat children with significant spasticity who may not be appropriate candidates for intrathecal baclofen therapy (see Chap. 25). This may include children who are too small or medically unstable to receive a baclofen pump or those who do not have access to this medical technology.

24.4.2 Diazepam

This medication has a long history of use in treating spasticity. Diazepam is a benzodiazepine which has an effect on GABA-A receptors in the dorsal grey matter of the spinal cord. The effect of decreased chloride conductance at this receptor

complex results in increased presynaptic inhibition of afferent inputs, resulting in a reduction in spasticity. The evidence for benefit in treating children with spasticity is limited. Mathew et al. conducted a randomised controlled trial involving 180 children with spastic cerebral palsy who received a low dose of diazepam at bedtime. They noted a significant reduction in hypertonia, improvement in the range of passive movement and an increase in spontaneous movement [16]. Earlier studies have noted a reduction in spasticity as well as additional benefits such as improved behaviour and coordination [17, 18]. More commonly described side effects include drowsiness, ataxia and impaired mental performance.

Diazepam is rapidly absorbed and a peak effect is seen approximately 1 h after oral administration. It has a long half-life and administration as a nocturnal dose may avoid daytime somnolence, although it can be given in divided doses. Diazepam can be commenced with a starting dose of 0.05 mg/kg/dose, gradually increasing to 0.3 mg/kg/dose given up to three times per day in severe spasticity. Baclofen has been described for use in children as young as 12 months of age, and diazepam in those less than 12 months of age, although the need for treatment at such a young age is an unusual encounter.

24.4.3 Dantrolene

Dantrolene reduces spasticity by decreasing calcium release from sarcoplasmic reticulum in skeletal muscle. In turn this interferes with excitation-contraction coupling required for muscle contraction [19]. Its half-life is approximately 15 h with peak concentrations occurring within 3–6 h. Dantrolene is metabolised by the liver. Liver dysfunction has been described in up to 1% of patients and hepatotoxicity may be irreversible [20].

There are a small number of studies which have evaluated dantrolene's efficacy in cerebral palsy. Two of these studies used similar doses (4–12 mg/kg/day) and found conflicting results. In one of the studies, participants showed a reduction in spasticity 6 weeks after commencement, compared to the use of placebo. Conversely, the second study showed no improvement in measures of spasticity and demonstrated a reduction in strength. Because of its prominent effect in reducing muscle contraction, weakness is a significant side effect. In addition, drowsiness and fatigue have been described [21, 22]. Dosing typically commences at 0.5 mg/kg/dose twice a day, increasing gradually up to 3 mg/kg/dose administered up to four times per day.

24.4.4 Tizanidine

Tizanidine hydrochloride is a centrally acting α2-adrenergic agonist, which is proposed to reduce spasticity by inhibiting the release of excitatory amino acids within the central nervous system, leading to a reduction in excess alpha motor neurone activity (see Chap. 15). There is limited evidence for its efficacy in children, compared with much more widespread use in adults, particularly with multiple sclerosis. Vasquez-Briceno et al. [23] studied the effect of tizanidine in a placebo-controlled study, treating 10 children at a mean age of 4.1 years with 0.05 mg/kg/day, and 30 children with placebo for 6 months. A significant reduction in spasticity was noted beginning 2 weeks after initiating treatment and was sustained throughout the trial. No side effects were noted, and the authors specifically monitored liver function tests, which remained normal [23]. Palazon Garcia et al. [24] described their experience in the use of tizanidine in 45 children with spastic cerebral palsy. They used 1 or 2 mg per day as initial doses in children less than 12 years old and dosing similar to adults for older children. Using these doses, most parents felt that their child responded well to the medication. Tolerance was excellent in the majority and sedation was the most common side effect [24].

Tizanidine has been compared to oral baclofen combined with botulinum toxin type A use in children with spastic equinus deformity [25] (for more see Chap. 22). Despite relatively small numbers in each treatment group, those who received tizanidine had higher GMFM and caregiver response scores at follow-up, with

fewer side effects than the baclofen group. Tizanidine is metabolised by the liver and therefore may be contraindicated in situations where hepatic impairment is present. Side effects have not been described in the paediatric population; however, in adults these include hypotension, sedation, dry mouth, dizziness, hallucinations and hepatotoxicity.

24.4.5 Clonidine

Clonidine is an α2-adrenergic agonist. There is no published record of experimental trial in children. Lubsch et al. [26] have described their experience with the use of clonidine in a paediatric clinic in which 31 children with cerebral palsy and traumatic brain injury were treated. The average dose was 0.02 mg/kg/day and average maintenance dose was 0.4 mg/day. Based on the use of predictive modelling for correlation between dose and location of spasticity and other demographics, the presence of quadriplegia and duration from brain injury showed significant correlation with efficacy. Only one patient showed side effects of sedation and hypotension, which are the more common side effects described with the use of clonidine in attentional disorders of childhood [26].

24.4.6 Gabapentin

Gabapentin is an amino acid which is structurally related to GABA and is readily absorbed across the blood-brain barrier. It is thought to increase both the concentration and production of GABA; however its role in the reduction of spasticity is unclear. The efficacy of gabapentin in the treatment of spasticity has been demonstrated in adults with both multiple sclerosis and spinal cord injury [27]. A recent observational study assessed the effect of gabapentin on severe dystonia in 69 children, 25 of whom had CP [28]. The average dose was 18.1 mg/kg/dose administered three times a day. There was a significant decrease in the severity of dystonia, and significant improvements were seen in overall muscle tone and involuntary movements, sleep amount and quality, mood, pain and seating tolerance. There is renewed interest in the role of gabapentin for the treatment of pain with hypertonia in CP, despite limited research evidence. Described side effects of gabapentin include somnolence, dizziness, ataxia, fatigue and nystagmus.

24.5 Treatment of Dystonia

There is evidence in animal models of perinatal asphyxia for the relative preservation of cholinergic interneurons in the striatum in comparison to dopaminergic neurons [29]. It is postulated that dystonia may occur when there is an imbalance of cholinergic to dopaminergic neurotransmitter activity, such that a pharmacological reduction of cholinergic activity by use of anticholinergic medication, or conversely a boost in dopaminergic activity by use of dopaminergic agents, changes this balance [30]. This forms the basis for use of both anticholinergics and dopaminergic medication in the treatment of dystonia.

24.5.1 Trihexyphenidyl

Trihexyphenidyl is an anticholinergic agent with a long history of use in the management of extrapyramidal disorders in children and adults. Its mechanism of action is unclear; however there are large numbers of cholinergic interneurons in the basal ganglia, where abnormalities noted on neuroimaging may be associated with the clinical features of dystonia. Two studies have evaluated trihexyphenidyl in using prospective or randomised control methods. A randomised, double-blind, placebo-controlled, crossover trial with 16 participants utilised assessments performed at baseline, week 12 and week 28 after study commencement. The primary outcome measure was the Barry-Albright Dystonia scale for global assessment of dystonia, and additional goal setting was undertaken [31]. Fourteen children (88%) completed the study and there were no measurable treatment effects. Side effects were common and included behavioural changes, constipation and dry mouth. In a small propor-

tion of children, an increase in movements was noted [3].

In a prospective study on trihexyphenidyl in 23 children with dystonia secondary to cerebral palsy, Sanger et al. demonstrated upper limb functional improvement at 15 weeks after study commencement. A worsening in movements was also seen in a proportion of participants [32]. Another retrospective survey of 22 children with extrapyramidal (dystonic) CP evaluated the effect of trihexyphenidyl on upper extremity and lower extremity function, expressive language and drooling, with positive improvements reported one third for upper extremity function and verbal expressive language and in a smaller proportion for drooling [33]. The dose of trihexyphenidyl used in studies in children shows considerable variation (range 0.15–2.0 mg/kg/day). Children may tolerate higher doses of trihexyphenidyl than adults, particularly when the dose increase is gradual [34].

24.5.2 L-Dopa (Levodopa)

Levodopa is an aromatic amino acid and is the metabolic precursor of dopamine. It is administered with carbidopa, which does not cross the blood-brain barrier, but enhances the availability of levodopa for passage across the blood-brain barrier and conversion into dopamine. The most detailed description of the use of L-dopa in children with neurological disability is in the treatment of Dopa-responsive dystonia (*Segawa's disease*). This rare but treatable cause of dystonia in childhood is a distinct entity from cerebral palsy [35]. Perhaps in part due to the profound success of L-dopa therapy in reducing the impairments in Segawa's disease, it has also gained use in children with cerebral palsy who have prominent dystonia. This is despite a limited understanding of the biochemical basis for dystonia in CP.

In a randomised, double-blind, placebo-controlled crossover study, levodopa was administered to nine children with quadriplegic cerebral palsy and upper limb dystonia. Function was assessed before and after 2 weeks of treatment using a range of measures of upper limb skills. No benefits were found on upper limb function [36]. A starting dose is recommended at 1 mg/kg/day, gradually increasing up to 10 mg/kg/day, given three times per day. It is recommended to trial this medication for up to 6 months, as a positive response may take some time to emerge [37]. It is no longer considered as a first-choice treatment in oral medication use for dystonic cerebral palsy. Side effects can include nausea and vomiting, sleep disturbance, weight gain and worsening of the movement pattern.

24.6 Treatment of Chorea and Athetosis

24.6.1 Levetiracetam

Levetiracetam's effect on seizure control is not clearly understood, but it may affect intraneuronal calcium concentrations in addition to effects on GABA activity. Its mechanism of effect in movement disorders is unknown. Vles et al. [38] reported on two children with severe perinatal asphyxia and dyskinetic CP characterised by choreoathetosis. They were treated with low-dose levetiracetam (5–10 mg/kg/day) to improve balance and fine motor skills. Treatment was evaluated by use of video and the Visual Analogue Scale to document the movement pattern. In both children an improvement of balance control and fine motor skills was observed. No side effect was noted. At later follow-up (26 months), treating clinicians and parents believed that the effect was maintained. This is the only reported use of medication in an uncontrolled setting for choreoathetosis in CP. It has been shown to be effective in the treatment of tardive dyskinesia in adults [39].

24.6.2 Tetrabenazine

Tetrabenazine is a benzoquinolizine which works by reducing the capacity of neurones to store monoamines through depletion of synaptic vesicles and blockage of the dopamine receptor. It has been used in adults to treat dyskinesias [40]. There is limited description on the use of tetrabenazine in CP. In a randomised, double-blind, crossover trial on 30 children, the majority of

whom were aged between 8 and 12 years, each was given up 100 mg/day. Whilst statistically significant improvement was noted in fine motor tests for those who received the active medication, the overall clinical improvement was minimal. Drowsiness was a common side effect [41]. In case reports on the use of tetrabenazine in young children who developed, or had an increase in pre-existing chorea, associated with cerebral palsy or acute onset encephalopathy, a reduction in the severity of movement disorder was observed. Daily doses ranged between 10 and 25 mg/kg. No side effects were observed [42, 43].

Conclusion

This chapter summarises the current evidence for the use of oral medication in children with hypertonia. A number of medications are in common use for both spasticity and dystonia and, to a lesser extent, chorea. In general the evidence for their benefit is limited, despite the duration of clinical experience. Many medication dose guidelines are extrapolated from adult experience, with limited basis for their safety in children with CP [44]. Although other treatments for hypertonia have received a greater research focus, there is general support for the role of oral medication as first-line treatment for generalised hypertonia and in certain cases for focal or segmental problems where alternate treatments are not available or acceptable. Clinicians should first evaluate the available evidence and consider whether a particular medication is relevant for their patient. The importance of measurement of treatment effect, such as scoring the results of goal setting, cannot be understated.

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Intrathecal Baclofen Therapy

25

Michael Vassilyadi

Abstract

Intrathecal baclofen (*ITB*) therapy is a good therapeutic, evidence-based option and effective treatment for spasticity in children with cerebral palsy. It has also been used in children with dystonic cerebral palsy. ITB results in decreased spasticity, with the lower extremities more relieved than the upper extremities, fewer spasms, improvement in ankle clonus and increased range of motion and improved ambulation in children with spastic diplegia. As well, ITB therapy can help in reducing contractures, improving functional abilities and facilitating patient care by parents and caregivers. ITB therapy involves the surgical implantation of a programmable pump in the abdomen with a catheter tracking into the spinal subarachnoid space and the baclofen venting into the cerebrospinal fluid. There can be surgical complications, as well as complications related to the patient's medical condition, to the hardware implanted and to the medication. Despite this, the overall perceptions of ITB therapy have been found to be positive with most parents or caregivers satisfied and would go through the process again if needed for their child.

25.1 Introduction

Baclofen is a gamma-aminobutyric acid (*GABA*) agonist whose therapeutic effects are attributed to impede the release of excitatory neurotransmitters (i.e. glutamate and aspartate) by presynaptic inhibition. Taken orally, baclofen has a low lipid solubility and poor blood-brain barrier penetrance (see Chap. 24). At high doses there are systemic *side-effects* such as somnolence, confusion, ataxia, urinary retention, headaches and insomnia. Baclofen is more effective when delivered into the intrathecal space. Intrathecal baclofen (*ITB*) doses are extremely small requiring an implantable programmable pump for safe delivery with cerebrospinal fluid levels reaching 30 times those achieved after oral administration [1]. A Cochrane systematic review reported that intrathecal baclofen is an effective therapy

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for reducing spasticity in children in the short term [2]. For the long-term control of spasticity of cerebral origin in children and young adults, ITB therapy has been shown to be effective with side-effects that can be managed with adjusting the baclofen dosage [3, 4]. The efficacy of ITB has also been reported in a randomized controlled trial [5].

25.2 Patient Selection

Children considered for ITB are usually those affected with more severe cerebral palsy. This would correspond to the *NYUMC* classification (see Chap. 26) Group IV (commando or belly crawlers, wheelchair bound) and Group V that are non-ambulatory and fully dependent. These children can have upper extremity spasticity as severe as in the lower extremities. The spasticity is usually chronic and a result of cerebral palsy, spinal cord lesions or central nervous system trauma. The gross motor function classification system (*GMFCS*) is commonly used to classify the severity of impairment; for more see Chap. 22. Like the NYUMC system, there are five grades that qualitatively assess the child's functional severity within various age groups. Most candidates for ITB therapy are usually in Level IV (able to sit when supported with very limited independent mobility) and Level V where they are wheelchair bound and lack independence. A systematic review found no evidence to support the use of ITB in ambulant children and adolescents with spasticity and dystonia of cerebral origin (*GMFCS* levels I–III) [6].

Children considered for ITB therapy are usually refractory or have unacceptable side effects at effective oral baclofen doses. Traditionally, children considered for ITB were not candidates for dorsal root rhizotomy (*DRR*) surgery and physiotherapy no longer as effective. As a non-ablative and potentially reversible therapy, ITB has been increasingly used for children with *spastic diplegia* and replacing DRR. Selected children are usually older than those considered for DRR, use spasticity to stand and often to walk, may lose the ability to ambulate if the spasticity is removed by DRR surgery and likely had prior orthopaedic procedures. This is in comparison with the ideal candidates for DRR who are young, ambulatory children with spastic diplegia and had no prior orthopaedic procedures [7].

Children with *dystonic* cerebral palsy can also be candidates for ITB, a contraindication for DRR surgery, with greater baclofen requirements compared with children who have spastic cerebral palsy. Albright et al. [8] reported that ease of care improves in 86% and function in one-third of children with severe generalized dystonia, particularly secondary dystonia, which is inadequately treated with oral medication. The effects have been found to last up to 7 years with approximately 8% of these patients losing their responsiveness to ITB. In cases where there are multiple and increasing revisions of the intrathecal catheter, *intraventricular* baclofen has been successfully used utilizing stereotactic *neuronavigation* [9]. Intraventricular baclofen was found to be as safe as intrathecal baclofen in the largest series to date [10].

Potential candidates for baclofen pump implantation undergo a screening trial of ITB (usually 50 μg) via a lumbar puncture or insertion of a lumbar catheter. Bleyenheuft et al. [11] reported that the trial can be performed more precisely with an external pump infusing ITB. There should be no hydrocephalus, intrathecal block to the flow of cerebrospinal fluid or any allergic reaction to the medication. The screening trial begins with a baseline assessment by physiotherapy and occupational therapy that is videotaped. Tone is graded using the Ashworth scale, in addition to assessment of deep tendon reflexes, clonus and spasticity. These are repeated 2–3 h after the ITB is administered. A report by Sayer et al. [12] suggested that with carefully selected patients by experienced professionals in the management of spasticity, an ITB pump could be implanted without a trial in the most severely affected GMFCS groups.

25.3 Surgical Implantation

The SynchroMed programmable pumps that are implanted are manufactured by Medtronic (Fig. 25.1). They are usually positioned subcutaneously or subfascially [13, 14] in the right or left subcostal space, as far away as possible from any gastrostomy feeding tube. A silicone catheter and more recently the Ascenda catheter (Fig. 25.1) attach the pump and track subcutaneously to the low mid lumbar region where the catheter is inserted into the intrathecal space via a lumbar puncture [15]. In children with severe scoliosis, a small lumbar laminectomy may be required to insert the intrathecal catheter. Traditionally, the catheter is inserted via a lumbar puncture and tracked rostrally. This may be challenging in situations where there are thoracolumbar fusions or severe scoliosis. In such cases, a posterior cervical approach for catheter insertion via a bilateral T1 *laminectomy* has been described [16], through the foramen magnum [17] or through a small one-level laminotomy to the right of the midline between C6 and T2 [18]. Under *fluoroscopic* guidance, the catheter's position and tip are verified. After all the catheters and connectors are in place, and the two incisions closed, the pump is programmed via telemetry (Fig. 25.2) to deliver a baclofen bolus and to start functioning. The whole surgery takes about 2–3 h. After a short stay in the hospital, the patients are followed up in the clinic to assess the degree of spasticity relief and to refill the pumps under sterile conditions.

Fig. 25.1 SynchroMed II pump with 20 cc reservoir, 19.5 mm in thickness (also available with a 40 cc reservoir, which is 26 mm thick), and two-piece radiopaque Ascenda catheter system that has increased resistance to kinking, cuts, occlusions and leaks when exposed to tensile and compressive forces compared to a regular silicone catheter as a result of a thermoplastic polyethylene terephthalate braid and a polyurethane outer jacket covering the inner lumen of the silicone tubing. The peristaltic pump propels the medication from the reservoir to the catheter port that is connected to the catheter system leading to the intrathecal space. The pump requires replacement generally every 7 years because of the built in battery life span. The central port is accessed during baclofen refills with a 22-gauge Huber-type needle. The side port is designed to be accessed with a 25-gauge needle, usually for diagnostic purposes (photo used with permission, © 2016 Medtronic)

Fig. 25.2 Medtronic N'Vision® hand-held wireless portable programmer device (model 8840) for the SynchroMed II programmable baclofen infusion system (photo used with permission, © 2016 Medtronic)

Catheter tip position has been studied as a means of providing greater upper extremity spasticity relief if positioned more rostrally in the spinal canal. Grabb et al. [19] found that by positioning the catheter tip in the midthoracic region at the T6-T7 level, compared with T11-T12, lower ITB doses were required to achieve better upper extremity spasticity relief without any changes in the lower extremity spasticity relief in children with spastic quadriparesis (bilateral). Albright et al. [20] suggested that for spastic diplegia, the catheter tip be positioned at T10-T12, at C5-T2 for children with spastic bilateral and even more rostral at C1-C4 for generalized secondary dystonia. Greater intracranial baclofen concentrations have been achieved in children with generalized dystonia by insertion of the catheter *directly* into the third ventricle using stereotactic *endoscopy* [21].

25.4 Complications and Side-Effects

Complications can be related to the medical condition of the patient, to drug overdose [22], to drug withdrawal [23], to refills or to the implantation. The latter includes catheter-related problems such as disconnections, kinks, fractures or migration [15]. Rarely, the pump may malfunction or even fail to operate. Infection can occur ranging from cellulites to skin breakdown to meningitis that may require pump removal. *Seromas* and *cerebrospinal* fluid leaks can also be problematic [24]. In a multivariate analysis, Spader et al. [25] identified that at young age (4–5 years), wound dehiscence and multiple surgical revisions were independent risk factors for infection; they suggested possibly deferring the ITB therapy until over the age of 6 years as a means of decreasing the risk of infection.

Borowski et al. [26] reported a 31% complication rate over a period of 3 years with 63% secondary to catheter-related problems and a 9% infection rate. Motta et al. [27] reported that the complication rate was higher in children less than 10 years old and in those with a considerable increase in tone (Ashworth scale score >3). In addition, they found that the subfascial implantation technique and a new preoperative prophylaxis protocol that they initiated decreased the infection rate from 10% to 4.8%. Long-term follow-up of the subfascial technique showed decreases in CSF leakage and complications from erosion, infection and catheter malfunction [14, 28].

Motta et al. [27] did not find any increased complications with ambulatory status or the presence of dystonia. Ward et al. [29] found the complication rate 2.8 times higher in children with dystonia, compared with children with spasticity, with a greater than five-time infection rate and four times more catheter-related problems. Turner et al. [9] surmised that the increased catheter occlusion problem may be related to intrathecal *arachnoiditis* that may occur in children with dystonia as a result of previous infections and spinal interventions.

Infection of the actual pump is uncommon and usually requires explantation [30, 31]. When that occurs, the patient's baclofen requirements may be partially managed with oral medication, with or without an external lumbar catheter to deliver intrathecal doses. Kallweit et al. [32] reported on the possibility of long-term intravenous antibiotic treatment without removal of the baclofen pump in selected cases. Motta et al. [27] explanted the baclofen pump in 8% of the patients because of infection and cerebrospinal fluid leaks and in 4% because of patient or parent dissatisfaction.

McCall and MacDonald [33] did not find any increased complications when the catheter tip was placed in the cervical region at C5-C7 as opposed to the thoracic region. Tubbs et al. [34] reported on the development of a Chiari I malformation that may have occurred as a result of lumbar punctures or chronic leakage of cerebrospinal fluid around the catheter or even through an unrecognized catheter fracture. In children that have ventriculoperitoneal shunts, it is essential that the shunt is confirmed to be functioning prior to baclofen pump implantation. As well, a shunt malfunction, and its subsequent revision, may alter the effects of the ITB [35]. An association of scoliosis development with ITB therapy has been identified compared with the natural history in

children with cerebral palsy [36, 37], and early bracing and spinal fusion recommended to prevent progression of the spinal deformity. This association, however, was not identified in other reports [38, 39].

25.5 Effectiveness

ITB results in decreased spasticity, with the lower extremities more relieved than the upper extremities, fewer spasms, improvement in ankle clonus and increased range of motion, with improved ambulation in children with spastic diplegia [40]. Speech is improved, as well as dressing, transferring, sitting time and toileting [41]. Bladder capacity can increase with an improved bladder management. There is decreased sphincter activity during bladder contraction. Sleep is improved, as well as self-care and overall quality of life [42–44]. In more severely affected patients, pain is significantly reduced and decubitus ulcers get a chance to heal. With ITB therapy, physiotherapy and occupational therapy become easier to implement. Despite these benefits, there remains some uncertainty about the optimal use of ITB [45]. In addition, with time, the range of baclofen concentration that offers reduction in spasticity without causing a global decrease in tone and weakness narrows [46]. Vles et al. [4] found that the ITB improvements reach a plateau at about 1 year after implantation, with minimal improvements expected as long as there are defined treatment goals; however, the positive effects on reduction of pain, ease of care and improved mental health were present up to 9 years after initiation of ITB.

Cost/benefit analysis of ITB therapy has been reported to be acceptable and justifies the use of ITB in patients with severe spasticity who have not responded to less invasive treatments [47, 51]. Compared with the patients in the selective dorsal root rhizotomy management plan, ITB therapy is at least three times more expensive [48]. Although DRR was traditionally performed in less affected children with spastic cerebral palsy and ITB reserved for patients with GMFCS Levels IV and V [7], this categorisation is not as well followed now with more patients who are less affected undergoing ITB therapy. These may be ambulatory patients, with or without assistive devices, with insufficient underlying strength in the lower extremities to ambulate without spasticity who have decided, or their families have decided, on the non-ablative, long-term, high-level medical management approach associated with ITB [52].

The *overall* perceptions of ITB therapy have been studied by Gooch et al. [49] and found to be positive; 81% of care providers strongly agreed, and 14% slightly agreed that they would have the procedure performed again. These were similar results to those of Campbell et al. [50] who reported that 94% of the goals (improvement in function, decreased pain, improved comfort, prevention of worsening deformity, improved care) were at least partly achieved and 72% completely or almost completely achieved. Borowski et al. [26] identified that 81% of parents or caregivers were satisfied with ITB therapy, and 87% would recommend it to others, with 90% reporting positive effects and 8% reporting no change. ITB therapy has been rated as a successful treatment for spasticity despite the complications, with 81–94% of patients or caregivers indicating that they were happy with their decision for ITB therapy and would go through the process again if they had to [4, 26, 49].

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Dorsal Root Rhizotomy for the Treatment of Spasticity

26

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Abstract

Dorsal root rhizotomy (*DRR*) surgery is an effective, ablative, long-term treatment in young children with spastic diplegia and has maximal effectiveness when combined with intensive physical and occupational therapies. This neurosurgical operation should be considered when evaluating prospective patients in a multidisciplinary spasticity clinic. DRR provides benefit to carefully selected children with spasticity as a result of cerebral palsy where spasticity is the main factor compromising gait and motor function. The risk of surgical complications is low in experienced centres. Selective dorsal root rhizotomy (*SDDR*), which includes intraoperative electrophysiology and physical muscle monitoring, is strongly recommended as an evidence-based procedure for reducing spasticity and improving gait kinematics. There is also evidence in the literature that SDDR improves gross motor function. Overall, the levels of satisfaction in adults who have undergone SDDR as children have been reported to be generally high, with no negative influence on life satisfaction. In most patients, the benefits remain throughout adolescences and adulthood.

26.1 Introduction

Dorsal root rhizotomy (*DRR*) is an evidence-based neurosurgical procedure that has been proven to offer a reduction in spasticity and an improvement in movement and posture in select patients afflicted with spastic diplegia, and less frequently in those with spastic quadriparesis, in both the short and long term [1–3]. As the proper selection of children is paramount to the success of this irreversible, ablative surgery, it is crucial to have an experienced *multidisciplinary* spasticity team composed of a paediatric neurosurgeon, paediatric neurologist and/or paediatric physiatrist, paediatric orthopaedic surgeon, physiotherapist and occupational therapist, in addition to a nurse to coordinate the clinic and a social worker.

Children who benefit from DRR have a history of prematurity, low birth weight, pre- or

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perinatal difficulties (such as prolonged intubation, low APGARS, intraventricular haemorrhage and seizures; see Chap. 6) and delayed motor milestones in the face of relative sparing of speech and intellect and are usually 3–8 years of age with no evidence of an evolving neurological condition. On physical examination there is velocity-dependent increase in tone, increased deep tendon reflexes and clonus with Babinski sign and scissoring gait with exaggerated lordosis; there should be adequate underlying strength, good protective responses, good balance and absence of multiple orthopaedic procedures, fixed severe contractures or dystonic features.

Some centres have widened the age criteria for surgery to include children between 2 and 14 years of age [4]. MacWilliams et al. [5] reported significant functional declines in children with spastic diplegia who underwent *SDDR* (selective dorsal root rhizotomy) after the age of 10 years and that these declines were worse than in children who did not undergo the surgery.

26.2 Patient Selection

In spastic diplegia, spasticity interferes primarily with the function of the lower extremities. Potential candidates for DRR surgery should have minimal evidence of dyskinesia and should be able to walk with or without assistive devices. Head and trunk control should be adequate for sitting upright without support and right in response to lateral challenges. There should be control of quadriceps and hip extensor muscles while rising to stand and returning to sitting, without the reliance on upper extremities for weight bearing. *DRR* is not recommended in children with severe weakness in hip adductor or calf muscles.

Children with spastic quadriparesis (bilateral) can also be candidates for DRR. These children have both upper and lower extremity spasticity that interferes with passive movement, positioning and care. As in children with spastic diplegia, there should be minimal evidence of dyskinesia, no severe truncal hypotonia and a lack of severe fixed contractures at multiple joints requiring orthopaedic surgery. Consideration is given to children who can stand for transfers, but not if lower extremity spasticity aids in performance of the standing transfers.

In a systematic review of the literature, Grunt et al. [6] identified that selection criteria varied considerably with no consensus on the selection process, and most were not based on standardised measurements such as the International Classification of Functioning, Disability and Health. With well-selected patients there would be less heterogeneity with respect to the functional benefits of SDDR.

A common classification used for preoperative ambulatory abilities in children being evaluated for DRR surgery is the five-level NYUMC (New York University Medical Center) system [7] where the best surgical outcome is found in Groups I, II and III [8]. Children that are independent ambulators (*Group* I) have the best chance of improving the appearance and efficiency of their walking. *Group* II consists of children that walk with assistive mobility devices (such as canes, crutches and walkers) and are anticipated to improve the quality of locomotion with less assistance. *Group* III is children that are quadruped crawlers, and the expectation is that they improve at least to the level of using braces or assistive devices. *Groups* IV and V are non-ambulatory patients that are less likely to improve with *DRR* surgery and may be offered alternate therapies such as intrathecal baclofen (see Chap. 25); however, there are recent reports of improvements in these groups with DRR surgery [9, 10]. The Gross Motor Function Classification System (*GMFCS*) is also a five-level evidence-based system for objective classification of motor disability that is used in patients with cerebral palsy; for more see Chap. 22.

Dudley et al. [1] identified a long-term predictive index for ambulation improvement based on four components: preoperative GMFCS assignment, preoperative Gross Motor Function Measure (*GMFM*), distribution of spasticity and the Ashworth scale. The best candidates for surgery had spastic diplegia with GMFM scores >60 and hip adductor tone <3 corresponding to GMFCS groups I, II and III (see Chaps. 17 and 22).

Grunt et al. [11] reported the potential predictive value of brain *MRI* with respect to improvement after SDRR surgery. The improvements in gross motor functioning were best in children with normal imaging and not significantly different in patients with a history of hydrocephalus. The degree of improvement did not correlate with the severity of the periventricular leukomalacia in children with spastic diplegia.

26.3 Surgical Treatment

DRR surgery is usually performed selectively and termed selective dorsal root rhizotomy (*SDRR*). Surgery involves performing a laminotomy, usually between L2 and L5 followed by partial sectioning an average of 15–70% of the dorsal (*sensory*) nerve rootlets from L2 to S2 at the level of the root exit foramina, with most centres cutting more than 40% of the rootlets and limiting the sectioning of the S2 roots [12]. Surgical approaches have also included performing limited laminectomies at either the level of the conus medullaris [13] or more caudal at L5/S1 [14] and various forms of laminoplasty [15]. An absolute requirement for SDDR surgery is intraoperative monitoring with at least an eight-channel muscle response monitor [16]. Intraoperative stimulation of nerve roots and rootlets will differentiate less abnormal from more abnormal responses recorded from the biceps, quadriceps, hamstrings and gastrocnemius muscles on each side. Electrophysiologic abnormalities in dorsal nerve rootlets include:

- Spread to ipsilateral but abnormal myotomes
- Spread to contralateral myotomes
- Sustained, persistent firing throughout the stimulus duration
- Firing after stimulation cessation
- Crescendo/decrescendo responses [17]

During the SDRR surgery, a physiotherapist is present in the operating room to accurately document the lower extremity muscle contractions by palpation. The involved paediatric neurologist or paediatric physiatrist is also present, with the neurophysiology technician, and participates in the decision-making prior to definitive nerve rootlet sectioning. Operating time is usually 6–8 h.

Centres that perform partial, nonselective DRR surgery report similar results to SDRR without the added intraoperative time and cost of all the additional personnel. The scientific validity of neurophysiology monitoring and its role in nerve rootlet sectioning has been questioned [18, 19]. Many of the original criteria have been revised several times and limited to a smaller number to assess if fewer rootlets can be sectioned without changing outcome. Steinbok et al. [20] found that partial spasticity relief may be adequate to achieve a good functional outcome.

Contralateral and suprasegmental spread (*upper extremities*, *neck* and *face*) along with sustained responses with incremental patterns are unique in children with spasticity [21]; all of the other electrophysiology patterns have been identified in children without spasticity, with even contralateral spread being questioned as an absolute criteria for nerve rootlet sectioning [22].

Variability exists in the way SDRR surgery is performed, and electrophysiology responses obtained may differ substantially with only a slight alteration in technique [12]. Examples include the type of anaesthesia; the dissection of the dorsal root into rootlets; the type and placement of the electrodes, e.g. their distance from the cerebrospinal fluid, from the ventral root, from the root exit foramen and the interelectrode distance; the tension applied; the placement of the cathode/node; the type of stimulator; the definition and determination of threshold; and the tetanic stimulation parameters (how much above the threshold intensity, frequency, duration). Important is the number of muscles used for recording and type of electrodes, the type of recording and interpretation of responses, the correlation with palpable muscular responses and the decision of which rootlets to cut and which to spare [19]. In addition, other factors that may influence outcome include the disease process itself, which is primarily in the brain, corticospinal tracts and disorganised spinal interneuron pools; DRR surgery attempts to reduce the disinhibition by sectioning dorsal nerve rootlets that are quite peripheral from the regions of pathology.

26.4 Effectiveness

DRR provides benefit to carefully selected children with spasticity as a result of cerebral palsy, as spasticity is the main factor compromising gait and motor function in these children. The report by Staudt et al. [16] demonstrates that the surgery is responsible for the improvements seen rather than the maturation of the child or physiotherapy alone. Intensive physiotherapy alone does not improve long-term motor outcome [23]. However, post-operative physiotherapy and occupational therapy are definitely required, usually after a 5-day convalescent period, of which there are three components: (a) muscle stretching to gain mobility and range of motion, (b) muscle strengthening to increase endurance and (c) re-education to impart a better pattern of muscle use. This was also shown by Engsberg et al. [24] who found that the benefits of intensive physiotherapy (gains in strength, gait speed and overall gross motor function) are compounded with the addition of SDRR surgery.

Results from many centres have shown spasticity to be reduced after surgery, with loss of opposition between agonistic and antagonistic muscle groups, allowing for greater range of motion. Deep tendon reflexes decrease significantly or disappear; the Babinski response may also disappear. Tone tends to normalise. Some patients may become hypotonic; muscle re-education and strengthening is particularly important in these cases. Gait velocity is improved with an increased stride length [25]. Assistive devices are reduced and orthotic needs may change. Sitting posture improves, there is no scissoring and movements are more isolated with less energy expenditure. Other improvements include speech, personality, seizure control, upper extremity function and bladder control [26]. Craft et al. [27] indicated that the improvement in cognitive performance may not only be due to improved mood and reduced physical discomfort but also possibly secondary to "*supra-segmental effects*" induced by the DRR surgery. Bloom and Nazar [28] showed improvements in self-care, mobility and social functioning with less caregiver assistance. Mittal et al. [29] identified improvements in activities of daily living using a validated evaluation measure with the functional improvements persisting 3 and 5 years after surgery. In a separate publication, Mittal et al. [30] also showed a sustained upper extremity functional improvement in children in NYUMC Groups I, II and III. Assessments during adolescence and early adulthood have shown lasting benefits [1, 31].

26.5 Complications and Side-Effects

Complications of DRR surgery are related to the medical status of the patients, the surgical exposure and the potential neurological consequences of cauda equina manipulation and sectioning. In 158 children who underwent SDDR, Steinbok and Schrag [32] identified intraoperative, immediately post-operative and postdischarge complications that occurred in 3.8%, 43.6% and 30% of the patients, respectively. The most common intraoperative complication was aspiration pneumonia that occurred in 2 patients (1.3%). Perioperative complications included items such as emesis (59%), constipation (37%), skin rash (10%), dysesthesia (7.6%), headache (2.5%), urinary retention (4.4%), dysuria (1.9%), wound infection (0.6%) and *CSF* leak in one patient (0.6%). *Complications* noted after discharge included back pain (delayed onset in 10.8% and severe in 2.7%), neurogenic bladder/bowel (12.7%; persisted in 5.1%), paraesthesia (6.3%), persistent sensory changes (3.8%), increased seizures (2.5%), increased constipation (1.9%) and root compression in one patient (0.6%).

Golan et al. [33] reviewed the risks of post-operative spinal deformities and found that children with more severe cerebral palsy were more likely to develop scoliosis after surgery. The less affected children that were ambulators were at risk of developing spondylolisthesis. In addition, older age at the time of surgery and female gender were associated with greater post-operative lumbar lordosis (see Chap. 34). Chicoine et al. [34] found that the strongest predictor of improved ability to walk after SDRR was the

preoperative gait score obtained quantitatively by videotaped gait analysis. O'Brien et al. [4] found that children in the 2–5 years age range improved their gait more than children operated between 6 and 14 years of age, with less requirement for future orthopaedic surgery in the younger group (34% versus 70%). In a systematic review, Grunt et al. [2] found that there is lack of evidence that long-term spine abnormalities after SDDR surgery can be attributed to the surgery itself.

In a *recent* systematic review of systematic reviews, SDDR was strongly recommended for reducing spasticity (moderate quality of evidence in the literature) and improving gait kinematics, e.g. low quality of evidence. There is evidence for SDDR to improve gross motor function, but weakly recommended for improving function and participation, such very low quality of evidence [35]. Overall, the levels of satisfaction in adults who have undergone SDDR as children have been reported to be generally high, with no negative influence on life satisfaction [31]. In Chap. 25 "Intrathecal baclofen therapy for the control of spasticity" will discuss the treatment of spasticity using intrathecal baclofen and will compare the two treatment options of DRR surgery and implantation of a programmable baclofen pump in children with cerebral palsy.

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Hyperbaric Oxygen Therapy in Cerebral Palsy

27

Marian S. McDonagh

Abstract

Hyperbaric oxygen therapy (HBO) is the inhalation of 100% oxygen inside a hyperbaric chamber pressurized to greater than 1 atmosphere. This treatment has been approved for use in several indications including decompression sickness, carbon monoxide poisoning, severe burns, or chronic infections. HBO has been studied in cerebral palsy (CP), based primarily on the concept of improving oxygen availability to damaged brain cells with potential for recovery, even in after chronic injury. The evidence on HBO in CP is limited in precision, control groups, and methodological flaws. Three randomized controlled trials provide moderate strength of evidence that HBO does not improve gross motor function compared with slightly pressurized room air or wait-list controls, but these findings are controversial due to the nature of the control used (e.g., pressurized room air) and the limited number of patients studied. Observational before-after studies stimulate the interest in HBO for CP but are limited by methodological risk of bias. Adverse events of HBO include middle ear barotrauma, often requiring myringotomy and tube placement, and a potential increased risk of seizures. The use of HBO in CP remains controversial.

27.1 Introduction

While some studies of the use of hyperbaric oxygen (*HBO*) treatment have seemed to indicate that it may be effective in the *treatment* of cerebral palsy (*CP*), the evidence of its true potential benefits and harms is far from certain. The research to date has been sporadic and flawed even, while the results of some of this research have been promising.

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The US Food and Drug Administration (FDA) has approved HBO treatment for a number of injuries and illnesses. The uses that are currently recognized by the FDA are listed in Box 27.1. This list of FDA-approved indications was based on a list of accepted indications produced by the Undersea and Hyperbaric Medical Society (UHMS) in 1978 and updated by the UHMS in 2002 [1] and 2014 [2]. For any given drug or treatment, the FDA's approval list is generally used by Medicare/Medicaid and other insurers in making their coverage decisions.

Box 27.1 US Food and Drug Administration approved uses for hyperbaric oxygen therapy [2]

1. Air or gas embolism
2. Arterial insufficiencies
   (a) Central retinal artery occlusion
   (b) Enhancement of healing in selected problem wounds
3. Carbon monoxide poisoning
4. Clostridial myonecrosis (gas gangrene)
5. Compromised grafts and flaps
6. Crush injuries and skeletal muscle-compartment syndromes
7. Decompression sickness
8. Delayed radiation injuries (soft tissue and bony necrosis)
9. Idiopathic sudden sensorineural hearing loss
10. Intracranial abscess
11. Necrotizing soft tissue infections
12. Refractory osteomyelitis
13. Severe anemia
14. Thermal burns

Hyperbaric chambers are classified as class II medical devices by the FDA and as such require the manufacturers to comply with specific regulations before marketing. The regulatory process requires the manufacturer to specify the intended uses of the device. Manufacturers applying for uses beyond the 14 already acknowledged are required to submit supporting evidence. The evidence would be reviewed by the Center for Drug Evaluation and Research (*CDER*) in consultation with the Center for Devices and Radiological Health (*CDRH*). An Investigational New Drug (*IND*) application would be required for studies of significant risk and Investigational Review Board (*IRB*) approval for any study [3]. Manufacturers cannot advertise or promote uses that are not approved by the FDA.

Further, the FDA has deemed hyperbaric chambers to be prescription devices. This designation requires that a valid prescription is required prior to use. Practitioners authorized to prescribe HBO vary by state. As is the case with other prescription devices and drugs, a physician who believes that HBO therapy is the best therapy for a patient with an indication that is not on the list may prescribe HBO for this "off-label" use.

While provision of HBO treatment for the indications in Box 27.1 may be fully accepted in many health systems, the use of HBO for conditions outside this list, such as CP, is mostly not accepted and therefore not a covered benefit. Many patient families have been willing to pay for these services "out of pocket." Information on the cost and charges for HBO is somewhat limited, but it is reported that in the USA Medicaid pays $400 per session for an inpatient facility, typically using a multiplace chamber [4]. Monoplace chambers, which are often located outside of major medical facilities, are reported to have lower start-up and operating costs (USD 48–66 per treatment session), but data on patient charges are difficult to find [5]. The total cost of treatment will depend on the duration and total number of sessions.

27.2 What Is HBO Therapy?

Hyperbaric oxygen therapy is the inhalation of 100% oxygen inside a hyperbaric chamber pressurized to greater than 1 atmosphere (atm). HBO therapy causes both mechanical and physiologic effects by inducing a state of increased pressure and hyperoxia. Hyperbaric oxygen pressure is expressed in multiples of atmospheric pressure at

sea level, where 1 atm is about 760 mmHg or 1 kg of pressure per square centimeter [6, 7]. The oxygen dissolved in blood at 1 atm (*sea level*) while an individual is breathing room air is 0.3 mL/dL, and this is in addition to hemoglobin-bound oxygen. Breathing 100% oxygen at 1 atm results in an increase in blood oxygenation to 1.5 mL/dL or about five times the blood oxygenation created while breathing normal room air. Increasing the pressure to 3 atm increases the blood oxygen (dissolved oxygen, not carried by hemoglobin) to 6 ml/dL [8, 9]; this *represents* a 20-fold increase in blood-borne oxygen, excluding hemoglobin-bound oxygen. At rest and with good perfusion, tissues require 5–6 ml/dL of oxygen, whether from dissolved or hemoglobin-bound oxygen. Hence, in situations where hemoglobin-bound oxygen is limited (e.g., *carbon monoxide poisoning*), tissue oxygen needs can be met with an increase in dissolved oxygen.

In addition to this hyperoxic effect, the increased pressure reduces the volume of gases in the blood by virtue of Boyle's law (in an enclosed space, the volume of a gas is inversely proportionate to the pressure exerted upon it). This is the mechanism relied upon in treating decompression illness and arterial gas embolism to reduce the size of the gas bubbles and allow replacement of inert gas in the bubbles with oxygen, which can be metabolized by tissues.

HBO can be administered in two primary ways, using a monoplace chamber or a multiplace chamber [6]. The monoplace chamber serves one patient at a time. It is the less-costly option for initial setup and operation but provides less opportunity for patient intervention while in the chamber. Monoplace chambers are generally constructed of clear acrylic or with acrylic view ports that allow for patient observation. Monoplace chambers are generally pressurized with 100% oxygen.

Multiplace chambers allow medical personnel to work in the chamber and care for acute patients to some extent. In the multiplace chamber, the chamber is pressurized with room air, and the 100% oxygen is delivered through a facemask, tight-fitting hood, or endotracheal tube. Because the entire multiplace chamber is pressurized with air, medical personnel may require a controlled decompression, depending on how long they are exposed to the hyperbaric air environment.

While the duration of an HBO session is typically 90–120 min, the duration, frequency, and cumulative number of sessions have not been standardized for treatment of any approved or "off-label" use. The type of chamber used may affect the dose received by the patient. For example, multiplace chambers using facemasks or hoods that do not fit snugly may result in dilution of 100% oxygen with room air.

27.3 Why HBO?

In *chronic* infected or nonhealing soft tissue wounds, local tissue hypoxia predisposes to infection and prevents effective healing [7]. Hyperbaric oxygen *reverses* local hypoxia, inhibits postischemic vasoconstriction, and promotes the formation of collagen matrix, which is essential for angiogenesis and restoration of blood flow to the injured tissue [6, 7, 9]. Although the biochemical and cellular effects of oxygen deprivation and oxygen therapy are well accepted for soft tissue injuries, the application of these concepts to brain injuries is controversial. Recent theories of neuronal damage and recovery implicate a complex cascade of events that begin with depletion of intracellular ATP and expression of immediate early genes leading to energy failure, mitochondrial dysfunction, oxidative damage to RNA/DNA, and functional or structural brain damage [10].

A detailed *examination* of the theoretical basis for the use of HBO in brain injury is beyond the scope of this chapter. While the theories of brain pathophysiology and recovery from injury, along with the animal experimental studies and human case studies supporting these theories, have been reviewed in detail elsewhere [11], the following *summary* provides the general outlines of these theories. The following discussion is not comprehensive but highlights some of the underpinnings of these theories and how they differ from other descriptions of brain injury and recovery.

27.4 Acute Brain Injury

Inadequate supply of blood and oxygen clearly causes injury and cell death in stroke, in which the artery supplying a region of the brain is blocked, and in anoxic-ischemic encephalopathy, in which perfusion to the entire brain is compromised by shock, hypotension, strangling, or another insult. In acute traumatic brain injury, hypoxia and hypotension are each independently associated with increased mortality and morbidity. Thus, secondary ischemia and oxygen deficiency are thought to be important mechanisms of cell death in traumatic brain injury [12].

Because of the devastating effects of hypoxia and hypotension in brain-injured patients, aggressive efforts to avoid or correct hypovolemic shock and to prevent cerebral hypoperfusion became fundamental principles of the management of trauma care. These principles, however, have recently been challenged by studies suggesting that management of perfusion pressure does not improve, and may worsen, the outcome of resuscitation. However, aggressive management of trauma reduces the frequency of hypoxic and ischemic episodes, but does not come close to eliminating it. For this reason, there is renewed interest in finding more effective strategies for ensuring adequate oxygenation and redistributing cerebral blood flow to injured areas of the brain.

Immediately after a brain injury, brain cells can be inactivated temporarily by local, injury-related sequelae such as ischemia and edema, which are thought to compromise local perfusion. This observation forms part of the rationale for the use of HBO therapy, which increases blood flow to the damaged areas of the brain, as documented by serial single-photon emission computed tomography (SPECT) scans and other techniques [13–16]; see Chap. 14.

In some *experimental* models of acute cerebral ischemia and acute carbon monoxide poisoning, HBO prevents cell death [11], but the mechanism is unclear. Even if redistribution of cerebral blood flow is a factor, the effects of oxygen on the cellular and inflammatory response to injury may be more important [11]. *Recently*, for example, in a rat model of focal cerebral ischemia, HBO reduced brain leukocyte myeloperoxidase (*MPO*) activity, which is produced by white blood cells (polymorphonuclear neutrophils) and is a marker of the degree of inflammation. Rats randomized to HBO had reduced infarct size and improved neurological outcomes compared with untreated rats, and the degree of neurologic damage was highly correlated with the level of MPO activity [17]. In a separate model of cardiac arrest and resuscitation, the same investigators found that dogs treated with HBO had better neurological outcomes and, histologically, fewer dying neurons than did dogs treated conventionally [18]. The magnitude of neuronal injury correlated well with the neurological outcomes, but was not related to cerebral oxygen delivery or to the rate of oxygen metabolism. Evidence of a clinical effect in humans is limited and was found insufficient to draw firm conclusions [19, 20].

27.5 Chronic Brain Injury

Many brain-injured patients progress spontaneously from coma to consciousness to recovery of some cognitive functions. This phenomenon of spontaneous recovery from brain injury implies that some brain cells that have lost function can regain it, sometimes after long periods of time. Several theories of recovery after injury in the central nervous system invoke the concept of temporary, reversible inactivity of brain tissue to explain this phenomenon.

The use of HBO for *chronic* brain injury, CP, and stroke is based on the theory that, in any brain injury, there are inactive cells that have the potential to recover. According to this theory, these "idling neurons" exist in the ischemic penumbra, a transition area of dormant neurons between areas of dead tissue and the unaffected healthy tissue [11, 21]. The theory is that oxygen availability to these cells stimulates the cells to function normally, reactivating them metabolically or electrically.

It is useful to distinguish between this theory and a popular theory in the field of neuropsychology. The neuropsychological theory postulates that

the neurons are inactivated by deprivation of innervation that had come from cells now destroyed by injury [22]. *According* to this theory, recovery occurs as surviving neurons establish new synaptic connections that can help reactivate cells that are temporarily inactive. Recently, however, a National Institutes of Health Consensus Development Conference conducted an independent, critical assessment of the animal and human evidence regarding this theory and clinical approaches based on it [22]. The panel noted, first, that synaptic reorganization and "sprouting" observed in the denervated animal brain had not been translated into functional improvements. Second, they noted the lack of evidence that any therapy actually promotes these physiologic processes, either in animal models or in humans. No animal experiments or human case studies have succeeded in linking the clinical observation of improved cognitive function with anatomic or physiologic measures of synaptic enrichment. In fact, human studies have found no relationship between the amount of treatment, frequency of family visits, and other forms of stimulation hypothesized to promote the growth of new synaptic connections. In a randomized trial in 120 active duty military personnel with moderate to severe traumatic brain injury (*TBI*), intensive in-hospital cognitive rehabilitation was no more effective than limited home rehabilitation program with weekly telephone support from a psychiatric nurse [23].

In contrast with the cognitive stimulation theory, the "idling neuron" theory views neuron inactivity denervation as the result of chronic hypoxia and postulates that restoring oxygen stimulates the growth of blood vessels and of new synaptic connections among previously dormant neurons. Supporters of the use of HBO in brain injury argue that this theory has a stronger experimental base than does the theory underlying restorative cognitive therapies [11]. In contrast to the theoretical effects of cognitive stimulation, the effects of the proposed treatment—pressurized oxygen—can be observed directly in animal models. As noted above, animal studies have examined HBO's effects on physiologic and anatomic endpoints, including neuronal death, infarct size, and, in some models, development or preservation of synapses. The physiologic effects of hyperbaric oxygen have also been examined in before-after treatment case studies in humans using SPECT imaging and markers of cerebral metabolism; see Chap. 14.

27.6 Adverse Effects of HBO

Adverse events can occur during compression, treatment, and decompression and are related to the increased pressure and/or the increased oxygen concentration. *Complications* such as pulmonary barotrauma or seizures can occur and be seen immediately, but more subtle adverse effects may emerge after a series of treatments. The findings of a recent study of HBO for acute carbon monoxide poisoning raise concerns over worse cognitive outcomes in patients receiving HBO compared with normobaric oxygen [24].

27.7 HBO and Cerebral Palsy

The evidence on the effects of HBO in patients with CP is limited to three small, randomized controlled trials (total of 186 patients enrolled) and five observational before-after studies (total of 455 patients). In 2003 a systematic review to examine what medical research would tell us about the benefits and harms of HBO for the treatment of CP among other medical conditions, *including* severe brain injury, was commissioned by the Agency for Healthcare Research and Quality in the USA [20, 25]. A systematic review follows a scientific protocol by which reviewers look at all of the available data from research on a given drug class, disease, procedure, or treatment in order to determine a summative estimate of scientific knowledge in a given area. At that time, only six very different research studies were found that had been explicitly designed to determine whether HBO treatment might offer some benefit to CP patients and/or their caregivers (Table 27.1), and no studies specifically studied what harms might result from HBO treatment among CP patients. Since the publication of that

Table 27.1 Study characteristics of studies of hyperbaric oxygen therapy for CP

Randomized controlled trials			
Study (quality)	Population	*N* Age range	HBO protocol Control protocol (type of chamber)
Lacey (2012) USA (fair)	Children with spastic CP who could tolerate a hyperbaric oxygen hood and could blow through a straw, blow the nose, or swallow on command	25 HBO 24 control 3–8 years	*HBO*: 100% oxygen at 1.5 atm × 80 min × 40 sessions Sessions 5 days/week × 8 weeks *Control*: a mixture of gases (14% oxygen) at 1.5 atm to simulate 21% oxygen at room air × 80 min × 40 sessions Sessions 5 days/week × 8 weeks (Multiplace chamber)
Collet (2001), Hardy (2002), Muller-Bolla (2006) Canada (fair)	Children with CP with history of hypoxia in perinatal period, motor development age of 6 months to 4 years, and psychological development age of 24 months or more	57 HBO 54 control 3–12 years	*HBO*: 100% oxygen at 1.75 atm × 60 min × 40 sessions Sessions 5 days/week × 8 weeks (Monoplace or multiplace chamber, depending on facility used) *Control*: room air at 1.3 atm × 60 min × 40 sessions. Sessions 5 days/week × 8 weeks
Packard (2000) New York (poor)	Children with CP secondary to prenatal insults, premature birth, birth asphyxia, and postnatal hemorrhage. Moderate to severe CP, no evidence of brain malformation. Developmental delay of at least 33% in one area and no active seizures for the previous 6 months	12 immediate treatment group 14 delayed treatment group 1–5 years	*HBO*: 100% oxygen at 1.5 atm × 60 min twice daily × 40 sessions Sessions 5 days/week × 4 weeks (Chamber type not reported) *Control*: delayed HBO treatment—6 months after immediate HBO group
Observational studies			
Mukherjee (2014) (Fair)	Children with CP	150 1–17 years	*HBO*: (plus intensive rehabilitation) (a) Room air at 1.3 atm × 60 min × 40 sessions × 6 days per week × 7 weeks (b) 100% oxygen at 1.5 atm × 60 min × 40 sessions × 6 days per week × 7 weeks (c) 100% oxygen at 1.75 atm × 60 min × 40 sessions × 6 days per week × 7 weeks (Multiplace chamber for 100% oxygen, "soft chamber" for air) *Control*: intensive rehabilitation only
Montgomery (1999) Canada (fair)	Children with CP and a functional diagnosis of spastic diplegia	25 3–8 years	*HBO*: 95% oxygen at 1.75 atm × 60 min × 20 sessions 10 patients received 1 treatment/day × 20 sessions 5 days per week × 4 weeks in a monoplace chamber 15 received 2 treatments/day × 20 sessions 5 days per week × 2 weeks in a multiplace chamber

Table 27.1 (continued)

Randomized controlled trials			
Study (quality)	Population	*N* Age range	HBO protocol Control protocol (type of chamber)
Waalkes (2002) USA (fair)	Children with varying diagnoses of CP	7 1–16.5 years	1 *HBO*: 100% oxygen at 1.7 atm × 60 min × 80 sessions. 1 treatment daily × 5 days per week × 4 months (Multiplace chamber)
Machado (1989) Brazil (poor)	Children with CP	230 <1 year–15 years	*HBO*: 100% oxygen at 1.5 atm × 1 or 2 maximum hours per day × 20 sessions (Monoplace chamber)

review, two additional studies have been published: one randomized controlled trial and a before-after study [26, 27].

The best evidence on the benefits and harms of HBO therapy in CP is provided by two similar randomized controlled trials [26, 28]. The two trials were similar in that they used a sham control group where patients entered the hyperbaric chamber and received slightly pressurized room air, enrolled all or mostly children with spastic forms of CP with mean age of 7 years in one and 6 years in the other, and evaluated changes in the 88-point Gross Motor Function Measure (*GMFM*) scale as the primary outcome measure (see Chap. 22). An increase of greater than 2.73 points from baseline is considered the minimal clinically important difference (*MCID)* [29]. The hyperbaric oxygen regimens differed somewhat, one providing 100% oxygen at 1.5 atm for 80 min and the other at 1.75 atm for 60 min, both given 5 days a week for 40 sessions. A total of 160 children were enrolled in the two trials.

Based on these trials, there is moderate-strength evidence that HBO does not improve motor functioning more than pressurized room air in children with CP. In the first study, at the end of the 2 months and 40 treatments, motor function scores improved in both groups in the earlier, larger trial [28]. The average change in GMFM was 2.9 in the children receiving HBO and 3.0 in the children receiving only pressurized room air. *Compared* with baseline, these improvements were statistically significant, but the difference between groups was not. In the more recent trial, the changes from baseline were small and not statistically significant (1.5 and 0.6 points in HBO and control). This trial was stopped early after two preplanned interim analyses indicated that continuing was very unlikely to change the findings. *Combining* these study results using meta-analysis finds an absolute difference in score of −0.11 (95% confidence interval −1.25 to 1.03, not statistically significant) (see Fig. 27.1). Both studies evaluated the children at longer follow periods (6 months in one and 3 and 6 months in the other) but again found no statistically significant differences between the groups.

In the Collet et al. [28] trial, secondary outcome measures, including neuropsychological tests, also did not show a difference between the groups [30]. When the caregivers' viewpoint was measured with the Paediatric Evaluation of Disability Inventory (*PEDI*), the caregivers of the children in the group treated only with pressurized room air estimated that their charges had significantly better mobility and social functioning [28]. *Similarly*, in the Lacey et al. [26] trial, secondary measures included the PEDI scale where significant differences were seen in both groups compared with their baseline scores, but statistically significant differences were not found between groups. This study also administered the Test of Variables of Attention (*TOVA*), but fewer than half of the patients were able to complete the test, and no differences were seen within groups compared with baseline or between groups.

This evidence is moderate strength, meaning that we have moderate confidence that additional studies would not alter the findings. While the

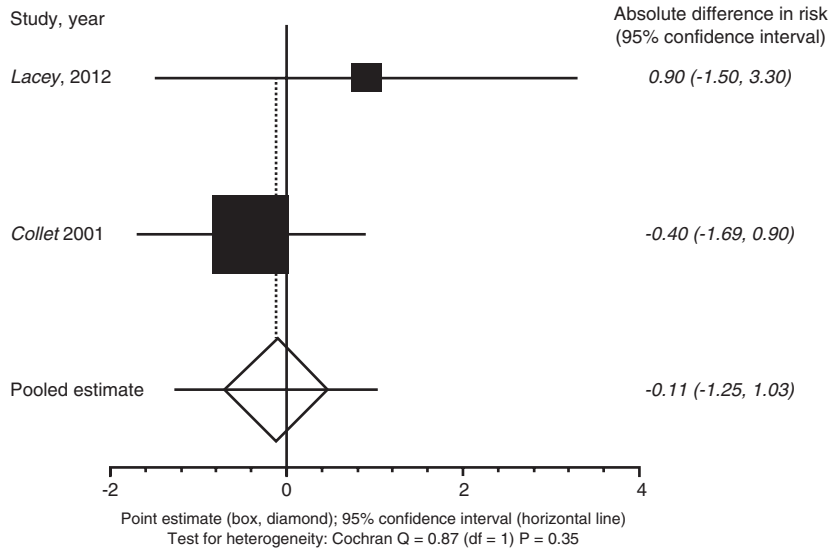

Fig. 27.1 Meta-analysis: difference in change in GMFM-88 scale scores after 40 HBO sessions versus sham treatment

study findings are generally consistent, the studies have a few methodological limitations, and the resulting estimate is not precise due to small sample sizes. However, the pooled estimate for the difference in change in GMFM scores was statistically significant, and the upper and lower bounds of the confidence interval are smaller than the minimal clinically important difference identified as 2.73 points [29].

While both of these trials were generally well designed and conducted, there were some methodological issues that could introduce bias. On the plus side, both were randomized appropriately and used validated scales to measure outcomes, but only the Collet et al. [28] study used blinding of physical therapists making outcome assessments. However, the success of keeping the order of random assignment concealed from researchers responsible for enrolling patients was not clear in Collet et al. [28], and there were significant differences between the two groups in presumed cause and type of CP, and the average difference on the GMFM scale between the two groups at the outset of the study was nine points. To manage this, the statistical analysis of change in GMFM was adjusted to accommodate for this initial difference in GMFM score. In the Lacey et al. [26] trial, the difference in baseline GMFM scale scores was 4.2 points, and there was a 1-year age difference between the groups (6.3 versus 5.2 years). For both studies, perhaps are more important potential limitations is that it was unclear whether the children included in the trials were representative of children with CP. In Collet et al. [28], 196 children were screened, with 111 being enrolled, and in Lacey et al. [26], 360 children were screened with only 49 being enrolled, although reasons for exclusion of the 311 children were provided. Of these, 89 were found eligible but did not participate, and the baseline characteristics and GMFM scores for these children were not reported.

In addition to these two studies, there is one other randomized controlled trial and five observational studies. The trial was a pilot study with serious flaws that showed mixed results [31]. In it, two small groups of children were assigned to HBO either immediately after enrollment in the trial or after a 6-month waiting period. A variety of methods (Bayley II, Preschool Language Scale, Peabody Motor Scales, PEDI) were used by blinded physical therapists and child psychologists to assess children in both groups at baseline, 1 month, 2 months, and 5 months. No meaningful differences between the two groups were found in any of these assessments. However,

caregivers assessed the children on the PEDI mobility sub-score and found significant improvement among the children assigned to immediate treatment. This trial, however, has many scientific flaws, including that the caregivers providing assessments knew which group their child had been assigned, which could have biased their assessments [25].

Historically, observational before-after studies of HBO for CP fueled the interest in this treatment, but the inherent bias in the study designs and flaws in study conduct do not allow these studies to meaningfully contribute to the body of evidence. The highest-quality observational evidence came from a study of 25 children that measured GMFM, among other tests (tone level using the modified Ashworth scale, fine motor strength using the *Jebsen* test, and an assessment of fine motor activities by videotape) [32]. This study is sometimes referred to as the McGill study and was conducted by the group of investigators that later conducted the largest randomized controlled trial (*above*) [28, 32]. The researchers found an average improvement of 5.3% in the GMFM score after HBO. The assessment of gross motor function indicated 67% were better after treatment, 29% were better before treatment, and one child in each group was not different or was not videotaped after treatment (videotapes were used for assessment so that the physical therapists conducting the assessment did not know to which group the child belonged). While the results appear to show improvement after HBO therapy, this trial also suffered from design flaws that could alter the results. The follow-up period was poorly defined and could have ranged from a few days to 1 month after the treatment. Hand movement, tone, and parental judgments improved, but the scales used to make these assessments and the number of participants improving were not reported. This *study* used different protocols at different centers and did not stratify the results based on this exposure difference. Children with a variety of complicating factors, including recent rhizotomy, and those on anti-spasticity medications were excluded, reducing generalizability of results. However, this study is considered the highest-quality observational evidence because (1) stable baselines were established, (2) outcome assessors were blinded, and (3) validated scales were used to evaluate the primary outcome measure.

A more recently published before-after study evaluated two different HBO regimens, a pressurized air regimen (all combined with intensive rehabilitation) and a control group receiving only intensive rehabilitation. The study combined the HBO groups with the pressurized air group and found these children had larger improvements in motor function than those receiving only intensive rehabilitation. Methodological issues include the lack of information on how control subjects were selected, no information on the timing of baseline measures in relation to starting treatment or that baseline measurements were stable (i.e., multiple measurements), lack of blinding of outcome assessors, and differences in baseline GMFM-66 scale scores of 0–4.7 points across the groups. This study was carried out over 10 years, but there was no information on the temporal timing of the two different HBO treatment regimens or when in this 10 years the control subjects were identified. The analyses controlled for age, but other baseline patient-level characteristics or study-level factors such as changes in other aspects of clinical management of children with CP over the 10-year period were not controlled for.

The other observational studies were either very small (seven patients) [33] or were very poor quality because they provided inadequate information to make assessments about risk of bias [34].

27.8 Evidence on Harms of HBO for CP

None of the six studies explicitly defined an a priori plan to monitor potential harms from HBO; however, ear problems or seizures were reported. In the Collet et al. [28] trial, significantly more children experienced middle ear barotrauma in the HBO (50% at 1.75 atm) group than did those in the control group (27.8% at 1.3 atm; relative risk 1.5, 95% CI 1.1–2.2, $p = 0.02$) [28, 35]. One of 57 children in the HBO group withdrew from

the study after receiving 32 of 40 sessions due to repeated middle ear barotrauma, and across both groups, 58.2% of children were treated with myringotomies with ear tube placement. In a follow-up publication, regression analyses did not identify factors that would predict middle ear barotrauma, although both baseline global GMFM and gender were positively associated with this adverse event [35]. Changes in motor function were similar in children with and without barotrauma: 3.3 ± 3.9 versus 2.7 ± 3.0 (p = 0.22). Sinus barotrauma occurred in three (3.6%) of the children in the HBO group and none in the control group.

The *second* trial did not report adverse events as extensively or as clearly [26]. One patient in each group withdrew: one in the HBO group due to three episodes of fluid in the ear or nose after a treatment and one episode of rectal bleeding that occurred at home and in the pressurized air group one patient who experienced a seizure (determined by the study to not be related to the treatment). Ear pain was the only adverse event reported and was reported only for children who had completed all treatments. There was no difference in the incidence of ear pain; 29% (7 of 24) in the HBO group and 36% (8 of 22) in the control group (p = 0.755).

In one study, 12% of children experienced seizures and withdrew, although the temporal sequence was not clearly reported [31]. Children with a history of *seizure* were excluded from another of the observational studies, but 8% of children still stopped HBO treatment due to various adverse events, including seizure.

27.9 Summary

Current evidence is inadequate either to establish a significant benefit or to identify the potential for harms of HBO for the treatment of children with CP compared with standard treatment. While observational studies reported improvements on subjective measures and on motor function as measured by GMFM, two controlled trials report similar improvements in children who did not receive HBO, indicating that HBO may not be the cause of improvements seen in the observational studies. Some proportion of children undergoing HBO will experience adverse events including seizures and the need for ear pressure equalization tube placement, but due to poor-quality methods of assessment, estimates of the prevalence of these are uncertain. Evidence from controlled trials is preferred here because these observational studies are less than good quality, and bias and confounding are serious concerns. Based on the grades of bodies, there is Grade A evidence that HBO is not different from pressurized room air for the treatment of CP, with only Grade C evidence supporting improvements in various measures after HBO.

While it is unknown how the effectiveness results would vary in a more broadly defined population, it is also unknown how the risk of harms would differ in a broader—generally sicker—group of patients. To date, one of the largest concerns about this evidence base is the lack of good-quality evidence on potential harms. In order to weigh the balance of benefits and harms, clinicians and patients need good-quality evidence for both. The evidence to date, good or otherwise, has examined the benefits while inadequately reporting adverse events. Ascertainment techniques were not defined, and it was not possible to determine whether they were non-biased and accurate. It was also unclear as to whether adverse events reported included all levels of severity. Importantly, it appears that adverse events are only reported for groups receiving HBO in trials and only during and immediately after HBO in observational studies.

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Visual Impairment in Cerebral Palsy

28

Nikolaos Kozeis and Saurabh Jain

Abstract

Cerebral palsy is a disorder of movement and posture due to damage to immature brain which can be either cortical, subcortical, or both. Early brain malformations and congenital or postnatal infections affect not only the motor areas of the brain but also many levels of the visual pathway leading to various visual disorders and to a misinterpretation of the visual world. Ocular and visual abnormalities are very frequent in cerebral palsy (50–90%). The severity of visual impairment is related to the area and to the extent of the brain damage. Most children experience difficulties with their visual acuity; visual fields; contrast sensitivity; binocular vision; ocular alignment; ocular motility (uncoordinated saccades and pursuits, paroxysmal ocular deviations, fixation instability, dyskinetic eye movement disorder, ocular motor apraxia); visual-guided movements; visual searching; recognition of faces, objects, and/or routes, visual attention, and in maintaining eye contact. Visual impairment plays a key role in psychokinetic development of these children. An early ocular, visual, oculomotor, and visuoperceptual assessment is very important. The accurate detection of visual disorders not only leads to a complete clinical diagnosis but also to an appropriate intervention plan.

28.1 Introduction

Cerebral palsy is a disorder of movement and posture due to damage to immature brain which can be either cortical, subcortical, or both. Causative factors include premature birth, hypoxic-ischemic encephalopathy, early brain malformations, and congenital or postnatal infections that affect not only the motor areas of the brain but also many levels of the visual pathway such as the retrogeniculate visual system and

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associated visual cortical areas. Damage to these areas leads to various visual disorders and to a misinterpretation of the visual world [1–3]. Visual processing is a complex cerebral activity that involves a significant proportion of the central nervous system. Visual deficits are common findings in neurodevelopmental disabilities like cerebral palsy (CP). With greater appreciation, they are now considered an integral part of the clinical presentation of CP and not just associated symptoms.

28.2 Ocular and Visual Abnormalities

Ocular and visual abnormalities are *very frequent* in CP (50–90%), being 10–70 times more common than in general pediatric population of equivalent age. The severity of visual [4] impairment is related to the area and to the extent of the brain damage. Most children with CP experience difficulties with their visual acuity; visual fields; contrast sensitivity; binocular vision; ocular alignment; ocular motility (uncoordinated saccades and pursuits, paroxysmal ocular deviations, fixation instability, dyskinetic eye movement disorder, ocular motor apraxia); visual-guided movements; visual searching; recognition of faces, objects, and/or routes; and visual attention and in maintaining eye contact [5]. Those with very severe attentional problems are at risk of being misdiagnosed as *blind* [6].

About two-thirds of CP children may present with cerebral visual impairment (*CVI*), a major cause of low vision in children worldwide. This is more common in children with PVL (*periventricular leukomalacia*), who experience difficulties in visual object recognition, visuospatial skills, and visual memory [7].

Up to 11% of children with CP have severe visual impairment (*SVI*) (see Chaps. 2 and 3). SVI by itself can constrain many areas of development in the early years of life including spatial awareness, posture and movement skills, use of hands and fine movement coordination, early concept development, speech and language development, social interaction and communication, and self-care skills. The level of visual loss is strongly related to the delay in psychomotor development. Half of CP children also have a form of a seizure disorder and 30% to 50% have some sort of *cognitive dysfunction* and learning, speech, and memory problems [8–10].

Ghasia et al. [11] showed that the severity of the visual impairment is associated with the degree of motor impairment. Only 4–9% of children with mild CP (Gross Motor Function Classification Scale—*GMFCS* level 1) have visual deficits, compared to 58%–60% of children with severe CP (*GMFCS* level 5). Seventy percent of the children with severe CP (GMFCS level 5) have more than one visual deficit. They are also at greater risk for high *myopia*, *dyskinetic strabismus*, severe *gaze dysfunction*, absence of fusion, optic neuropathy, and CVI.

It is not clear why myopia occurs with greater frequency in the children with more severe levels of CP. It is hypothesized that the cytokines implicated as the cause of cerebral damage may also interfere with emmetropization by mechanisms that are currently unknown [11, 12].

28.3 Refractive Errors

Refractive errors are common in CP children, probably due to the lack of development of a normal optical system. Hypermetropia is the most common refractive error in mild to moderate CP, while myopia is commoner in severe CP. Anisometropia may also be detected in 10–20% of all CP children. Correction of the refractive errors is important to improve the focusing and to improve communication and guidance of movement. Correction of even a small degree of hypermetropia can magnify the text and help those with reading difficulties [5, 11, 13].

The best corrected visual acuity (BCVA) may be low in many CP children (35–65%), despite normal pupillary responses and normal ophthalmic examination findings. But total blindness is rare. The reduction in visual acuity is probably due to a disruption to the process of emmetropization. Just measuring the BCVA is not enough to assess functional vision (or vision for

everyday living), which requires attention and concentration. CP children with reduced BCVA can be helped by increasing the size and/or the proximity of text and images (enlarging the print, double-spacing text, and presenting written material in small sections). Visual acuity may also improve by limiting distractions [14].

Amblyopia is also common, mainly in strabismic CP children (70%). Dyskinetic strabismus is seen exclusively in these patients where the ocular deviation fluctuates from an esotropia to an exotropia under the same accommodative conditions. Surprisingly these children do not usually develop severe amblyopia, presumably as this type of strabismus does not promote chronic amblyogenic suppression of vision from one eye [15].

Fundus abnormalities are not uncommon in this cohort (30%). A pseudoglaucomatic cupped optic disc (due to subcortical insult of the immature visual system in premature babies) and a temporally pale optic disc (due to cortical insult to the mature visual system in full term babies) are common findings in CP and may be associated with some visual dysfunction. It has been hypothesized that a mechanism of transsynaptic degeneration is involved [5, 16].

The color vision appears to be grossly normal. However, acquired damage to the temporal lobes in older children can lead to abnormalities of color perception and interpretation [17].

Contrast sensitivity is a very important component of visual function. The contrast sensitivity threshold can be significantly reduced in CP children (25–90%). CP children with poor vision are also unable to see low contrast targets, creating difficulties in activities of daily living. These children require their toys and educational material to be bright and clear, as well as distinct color boundaries [5, 18].

Visual fields are usually impaired in CP children (20%) with the types of visual field defect depending on the area of brain affected. Damage to the occipital lobes leads to homonymous lack of visual field on the contralateral side. Damage to the posterior parietal region on one side causes lack of attention on the opposite side (inattention), imitating homonymous hemianopia, but with a few differences. Children with homonymous hemianopia have a conjugate gaze deviation toward the hemianopic field; however, children with visual inattention compensate by rotation of the body toward the problematic area. Bilateral superior posterior parietal damage, affecting *periventricular* white matter, commonly causes lower field impairment, and the affected children look down when they walk as they probe floor boundaries with a foot to check for height change. *Bilateral* posterior parietal damage also causes inability to see multiple targets simultaneously and impaired guidance of motion (*optic ataxia*) [14, 19].

Stereopsis and binocular vision are very commonly affected in CP children (50–85%), either due to retrogeniculate damage, amblyopia, or oculomotor dysfunction [20, 21].

Marked abnormalities of eye movements have been found in all types of CP children. Gaze disorders, saccade, pursuit and OKR asymmetry, and nystagmus are evident in severe CP children. A *horizontal tonic gaze deviation* usually accompanies cortical damage, while a tonic down gaze deviation is associated with subcortical damage. Those with severe oculomotor disorders, but good head and neck control, use horizontal or vertical head thrusts to facilitate gaze shifts.

A significant proportion of CP children displays altered fixation (25–80%) that may be either absent or eccentric and is associated with injury to periventricular white matter. As in those with very severe attentional problems, these children are also at risk of being misdiagnosed as *blind* [22–24].

Smooth pursuits are tracking movements to follow a slowly moving target, and they are significantly impaired in CP children (60–98%). Affected children appear with difficulty in seeing multiple targets at once. They also have problems following moving targets, like watching cartoons on the TV [24].

Saccades are fast eye movements to alter fixation quickly. These movements are often affected in CP children (60–100%), being either absent, hypermetric, or hypometric. These children adopt compensatory strategies, such as brusque head movements, frequent blinking, or both; they also

present with hyperfixation and conjugate gaze spasms (*upward and lateral*) [17]. Kozeis et al. [21] studying school-aged CP children found that the microsaccades, being used in reading, are also markedly affected.

Convergence and *divergence* are disconjugate movements, used to maintain fixation on a target as it moves toward or away from the child's face. These movements are impaired in many CP children (30–50%) interfering with the focusing [25].

A markedly increased incidence of strabismus is observed (40–80%) in these children [26]. Nonparalytic esotropia is commoner than exotropia and is commonly accompanied by vertical incomitant deviations and A/V patterns (65–85%) [5]. *Dyskinetic strabismus* is a distinct type of strabismus characterized by variability of the direction and magnitude of the strabismus. It is unique to cerebral palsy, unrelated to accommodative effort or attention, and it is noted only in severe cases of CP. These children are poor candidates for surgical correction, while children with stable deviations respond favorably to cautious strabismus surgery [26]. Some esotropic CP children convert spontaneously to an exotropia over several years [24, 25].

Nystagmus is also common in CP children (30%), although some believe that nystagmus does not occur in retrogeniculate disease. This is probably due to the coexistence of anterior visual pathway involvement. Motor nystagmus usually improves as the vision does [3].

The optokinetic reflex (OKR) causes eye movement in response to objects moving in the periphery while the head is stationary. It combines saccades and smooth pursuit eye movements and maintains the balance of the body in a moving visual environment. It interacts with the vestibular optic reflex when the head is rotating in stationary visual environment. This reflex plays an important role in everyday experience for most people in the context of driving, as objects tend to move rapidly past the driver in the periphery, which requires a rapid ocular response, while maintaining primary fixation on the road. A high percentage of CP children appear to have altered OKR (55–87%) [25].

The vestibulo-ocular reflex (VOR) stabilizes the image on the retinas during head movements, by producing eye movements in a direction opposite to the head movement, preserving the image on the center of the visual field. It thus maintains the balance of the body by keeping the world steady when the head moves. VOR is impaired in CP children (50–80%) [25].

Accommodation is a reflex, which is elicited in response to focusing on a near object. It comprises coordinated changes in vergence, lens shape, and pupil size. Accommodation is impaired in CP children (55–65%). These children find it difficult to see near objects and could be misdiagnosed as inattentive. Near vision glasses are a simple and very effective solution [17, 27].

The pupillary reflex controls the quantity of light entering the eye. These may be sluggish especially in tetraplegic CP children (5–75%), rendering them photosensitive [5].

Perception is the ability to incorporate and interpret sensory and cognitive information. It seems that there is a dynamic self-organized system in which perception and action are closely related. This is the way we understand the environment, act and interact [28].

Many CP children (>60%) appear to *have visuoperceptual* and *visuocognitive problems* due to damage to the associated cortical areas (inferotemporal cortex, parietal lobes, frontal eye fields, occipito-parieto-temporal junction) and/or the streams (ventral and dorsal) connecting the primary visual cortex with these areas. These children may present with delay in the learning process, as well as the development of perceptual experiences [21].

The ventral stream connects the occipital (*visual*) cortex to the inferotemporal cortex (storage of prior visual experiences), allowing recognition and appreciation of shape, color, texture, recognition of people, and orientation within the surroundings. Damage to the temporal lobes can lead to impaired visual recognition of faces and interpretation of facial expressions despite adequate vision (prosopagnosia) and impaired recognition of objects, shapes, letters, and route finding, particularly in new places (*topographic agnosia*) [29, 30].

The dorsal stream on each side connects the occipital (*visual*) cortices to the posterior parietal lobes and subconsciously maps the environment in three dimensions helping the motor cortex to organize accurate body and vision-guided movements. It also connects the occipital lobes to the frontal eye fields to initiate rapid, accurate head and eye movements to assist fixation at chosen targets.

Dorsal stream damage can lead to impaired visual guidance of movement or optic ataxia, limited capacity to simultaneously see many items at once, and inability to move the eyes to a target despite an intact oculomotor system, known as apraxia of gaze (triad of Balint's syndrome). Visual search is also impaired, making the affected CP children unable to handle complex visual scenes. They have difficulties in locating a toy on a patterned carpet or in a basket of toys, reading crowded print, and recognizing people in a crowd or in the distance. Route finding in crowded environments tends to be difficult, and they tend to watch television from very close. Some children get distressed or angry when other children in the classroom cause distraction. Inaccurate visual guidance of movement or optic ataxia of upper and/or lower limbs may be misinterpreted as clumsiness, due to accompanied motor disabilities [31, 32, 38].

The *occipito-parieto-temporal junction* (o-p-t junction) area is the center for movement perception. Damage to periventricular white matter in the parieto-occipital region can cause impairment of movement perception or dyskinetopsia. Children with intact o-p-t area but with severe occipital lobe damage may exhibit perception of movement as the only visual function [33].

Although it is not easy to diagnose visuoperceptual and visuocognitive problems, detailed history taking and careful observation of the child's visual behavior helps distinguish between CP children with visual, oculomotor, visual cognitive, and perceptual difficulties and those without [2]. *However*, CP is not a uniform group; it consists of various subgroups.

Visual disorders are more common in spastic bilateral CP than in any other type. More than 65% of the children in this group have *hypermetropia*, more than 70% with no *binocular vision* and *stereopsis*, more than 60% present with reduced best corrected visual acuity, 30% with optic disc abnormalities, 7% with visual field defects, and 15% with CVI. *Esotropia* and/or vertical deviations are the most common types of strabismus (50–15% of them have dyskinetic strabismus). Ocular movement and gaze disorders are also common (saccadic and pursuit asymmetry 51%, nystagmus 15%, gaze apraxia 17%, and fixation instability 12%) [39].

28.4 Type of Cerebral Palsy

Bilateral spastic CP (Q-CP) children are the most severe visually impaired. A high percentage of them (20–47%) have markedly reduced or not assessable best corrected visual acuity (BCVA < 1.0 logMar) and reduced contrast sensitivity (90%). They also show high percentage (30%) of optic nerve disc abnormalities (sectoral pale optic disc, cupped optic disc, optic nerve hypoplasia). 77% of them have gaze dysfunction and more than 75% of the children have a significant refractive error (hyperopia 32%, myopia 67%, and anisometropia 12%). *Anisometropic* amblyopia (20%), esotropia (40%), and vertical and dyskinetic strabismus are also very common (30%). The majority of the children (80%) have no binocular vision and stereopsis, gaze and movement disorders (40%), CVI (30%), and visual field defects (11%).

There is a strong correlation between spastic diplegia-CP (SD-CP) and prematurity, due to the high possibility of hemodynamic and respiratory instability of the premature newborn resulting in periventricular leukomalacia (PVL) [34]. A review study has helped establish a correlation between visuoperceptive, visuospatial, and visuoconstructive deficits and neuroimaging findings in individuals with SD-CP and PVL [35]. Strabismus in patients with CP, especially in patients with spastic diplegia, is much higher than in neurologically normal children. The visual profile of diplegics CP is characterized

mainly by moderately reduced visual acuity (20%), significant refractive errors (70%) of which hyperopia is the most common 50–73%), absence of stereopsis, reduced contrast sensitivity (57%), amblyopia (60%) (mainly strabismic), and strabismus (mainly esotropia (60%), dyskinetic strabismus (6%)). More than 65% of the children have no binocular vision and stereopsis and impaired ocular motility (especially saccades). Fundoscopy reveals optic disc abnormalities in 12% of the cases. Visuocognitive dysfunction is a typical finding in individuals with spastic diplegic CP (50%).

The visual profile of spastic unilateral cerebral palsy is characterized by a slight reduction in best corrected visual acuity (47%) (frequently unilateral); significant refractive errors (70%) (mainly hyperopia); reduced contrast sensitivity (25%); amblyopia (60%), that is, mainly strabismic, strabismus (35%) (equal incidence of exotropia, esotropia, and vertical strabismus); reduced visual fields (12%); no binocular vision and stereopsis (50%); and oculomotor impairment (35%) particularly in smooth pursuit and saccades and CVI (12%). Fundoscopy reveals optic disc abnormalities in 12% of the cases [5, 11, 13].

Dyskinetic cerebral palsy is not as common as spastic cerebral palsy (2.6% of all CP cases). It is due to damage to the basal ganglia, leading to ocular, muscular, emotional, cognitive, and learning disorders. *Myopia* is a common finding (56%). Almost 65% of the children have no binocular vision, none of them have stereopsis, many children are amblyopic (44%) (mainly anisometropic), and 22% of them present with optic disc abnormalities, 22% with cerebral visual impairment (CVI), and 11% with visual field defects. *Esotropia* and *exotropia* are the most common types of strabismus (45% each). Ocular and gaze movement dysfunctions are also present in almost one-third of the cases. The fixation pattern however appears to be normal.

Choreoathetotic CP children are characterized by a mixture of hypotonia and hypertonia, muscular tone fluctuation, and involuntary movements of the face, torso, and limbs. It is caused by damage to the brain's basal ganglia and/or cerebellum. The basal ganglia regulate the voluntary motor function and eye movements, while the cerebellum controls balance and coordination. The ocular movements are highly affected in these children.

Ataxic CP babies and children exhibit irregular movements leading to balance and coordination problems, due to cerebellar dysfunction. They are shaky and struggle with precise movements (e.g., writing and grasping small objects). Slow eye movements and inability to precisely targeting what they are looking at lead to problems with depth perception.

Sometimes damage to the developing brain is not confined to one location, leading to a variety of symptoms. This is called mixed CP and entails both spastic and non-spastic characteristics [9, 36]. Hoyt [37] found that children with cortical damage showed visual improvement much more frequently (78%) than the others (42%), suggesting that children with PVL are less likely to show visual improvement. He also found that the incidence of strabismus, nystagmus, and optic atrophy in the PVL group is significantly higher.

Conclusion

Visual disorders due to cerebral palsy can present in many different ways. Any of the problems described above can be present, in any combination and to any degree. Visual impairment plays a key role in psychokinetic development of CP children. An early ocular, visual, oculomotor, and visuoperceptual assessment is very important. The accurate detection of visual disorders not only leads to a complete clinical diagnosis but also to an appropriate intervention plans.

Visual assessment requires a multidisciplinary step by step approach, planned according to the child's age and the severity of CP. Assessment of visual function (use of vision for daily living) is also essential. The aim of the management is to identify the problems and to design practical solutions. Due to the plasticity of the visual system in CP children, proper visual training programs are required to enhance visual function.

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Pulmonary Management of the Patient with Cerebral Palsy

29

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Abstract

Pulmonary problems are a major source of morbidity and mortality, especially among patients with severe cerebral palsy. The respiratory problem can exist at multiple levels, including the respiratory centers of the brain, airways, lung parenchyma, pulmonary vasculature, and chest wall. Careful assessment and therapies targeted to each are needed to optimize care. Immunization against respiratory diseases is of paramount importance. Invasive management, such as orthopedic procedures, or the institution of mechanical ventilation must be carefully considered in the context of the patient's medical condition, family's value system, and capabilities of the home and local medical system.

29.1 Introduction

Although cerebral palsy (CP) is caused by an insult to the developing central nervous system, it is well recognized that multiple body systems are involved. Problems with the respiratory system are of particular importance. Pulmonary problems are the leading cause of death among children and adults with CP, ranging from 68% to 78% in different population-based series [1, 2]. Pulmonary problems are also the leading cause of hospitalization for patients with CP [3].

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29.2 Review of Pulmonary Physiology, with Special Attention to Issues Common in CP

Simply put, the respiratory system includes the conduits between the nose and mouth, and alveolus where gas exchange occur, the respiratory centers of the brain which control breathing, and the musculoskeletal system which supports the lungs and provides the force that allows for gas exchange. Patients with CP may potentially have difficulty with any (or *several*) of these, leading to respiratory problems.

The *nose* and *oropharynx* provide an important filtering function as air is breathed in and out. It is not uncommon for patients with CP to have a tracheostomy, which bypasses this filter; such patients are thus at higher risk for respiratory

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infection. A tracheostomy may be placed in patients with CP to bypass obstructive breathing (such as with tracheomalacia), or to allow for mechanical ventilatory support. These are particular issues for children born prematurely, but any patient with CP might be prone to obstructive breathing because of poor airway tone.

Swallowing issues are extremely common in cerebral palsy, particularly among more heavily impaired patients [4], see Chap. 30. Dysphagia can lead to chronic lung inflammation and infections, often with organisms heavily resistant to antibiotics [5]. The lungs are also vulnerable to aspiration from gastrointestinal reflux, which is highly prevalent in CP, particularly among patients requiring tube feeding [6]. The presence of reflux is an independent predictor of an increased risk of respiratory illness requiring hospital admission [7].

An important component of lung health is the ability to clear secretions from large and small airways through effective coughing. This is often impaired in patients with CP due to muscular weakness and skeletal deformities [8].

More impaired individuals with CP are prone to hypoventilation as a result of muscular weakness and skeletal deformities which decrease the efficiency of gas exchange. The overall level of gross motor function is closely tied to the neuromuscular performance of the respiratory system [9–11] .

At the level of the *alveolus*, there may be abnormal gas exchange because of chronic lung infections or bronchopulmonary dysplasia related to prematurity. These can lead to both inadequate oxygenation and ventilation, with chronic hypoxia and/or hypercarbia.

Lastly, abnormalities of the pulmonary vasculature may interfere with transfer of oxygen between the alveoli and pulmonary circulation. Pulmonary hypertension, a microvasculature problem, may be prevalent in patients with CP who were premature, have underlying heart disease, or are affected by sleep-disordered breathing [8]. By contrast, pulmonary embolus (*PE*) is an obstructive problem of larger blood vessels, usually originating from a deep venous thrombosis (*DVT*) in the legs. Although patients with severe CP would be expected to have a high rate of DVT/PE because of immobility, this has only been reported rarely [12], or as a result of screening for asymptomatic DVT [13]. The true risk of PE in this population is unknown.

29.3 Assessment of the Respiratory System in Patients with CP

The *pulmonary* assessment in patients with CP is often multifaceted and challenging. Many patients cannot cooperate with the physical exam well enough to allow for adequate auscultation of the lungs. General inspection of the patient is often more revealing and might include evidence of airway obstruction, excessive oropharyngeal secretions, and accessory muscle use. Skeletal abnormalities such as kyphoscoliosis should be noted. Pulse oximetry can usually be performed in the office setting and can augment the physical exam. It is helpful to know what a particular patient's oxygen saturation is when he or she is well as a comparison for an acute illness.

Chest radiography is often used to supplement the physical exam, though there are challenges of interpretation. The standard technique for chest x-ray is to take the exposure at full inspiration; as above, this can be difficult for a patient who cannot understand directions. In *addition* to visualizing the lung parenchyma, the x-ray can provide information about the patient's airway, skeletal abnormalities, heart, pleura, and upper abdomen, all of which may affect the breathing.

In the *acute* setting, the respiratory status can be assessed using an arterial or venous blood gas; the former provides information about both oxygenation and ventilation, while the latter only assesses ventilation. *Chronic* hypoxia may be detected by an increase in the blood hemoglobin and hematocrit, as the body responds to low oxygen tension by increasing erythrocyte production. Conversely, chronic hypercarbia may be discovered as a high serum bicarbonate, as the body responds to chronic respiratory academia with increased bicarbonate production.

Formal pulmonary function tests (*PFT*s) are a mainstay of pulmonary assessment, but require cooperation by the patient, so are of limited utility in younger patients or patients with severe intellectual disabilities. When possible, PFTs should be performed as they distinguish between restrictive deficits, such as neuromuscular weakness, and obstructive problems, such as asthma or airway issues. These can often coexist. As a group, patients with CP perform more poorly on PFTs than controls [14, 15]. There are emerging techniques of pulmonary function measurement that do not require the cooperation of the patient [16], but these are not yet commonly available.

Echocardiography is an important part of the assessment if pulmonary hypertension is a consideration, or if there might be concomitant myocardial or valvular disease. Occasionally, direct measurement of pressures by catheterization is warranted.

29.4 Sleep-Disordered Breathing

Sleep-disordered breathing (*SDB*), which might include *problems* with the neurological respiratory drive (central sleep apnea) or obstruction of the airway (obstructive sleep apnea), is common in patients with cerebral palsy, particularly those who are severely affected or have epilepsy [17]. Medications which decrease alertness or airway tone may increase the risk of SDB. These include medications to treat pain, spasticity, seizures, or behavioral problems.

Recognition of the potential for SDB is the first step toward management. Patients may present with obvious signs, such as observed apneas or choking while sleeping, or with vague signs such as daytime sleepiness, morning headaches, worsening cognitive performance, or laboratory abnormalities such as polycythemia or hypercarbia.

When SDB is suspected, overnight polysomnography should be performed. Standard methods of interpretation are utilized. As in other patients, people with CP and SDB can be treated with airway procedures (tonsillectomy, adenoidectomy, uvulopalatopharyngoplasty, tracheostomy), or positive pressure (continuous positive airway pressure (*CPAP*) or bi-level positive airway pressure (*BiPAP*)). In extreme cases of central sleep apnea, nocturnal mechanical ventilation may be instituted.

29.5 The Importance of Immunizations

Immunization against preventable respiratory diseases is of paramount importance to maintaining optimal pulmonary health. *Immunization* recommendations are frequently updated; in the USA, the current recommendations can always be found at http://www.cdc.gov/vaccines/index.html. Unless there are medical contraindications, children and adults with CP should receive the standard immunizations on the standard schedule, especially those for pertussis, pneumococcus, and the annual influenza vaccine. Close contacts of the patient with CP should also be immunized to *cocoon* the individual [18].

29.6 Orthopedic Interventions and the Respiratory System

The role of orthopedic interventions in maintaining respiratory function is controversial. Despite the fact that *kyphoscoliosis* and chest wall deformities are a major cause of respiratory problems in patients with CP, surgical correction has not been definitively shown to improve pulmonary function or reduce respiratory morbidity [19]. As discussed above, the assessment of respiratory function in people with CP can be very difficult, which interferes with ascertainment of the effect. Proxies for respiratory function, such as the number of pneumonias [20], or the need for respiratory medications [21] has not supported a positive effect for scoliosis repair. Newer techniques which focus on the chest wall deformity, such as the vertical expandable prosthetic titanium rib or growing rods, may be more beneficial as they expand the space available for the lungs [22] .

However, parents of patients with CP report that prevention of cardiopulmonary problems

was their number one goal of scoliosis surgery, and a large proportion perceived improved respiratory status following surgery, and that they were satisfied with their decision to have their child undergo surgery [23]. *Further* work is clearly needed in this area.

29.7 Therapies for Respiratory Problems in Patients with Cerebral Palsy

Prevention of infection or aspiration is important for maintaining good pulmonary health. In addition to the immunization strategies above, patients and parents should be counseled to avoid tobacco smoke and other environmental exposures which could exacerbate an underlying respiratory condition. Close attention to hygiene is also needed to reduce the risk of infectious transmission. When there is an aspiration risk of food or fluid, this can often be reduced by manipulating textures or size of the oral bolus. Reduction of salivary volume through the use of anticholinergic medications or salivary procedures can also decrease the risk of aspiration [24]. The risk of aspiration from gastroesophageal reflux can be reduced by the use of medications, or surgical options such as fundoplication or post-pyloric feeding [25].

Patients with *tracheostomy* are prone to chronic respiratory infections, especially with highly resistant organisms. Efforts to keep the tracheostomy and tube clean are important, but all will eventually be colonized [26]. In a small series, prophylactic-inhaled antibiotics targeted to resistant organisms were shown to reduce the frequency of pneumonia in children with CP and tracheostomy [27].

Artificial means of mucus clearance are especially important for patients with reduced ability to cough or to handle pulmonary mucus once it reaches the oropharynx. Chest physiotherapy, including positioning, hand percussion, and vibration, is effective and easily taught and does not require specialized equipment, unless suctioning is also needed to clear the airway [28]. High frequency chest wall oscillation therapy by means of a vibrating vest is commonly used and usually well tolerated [29, 30]. Newer devices, which insufflate and exsufflate the lungs through a mask, are frequently used in patients with neuromuscular disorders [31], and have started being applied to patients with cerebral palsy with deficient cough.

In *patients* that are able to cooperate, incentive spirometry exercises have been shown to improve parameters of pulmonary function [32], as has respiratory muscle feedback training [33].

Dynamic airway obstruction may be treated with a tracheostomy to bypass the obstruction or with positive airway pressure delivered via nasal or mouth mask, which "*stents*" the airway open. This may be accomplished by continuous pressure (*CPAP*) or bi-level pressure (*BiPAP*) which also provides for noninvasive ventilation. Both CPAP and BiPAP treat obstructive sleep apnea, if present. Some patients may find BiPAP easier to tolerate than CPAP. Surgical approaches to airway obstruction may include tonsillectomy, adenoidectomy, or uvulopalatopharyngoplasty to remove excessive tissue in the upper airway that is prone to collapse.

Patients with respiratory insufficiency or failure as a result of intrinsic or restrictive lung disease may be treated with mechanical ventilation. Ventilatory support may be applied via nasal or full face mask by BiPAP or through a tracheostomy by traditional ventilator (trach/vent). The decision to commit a patient with CP to this therapy is not made lightly. Careful consideration of the proposed benefits, risks, and burden to the individual and family is needed. The choice between BiPAP, trach/vent, or forgoing artificial ventilation must be individualized and must be based on the individual circumstances of the patient, values of their family, and capabilities of the home and health care system. The involvement of a palliative care team to help the family and primary care team sort through these issues is desirable [34].

29.8 Summary

The care of patients with cerebral palsy is incomplete without careful attention to the problems of the respiratory system. Pulmonary problems are a

major source of morbidity and mortality, especially among patients with severe CP. The respiratory problem can exist at multiple levels, including the respiratory centers of the brain, airways, lung parenchyma, pulmonary vasculature, and chest wall. Careful assessment and therapies targeted to each are needed to optimize care. Immunization against respiratory diseases is of paramount importance. Invasive management, such as orthopedic procedures, or the institution of mechanical ventilation must be carefully considered in the context of the patient's medical condition, family's value system, and capabilities of the home and local medical system.

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Gastrointestinal Problems in Children with Cerebral Palsy

30

Peter B. Sullivan and Morag J. Andrew

Abstract

Feeding and gastrointestinal difficulties are common in children with cerebral palsy and if not appropriately managed can result in undernutrition, poor growth and worsened general health. Gastrointestinal difficulties include oropharyngeal dysfunction, drooling, foregut dysmotility and gastro-oesophageal reflux as a result of gastro-oesophageal dysmotility, retching, delayed gastric emptying and chronic constipation. The assessment and management of children with cerebral palsy and comorbid gastrointestinal problems are best performed within a multidisciplinary team experienced in the management of children with CP and gastrointestinal problems. This chapter considers the gastrointestinal problems experienced by children with cerebral palsy and outlines current management strategies.

30.1 Introduction

Gastrointestinal problems are encountered in at least one third of children with cerebral palsy (*CP*). These include feeding and swallowing disorders (with associated chronic pulmonary aspiration), regurgitation and vomiting, abdominal pain and constipation.

Effective oral *feeding* requires the coordination of sucking, swallowing and breathing and is the most complex sensorimotor process the newborn infant undertakes. Weak suck and poor feeding in small infants may herald neurological impairment [1]. Because development of oral-motor skills mirrors general neurological

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maturation, those children with the severest motor deficit (bilateral CP) are also those with the highest degree of oropharyngeal dysfunction [2]. Oropharyngeal dysfunction is a problem in more than 50% of children with CP and is closely related to the severity of the neurological impairment and should be considered in all children with CP even in the absence of obvious clinical signs and symptoms. Evaluation of oropharyngeal function should include both feeding history starting from early infancy and direct visual assessment of feeding carried out by appropriately trained professionals. Videofluoroscopy is indicated where there is suspicion of an abnormal pharyngeal phase of swallowing and/or concerns about aspiration. Speech and language therapy input should be considered in the treatment of children with oropharyngeal dysfunction and may include modification of the consistency of feeds, but there is little evidence for the effectiveness of oral-motor therapy in this group [3]. Oral-motor dysfunction leads to limited food intake and clinically significant undernutrition in children with moderate to severe CP [4]. Nutritional impairment from limited food intake may be further exacerbated by a constellation of other factors including impaired communication, immobility, medication, constipation and excess losses following vomiting and gastro-oesophageal reflux.

Oropharyngeal dysfunction in children with CP is associated with significant rates of morbidity and mortality, and the associated nutritional and growth consequences have been well described [2]. Increasingly, gastrostomy tube feeding is being employed to maintain nutritional status in children with severe CP.

30.1.1 Indication for Gastrostomy

The range of indications for insertion of a gastrostomy feeding tube is extensive, but the commonest indication for gastrostomy insertion in paediatrics is to overcome oral-motor impairment and feeding difficulties in children with neurological impairment; the largest single group is children with CP.

Insertion of a gastrostomy feeding tube is an increasingly common intervention in neurologically impaired children who:

- Have a clinically unsafe swallow
- Are unable to maintain a satisfactory nutritional state by oral feeding alone
- Have an inordinately long (>3 h/day) oral feeding time
- Are dependent on nasogastric tube feeding

30.1.2 Benefits of Gastrostomy Tube Feeding

In children with neurological impairment, gastrostomy placement has been shown to significantly increase weight gain and to be associated with a reduction in feeding time, drooling, feed-related choking episodes, vomiting and frequency of chest infections. Malnourished children with severe CP show significant increases in body fat and protein with gastrostomy tube feeding. Such children have a rapid response to nutritional support through gastrostomy with catch-up growth regardless of age, even though there is a more pronounced state of malnutrition as age increases. Furthermore, death rates are distinctly higher in the subgroup of children with the most pronounced state of malnutrition and multiple secondary chronic conditions before gastrostomy.

Anecdotal reports in different studies have suggested that early developmental progress, pubertal development and emotional temperament improved following gastrostomy feeding, but this needs more detailed research.

Family stress is significantly reduced, and quality of life of parents increases after gastrostomy insertion to assist feeding. Parents spend less time on child care once tube feedings are initiated and find feeding less difficult. This leads to evidence of caregiver satisfaction with gastrostomy tube feeding in the majority of studies.

30.1.3 Complications of Gastrostomy Tube Feeding

It is difficult to make meaningful statements about risks and complications of gastrostomy tube feeding from the published data because types and rates of complications are not reported in a standard way and some children experience multiple complications [5]. Insertion of a gastrostomy feeding tube carries with it a relatively low risk of complications. Published literature suggests a procedure-related mortality of 1%, a major complication rate of 3% and a minor complication rate of 20% [6].

Reported major complications of gastrostomy insertion include adverse anaesthetic events, oesophageal laceration, pneumoperitoneum, peritonitis, colonic perforation and cologastric fistula formation. Many of these complications are now avoided or reduced in likelihood by refinements to the technique of insertion.

Later complications include stoma leakage, cellulitis, granulation tissue formation around the gastrostomy site and displacement. Gastrostomy site infection is the commonest problem occurring in up to 20% of cases but is easily and successfully treatable. More serious later complications such as bowel obstructions, gastrointestinal bleeds, ulceration and peritonitis are rare. Other later gastrointestinal complications include constipation, diarrhoea, cramping and vomiting. Gastrostomy insertion may worsen GOR, necessitating the use of antireflux medication or surgery.

Death rates following gastrostomy range from 14% (after 1 year) to 26% (after 5 years). Most workers concur that these death rates are indicative of the severe morbidity, e.g. usually related to chronic secondary conditions including oesophagitis and lung disease from repeated pneumonias, in the children before gastrostomy [6].

30.1.4 Risk of Overfeeding

Immobile children with spastic quadriplegic CP who are exclusively gastrostomy tube fed grow consistently on an energy intake of less than 7 kcal/cm, i.e. diets ranging from 500 to 1100 kcal/day. Remarkably, this intake is 16–50% less than the recommended daily allowance. These extremely low energy intakes often make doctors, nurses and dieticians hesitant to accept the adequacy of such diets. The *consequences* of this may be overfeeding with the attendant risk of excessive fat storage. Use of high energy proprietary enteral feeds in children with CP fed by gastrostomy tube exacerbates the risk of overfeeding and a potentially adverse effect on body composition. Conversely, low energy but nutritionally complete enteral feeds can produce weight gain without excess fat deposition.

30.1.5 Principles of Nutritional Management

The most important consideration when determining what and how to feed a child with CP via a gastrostomy tube is to determine the amount of energy that the child requires to grow optimally. It is increasingly recognised that measurement of body composition is an essential component of the nutritional assessment in children with CP. There is a wide variation in total energy expenditure (largely attributable to variations in physical activity levels) in immobile children with CP. This individual variation, together with the lack of any suitable reference standards, compounds the difficulties in writing an accurate dietetic prescription. Fortunately there are some common sense ‘rules of thumb’ derived from experimental and clinical observations that can guide the clinical management of children with CP. For instance, as the energy requirement for growth relative to maintenance is small (about 10 kJ/g), satisfactory growth can be used as a sensitive indicator of whether energy needs are being met. It is surprising how little may be required to achieve this. Thus, exclusively gastrostomy tube-fed children with CP grow consistently on an energy intake of less than 7 kcal/cm, i.e. diets ranging from 500 to 1100 kcal/day, which is 16–50% less than the recommended daily allowance [7]. Such extremely low energy intakes often make paediatricians, nurses and

dietitians hesitant to accept the adequacy of these diets. The consequences of this, particularly in the gastrostomy fed child with CP, may be overfeeding and the risk of excessive fat storage [8]. The use of a low energy feed has been shown to be associated with satisfactory weight gain without an adverse effect on body composition [9].

30.1.6 Drooling

The pooling of excessive saliva in the anterior part of the mouth and its subsequent escape through poor lip closure leads to drooling in children with oral-motor dysfunction. Drooling affects around 35% of children with CP [10, 11]. Children with Gross Motor Function Classification Scale (GMFCS) level IV–V are most likely to experience problematic drooling [10]; see Chap. 22. Excessive drooling may have distressing consequences including skin chapping and breakdown, unpleasant odour, soiled clothing, dehydration, perioral and oral infections, difficulties with mastication and speech, social exclusion and damage to equipment such as communication aids [12, 13].

Uncoordinated swallowing increases the risk of pulmonary aspiration which may or may not be identifiable by recurrent coughing, choking with feeds and recurrent chest infections requiring antibiotic therapy; see Chap. 29.

A range of treatments including *anticholinergic* medications, *botulinum* toxin salivary gland injection and salivary gland surgery all aim to reduce salivary production; however, there is no consensus on which treatments are the most effective [14]. Anticholinergic medications such as hyoscine hydrobromide and glycopyrronium are common first-line treatments but can have unpleasant side effects such as constipation, urinary retention, blurred vision, sedation, irritability and increased seizure frequency in children with epilepsy [13]. Results of the first randomised controlled trial of hyoscine versus glycopyrronium in children with CP are awaited [15]. Botulinum toxin injection of the salivary glands can also be beneficial; however, treatment usually requires a general anaesthetic, must be repeated every 6–12 months and is only available in a small number of specialist centres. Salivary gland excision or re-routing is invasive and can lead to permanent excessive saliva reduction leading to problems with mastication.

Given the current lack of evidence concerning salivary management, clinicians must make therapeutic decisions on an individual basis, taking into account the age of the child and the severity of the problem. *Conservative* management should precede more invasive surgical options. Assessment and management is best conducted within a multidisciplinary setting, with the overall aim of improving quality of life whilst minimising unpleasant side effects or compromising oral health [13].

30.1.7 Foregut Dysmotility

Gastrointestinal dysfunction manifests primarily, but not exclusively, as a *dysmotility* in the foregut. The foregut starts at the mouth and ends in the second part of the duodenum and is the most severely affected because of its great density of extrinsic innervations. These arise either from the spine via prevertebral ganglia (*spinal arc*) or directly from the medulla in the two-way traffic in the vagus nerve. Break down in efferent control is associated ultimately with electromechanical disassociation leading to abnormal motility and symptoms. *Modulation* of the neural activity in the enteric nervous system by extrinsic innervation is abnormal in children with central nervous system disorders. Vagal nerve dysfunction causes a relaxation of the proximal stomach and retroperistalsis secondary to inhibition of the gastric pacemaker. This leads to a gastroduodenal dysrhythmia and electromechanical uncoupling. The effect of this is distention of the fundus of the stomach, which leads to transient relaxation of the lower oesophageal sphincter and gastro-esophageal reflux. Typical symptoms of foregut dysmotility include vomiting, retching, gagging and bloating [16]. Gastro-oesophageal reflux (GER) is the commonest manifestation of foregut dysmotility.

30.1.8 Gastro-oesophageal Reflux

Gastro-oesophageal reflux (*GER*) occurs in 19–75% of children with CP [17], being caused primarily by central nervous system dysfunction. Additional contributory factors include hiatus hernia, adoption of a prolonged supine position and increased intra-abdominal pressure secondary to spasticity, scoliosis or seizures [18, 19]. Gastric dysmotility and delayed gastric emptying may also predispose towards GER in children with neurological impairment [20–22], although this relationship has not been demonstrated in all studies [23–25]. Peptic *oesophagitis* often becomes a chronic symptom and may progress to mucosal ulceration and stricture formation. In children with neurological impairment, the objective hallmark of gastro-oesophageal reflux disease (*GERD*) is recurrent vomiting which occurs in over 80% of cases and which, as noted above, may further compromise their already precarious nutritional state. Vomiting, haematemesis, anaemia, rumination and regurgitation are all more common in individuals with neurological impairment who are suspected of having GERD than in those in whom GERD is not suspected [26]. Objective diagnosis of GERD (by oesophageal pH or pH/multichannel intraluminal impedance monitoring and/or upper GI endoscopy) is recommended; however, due to the high prevalence of GERD in this population, a trial of proton pump inhibitor (*PPI*) treatment with careful follow-up is acceptable in children unable to tolerate these investigations.

30.2 Medical Management of Gastro-oesophageal Reflux

The advent of PPI for use in children has had a very significant impact on the treatment of GER [27]. Just as increasing experience of the complications following fundoplication has been shown to raise the threshold for performing this operation in children with neurological impairment [28], so has the efficacy of PPI as medical treatment been associated with a dramatic decrease in the number of surgical antireflux procedures performed in children [29].

In *conjunction* with PPIs, therapy strategies to control reflux include a change from bolus to continuous pump feeding [30] and use of whey-predominant enteral milk formulae which have been shown to be associated with faster gastric emptying [31]. The effect of whey-predominant feeds on GERD is less certain [32].

It is important to know that not all *vomiting* in children with CP should be assumed to be caused by GER, as activation of the emetic reflex is another important mechanism [33]. Retching is a key symptom of activation of the emetic reflex.

30.2.1 Retching

Retching refers to the laboured rhythmic activity of the diaphragm and anterior abdominal wall musculature which precedes vomiting and is the first part of the emetic reflex. The sensory and motor pathways of the *vagus* nerve, the area postrema and the nuclei of the *vagus* nerve play a major role in the emetic reflex. Gastric vagal afferents are potent activators of the emetic reflex, and it is possible that in some children with neurodisability the emetic reflex is hypersensitive, or there may be loss of its physiological inhibition. Such emesis is characterised by a prodrome of salivation, tachycardia, peripheral vasoconstriction, nausea and retching, and, in contrast with the relatively effortless vomiting associated with GER, it is forceful. Vomiting accompanied by retching is seen more often in children with neurodisability than in typically developing children. When this occurs preoperatively, they are three times more likely to retch following fundoplication than non-retchers [34].

30.2.2 Delayed Gastric Emptying

Delayed gastric emptying (*DGE*) accompanies many (28–50%) cases of GER [35, 36]. Children with DGE are more at risk of developing gas

bloat and persistent retching after fundoplication [18]. Del Giudice (1999) reported that 67% of children with cerebral palsy and GER had delayed gastric emptying [37]. This association, however, may to some extent depend upon the type of food given [38]. Nevertheless, trying to treat GER without effectively treating DGE may be one of the reasons why both conservative and surgical treatment of GER in profoundly disabled children gives such poor results [28, 39, 40].

30.3 Constipation

Children with CP regularly suffer from constipation; the reported prevalence ranges from 24% to 74% of all children with cerebral palsy [37, 41]. *Contributory* factors include prolonged immobility, skeletal abnormalities, extensor spasm or generalised hypotonia as well as abnormal bowel motility associated with certain neurological lesions [42]. Dietary factors such as low fibre and fluid intake (often due to associated feeding difficulties) are important contributors. The use of anticonvulsant, opioid, antispasmodic, antihistamines or aluminium antacid medications may also predispose to constipation.

Constipation in children with disability may be overlooked in the presence of more pressing medical concerns or the inability of the child to communicate effectively. Symptoms are often present for months or years before appropriate treatment is provided.

Chronic constipation has been associated with impaired quality of life, urinary symptoms (e.g. poorly voiding bladder, recurrent urinary tract infection) as well as gastrointestinal manifestations such as recurrent vomiting, chronic nausea, chronic or recurrent abdominal pain and early satiety. Constipation is diagnosed through careful history and abdominal, perineal and if necessary rectal digital examination.

Constipation in the child with CP represents a significant therapeutic challenge, and standard treatment regimens may prove to be insufficient.

30.3.1 Treatment of Chronic Constipation

Treatment of chronic constipation requires a consistent approach and willing parents or carers. Unrecognised chronic constipation can result in complications such as *megarectum*, altered bowel motility, anal fissure and soiling. The treatment of constipation in children with CP should be as for typically developing children. Management of chronic constipation aims to evacuate retained faeces followed by maintenance therapy to ensure *defaecation* is regular and painless. The use of a diary detailing the bowel habit, frequency, size and consistency of stools as well as the laxative treatment used can be helpful to both parents and physicians in assessing the response to treatment.

30.3.2 First-Line Treatment

In children with mild constipation and no evidence of megarectum or soiling, the approach is simply to ensure the regular passage of soft stool. Initial attention should be directed towards dietary manipulations. In children who are fed solely via gastrostomy, a similar approach is the usage of a *formula* with added fibre.

Once *dietary* issues have been addressed, a stool softener such as lactulose may be used. This synthetic disaccharide is fermented by colonic bacteria and results in an osmotic diarrhoea. The aim is for a porridge-like consistency of stool which is able to be passed without discomfort. Gas is produced as a result of the bacterial fermentation which may result in side effects of abdominal distention and pain.

The use of preparations containing polyethylene glycol or mineral oil should be used with great caution in children with concomitant neurological abnormalities and gastroesophageal reflux due to the significantly increased risk of aspiration [43].

Stimulant medications may also be required. A mild stimulant such as senna may be helpful in

ensuring that defaecation occurs at least three times a week. Carers should be informed that colicky abdominal pain may occur with the use of stimulant medications especially in the continued presence of firm stools. If this side effect is seen, attention should be given to softening the stool further, and if pain continues, the dose of stimulant may be reduced.

30.3.3 Second-Line Treatment

In children with rectal impaction and megarectum, disimpaction should *first* be attempted. The use of sodium citrate or sodium acid phosphate enemas is an effective way to clear the rectum before commencing stool softeners and stimulant medication. *Enemas* may be given under mild sedation if the child is likely to become distressed.

Docusate sodium is a synthetic anionic detergent that decreases surface tension allowing penetration of water and fat into faeces. It is thought to have both stool softening and stimulant properties and may be useful in children who have failed to respond to first-line treatments. *Psyllium* husk consists of the ground husk of the psyllium seed and is a useful source of soluble fibre. A randomised, double-blind, parallel-design study in adults found that when compared with docusate sodium, psyllium was more effective in softening stools and had a greater overall laxative efficacy.

Soiling results from chronic untreated constipation and is associated with a significant degree of faecal loading. Often local enema treatment is ineffective in treating children with CP and chronic constipation, especially if the faecal mass extends throughout the colon.

In patients with an *anal fissure*, treatment should firstly address their constipation with the use of stool softeners. Topical lidocaine may lessen pain on defaecation, and topical glyceryl trinitrate (*GTN*) has been used to relax the internal anal sphincter [44]. The use of GTN is limited by the side effect of headache. Injection of botulinum toxin into the anal sphincter is a relatively novel treatment which has been shown in adult studies to be more effective in treating anal fissure than GTN [45].

30.3.4 Surgical Treatment

Surgery is usually reserved for patients who have *failed* medical management. The original Malone antegrade continence enema procedure relied on a reversed appendix brought to the skin to form a stoma. There have been some surgical adaptations since the procedure was originally described, and there is now a laparoscopic technique available as well as a percutaneous left colonic approach producing a percutaneous colostomy. A *catheter* may be introduced through the stoma allowing lavage of saline, phosphate enema solution or polyethylene glycol to achieve defecation. The ACE procedure has an 80% reported success rate. Best results are achieved in children greater than 5 years old with a neuropathic bowel or anorectal malformation who are highly motivated to remain continent [46].

Conclusion

Gastrointestinal symptoms are common in children with CP. Much of the available literature on the gastrointestinal problems in children with CP has a relatively low evidence base and arises from retrospective case note reviews of relatively small numbers of cases. Those studies that report very substantial numbers of cases often have serious methodological flaws that yield inconclusive results. Children with CP who have gastrointestinal problems as part of their presentation should be managed within a multidisciplinary team so that all contributing factors can be addressed. This multidisciplinary team should include a disability paediatrician, a paediatric gastroenterologist, paediatric surgeon, occupational therapist, dietician and speech and language therapist as a minimum. Gastrointestinal problems in children with CP should always be considered within the broader family and social circumstance.

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Nutritional Management of the Patient with Cerebral Palsy

31

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Abstract

Nutritional status is intimately related to health in patients with cerebral palsy. There may be numerous difficulties, including poor oromotor function, dysphagia, gastroesophageal reflux, intestinal malabsorption, or constipation, all of which might interfere with oral feeding. Feeding tubes are commonly used as an alternative or supplement to oral feeding. It can be difficult to assess the nutritional status of individuals with cerebral palsy, and each nutritional intervention needs to be individualized and followed closely to ensure that the patient receives proper nutritional support. The best nutritional management is accomplished through an active partnership between the patient, family, and care team.

31.1 Introduction

Parents, doctors, and other clinicians who care for patients with cerebral palsy (*CP*) recognize that nutritional issues are a daily challenge for many. From birth, patients may be challenged to take enough oral nutrition to sustain them. This is especially true in patients with underlying airway or gastrointestinal disorders or those who were treated in a neonatal intensive care unit (*NICU*) [1]. Such patients often have difficulties with oromotor function, dysphagia, gastroesophageal reflux (*GER*), intestinal malabsorption, or constipation, all of which might interfere with oral feeding.

When oral feeding is inadequate for growth, supplemental feeding is often recommended, usually by nasogastric (NG), gastrostomy (G), or jejunostomy (J) tube (for more see Chap. 30). While these measures are often very effective in providing adequate nutrition, they commonly have complications [2] and are also associated with psychosocial distress by families [3]. As feeding their child is the first task of a new parent and an ongoing source of attachment, the inability to do so is upsetting for many families.

Nutritional status is intimately related to health in patients with CP. Brooks et al. [4] showed a clear relationship between weight

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status and mortality, underscoring the importance of careful and proactive nutritional management in this population.

31.2 Challenges in Measuring Nutritional Status

Determining the nutritional status among patients with CP is challenging. Usual methods of measurement can be problematic and may require careful planning to make sure that accurate measurements are made.

Weight should be measured with a *dry diaper* or underwear, without braces, and with as few clothes as possible. The weight of a patient who is unable to stand may be difficult to measure without specialized equipment, such as a scale built to accommodate a wheelchair or with a built-in handrail. Patients who use wheelchairs may be weighed in them, and then the weight of the wheelchair subtracted. The *wheelchair* should be reweighed at each clinic visit to ensure consistency between readings. This requires the patient to get out of the wheelchair, so the clinic should have a mechanical lift device or ample help for safe transfer to the clinic table.

Brooks et al. [4] constructed growth charts for patients with CP, stratified by Gross Motor Function Classification System (*GMFCS*) level. At GMFCS Levels I and II, weight below the 5th percentile for age was associated with a mortality rate 2.2 times that of patients at higher weight percentiles; for GMFCS Levels III, IV, and V, the mortality hazard ratio for patients below the 20th percentile was 1.5; see Chap. 22. If possible, we recommend that the weight of patients with CP be plotted on these growth charts.

However, weight of a patient alone is inadequate to assess nutritional status. In the general population, it is usually paired with height measurement to assess for proportionality, either by weight-to-length ratios or body mass index (*BMI*). Assessment in patients who are able to stand and be measured by stadiometer usually can be done so accurately; however patients with CP may have musculoskeletal abnormalities, such as *contractures* or *kyphoscoliosis*, which can make measurement of length inaccurate. To combat this, segmental measures may be used to extrapolate the patient's height [5]. Such measures can be done in the clinical setting and include knee height, upper arm length, and others.

Assessment of an at-risk patient's nutrition needs to go beyond their weight and height approximation. Body composition has been shown to be a better indicator than BMI or weight for length of the nutritional status in children with cerebral palsy and other neurological disabilities [6]. These require specialized equipment that can often be utilized in the clinical setting. Body fat assessment can help to distinguish those patients that are underweight but nutritionally replete from those that are malnourished. Tools to measure body composition include triceps and subscapular skinfold thickness, bioelectrical impedance, and dual-energy absorptiometry. Dual-energy absorptiometry is considered the gold standard for measuring body composition [7]. However, it is not available everywhere, cost may be prohibitive, and it is inaccurate in patients with implanted medical hardware or devices. Both bioelectrical impedance and skinfold measures are reasonable measures of body fat for ambulatory children with cerebral palsy which can be more easily completed in the clinical setting [8].

When prescribing a nutritional regimen for patients with cerebral palsy, it is important to consider the caloric, protein, and fluid needs of the individual. There must be enough intake of all three to allow for maintenance of body function and, in the case of children, growth. In this regard, the assistance of a registered dietician is invaluable.

An important first step is to estimate the patient's resting energy expenditure (*REE*). The REE is dependent on several factors, including age and gender, the amount of typical daily activity, efficiency of movement, fat mass, and underlying medical illnesses. Ambulant children with CP have an REE roughly equivalent to that of typically developing children, while nonambulant children with CP have an REE that is approximately one-third lower [9]. Nonambulant

children who use mechanical ventilation have an extremely low REE, reported to be half that of typically developing children, and overfeeding may interfere with the ability to liberate them from the ventilator [10].

When energy intake exceeds what is needed for maintenance and growth, overweight and obesity may develop. This appears to be an increasing problem among children with disability at all functional levels [11] and may lead to poor cardiopulmonary fitness among adults with CP, along with decreased ambulatory ability, which in turn leads to even poorer fitness [12]. Low-calorie diets are often prescribed to children with severe CP to counteract this.

Protein needs do not seem different for patients with CP compared to typically developing children [13]. This is problematic in severely affected patients on *hypocaloric* diets, as commercial formulas are designed to match calorie and protein intake. When the volume of formula is restricted, extra protein may need to be added as a supplement, as well as micronutrients and extra water.

31.3 Aetiologies of Undernutrition in Patients with CP

Many patients with cerebral palsy have undernutrition because they have difficulty with the mechanics of getting food into the body. Samson-Fang et al. [14] found that severe feeding dysfunction was associated with lower triceps and weight. Many studies have shown that feeding issues increase as the GMFCS level increases, with GMFCS Level V having the most significant issues [15–17]. There can be difficulty with the patient being able to get the food to their mouth to begin the phases of eating. Depending on the GMFCS level, the patient may not be a self-feeder at all. Those who are Levels II–III may be self-feeders, but getting the food into their mouths may take increased time. Children who are school aged may require extended time for eating which may not be allotted to them by the school schedule. At home, busy family schedules may affect the number of eating opportunities there are for the child and the amount of time available for them to eat. Henderson et al. [18] found after controlling for age, GMFCS level, and use of a feeding tube, living in a residential center was associated with improved growth and skinfold thickness. This improved growth may be due to the fact that the feeding schedule may be more consistent and the nutrition monitored more closely than it can be at home.

Once food (*solid and liquid*) is in the mouth, several things may interfere with food getting to the back of the mouth to be swallowed. For some patients, there can be difficulty with lip closure resulting in a significant amount of food or liquid falling from the front of the mouth. This may be underappreciated by family members when they are trying to account for food consumption and the amount of calories actually consumed.

Difficulties with mastication may be another cause for feeding difficulties. The patient may not have the ability to chew solid food sufficiently or efficiently enough to be able to swallow safely. This is a particular problem in patients with *dystonia*. Once a child transitions to solid food, meals may take longer, sometimes up to 2 h a meal. Because the child is unable to chew the food, she may pocket the food in the cheek for hours. If it is a dissolvable solid, eventually the food may be swallowed. If not, it may be spit out or removed at a later time. Many families do not recognize that this is a sign of *dysphagia* and the child may need to have altered textures of food in order to consume what they need to grow (see Chap. 30).

Tongue lateralization is also a necessary part of preparing the food for swallowing. Patients with dystonia and increased tone in the tongue and oral muscles may have difficulty moving the bolus of food to the molars for mastication and then propelling the bolus to the pharynx to initiate a swallow.

As the bolus enters the pharynx and a swallow is triggered, a number of coordinated muscle actions are needed to protect the airway and propel food to the esophagus. There may not be enough strength in the muscles to push food out of the *vallecula*, resulting in pooling. This leads

to an increased chance for aspiration. An uncoordinated swallow may result in frank aspiration during the swallow. As meal duration increases, muscles may become fatigued, worsening the ability to propel the food to the esophagus and worsening coordination of the swallow, again leading to aspiration.

Behaviorally, a child may learn that eating is scary and not enjoyable and may refuse to eat. Because mealtimes are long and lack pleasure, they may choose not to participate. This can lead to a struggle between the parents and the child surrounding mealtime. As a result, families and children, including siblings, feel anxious at mealtime. Other mealtime behaviors may occur, including screaming, crying, kicking, hitting, throwing food, and spitting. Parents have reported chasing their children around the house with food trying to get them to eat. The result is less food getting into the child than is needed for growth and development. Parents may resort to only offering the foods that they know their child will eat. A limited variety of foods increases the likelihood of macro- and micronutrient deficiencies. Many of the foods that the children want to eat are of low nutrient value and high in carbohydrates. The child may become brand specific, making it difficult for the family to eat, except when they are at home or if they bring the food with them.

Another challenge for patients with CP is feeding intolerance. Many have problems with *dysmotility* of the gastrointestinal tract, resulting in retching, gagging, and vomiting during feeding; see Chap. 30. There may be delayed gastric emptying leading to early satiety and discomfort during feeding. Constipation may be a problem because of slowed colonic movement, poor hydration, and limited fiber in the diet, further decreasing appetite. The patient may not be able to tolerate increases in the volume of food and drink in the stomach leading to more vomiting. Certain medications may decrease or increase gastrointestinal motility. Increasing the caloric density may increase the osmolarity of the formula and cause gastrointestinal symptoms including vomiting or diarrhea, further limiting calories available for maintenance and growth.

Table 31.1 Medication effects on eating and swallowing. Compiled from Carl and Johnson [19]

Medication category	Possible effects on eating and swallowing
Atypical antipsychotic medications	Sedation, anticholinergic side effects, extrapyramidal side effects, unpleasant taste (*risperidone*)
Antidepressant medications – Tricyclic/tetracyclic – Selective serotonin reuptake inhibitors – Atypical antidepressants	Anticholinergic side effects, mild gastrointestinal side effects, sedation, loss of taste, unpleasant taste Gastrointestinal side effects, mild sedation, mild anticholinergic side effects Sedation and mild gastrointestinal side effects
Antianxiety medications	Sedation, decreased coordination, decreased concentration, gastrointestinal side effects, loss of taste, unpleasant taste
Anticonvulsant medication	Sedation, decreased coordination, decreased concentration, gastrointestinal side effects, gingival hyperplasia (*phenytoin*), loss of appetite, loss of taste
Pain medications – Salicylates – Nonsteroidal anti-inflammatory medications – Opioid medications	Gastrointestinal upset/ulceration, loss of taste, unpleasant taste Gastrointestinal upset/ulceration, loss of taste, unpleasant taste Sedation, constipation, gastrointestinal side effects, anticholinergic side effects
Antispasticity medications	Loss of taste, unpleasant taste
Antibiotics	Loss of taste, unpleasant taste, gastrointestinal side effects
Gastrointestinal medications – Histamine H2 blockers – Proton pump inhibitors – Laxatives – Antidiarrheal medications	Gastrointestinal side effects, anticholinergic side effects, loss of taste, unpleasant taste

Problems with the pulmonary system may affect the caloric needs of the child. Chronic lung disease that is not well controlled causes increased inflammation, increasing caloric needs. An increased respiratory rate increases the basal metabolic rate and the need for more calories. There could be laryngo-, broncho-, or tracheomalacia which causes airway obstruction, further increasing the basal metabolic rate and affecting the ability to eat.

Children with cerebral palsy are often on medications that affect the nutritional status. These may include anticonvulsants, antipsychotic medications, and antibiotics, which can affect appetite and the tastes of foods (Table 31.1). Chronic benzodiazepine use can result in significant pharyngeal phase dysphagia, especially cricopharyngeal and hypopharyngeal incoordination, resulting in aspiration. Phenytoin can result in atrophy of the cerebellum leading to skeletal muscle dysfunction, ataxia, and oropharyngeal dysphagia [19].

31.4 Assessing the Nutritional Status of Patients with CP

A thorough nutritional history is the cornerstone of assessment. Finding out what happens throughout the course of the day and night is the first step. This will inform the team how many opportunities for eating are available to the child and how long it takes a child to eat their meals. Important *historical* points include where the child eats the meals, what utensils are used, if there is coughing or choking during eating, and if there is any pain while eating. The family should be asked which foods are favorite foods and which foods are most difficult to handle. The family may have already begun offering special formulas, nutrient-dense foods, or additives such as vitamins, minerals, oils, fats, or sugars.

The clinician should evaluate the elements of the past medical history that may cause an increased need for nutrients or a decreased ability to take in or utilize them. This includes whether there has been chronic lung disease, bronchopulmonary dysplasia, or history of pneumonia; see Chap. 29. Congenital heart and other birth defects may affect basal metabolic energy needs. In addition, the work of eating increases energy consumption resulting in early fatigue. Gastrointestinal defects may affect GI motility, feeding tolerance, and appetite. Chronic infection can lead to an increased metabolic rate or anorexia. Chronic pain may also affect nutrient needs and appetite.

Taking a complete social history is important because there may be factors which impact the patient's ability to get the nutrition they need. Families may not be able to afford nutritionally adequate foods or specialized formulas. Caregiver mental health is important because depression may impact the motivation to feed a child for 45–60 min. There may be other caregiver stressors impacting the ability to feed the patient including intellectual disability, anxiety, or substance abuse.

The *nex*t important part of the assessment is to observe a feeding. The family should attempt to recreate a typical feeding session, including using the usual bottle, cup, or utensils. The child should be observed for self-feeding ability as well as posture and seating during the feeding session. Anterior spillage or coughing with eating and drinking should be noted. The most important to note is the interaction between caregiver and child to identify difficulties with attachment and reading cues.

Laboratory studies may be helpful in the nutritional management of the patient with cerebral palsy. There are often deficiencies in vitamin D, zinc, selenium, iron, folate, and vitamins E, B6, and B12 [20]. Lark et al. [21] found that prealbumin and albumin were rarely below normal and showed little correlation to body composition. It is recommended to measure the complete blood count, blood chemistries, and levels of iron and 25-hydroxylated vitamin D [22].

31.5 Managing Nutrition for the Patient with CP

Taking steps to ensure an adequate volume of feeding and improving feeding efficiency improves the likelihood that the patient receives the macro- and micronutrients needed for optimal health, growth, and development. Changes in

the eating position may allow better support for eating and swallowing (see Chap. 30). Slowing the flow of the drink or decreasing the size of the bite of food may make bolus formulation easier and allow more time to organize the swallow. Liquids may be thickened for the patient who has aspiration. Modifying the texture of food such as pureed, fork mashed, or finely fork mashed may make manipulation of the food in the mouth more efficient. Swallowing safety, feeding efficiency, and energy and fluids all need to be considered [23]. Involving a speech and language pathologist or occupational therapist with experience in pediatric feeding problems may help the child and family improve oral motor skills, although few studies have been done to show which interventions are most beneficial. Treating other medical conditions, such as GER, constipation, and underlying infection, may improve the patient's desire to increase the amount they are willing to eat and drink.

Nutritional supplements may be needed to provide for the daily nutritional needs, and these can be given by mouth or by tube. Most patients will tolerate a casein-/whey-based formula; if not, many formulas are available in which the larger proteins or starches are broken down into smaller components [24].

Increased calories may still be needed to reach the goal. Increasing the caloric density of the formula may allow for increased energy needs without increasing the volume. Some concentrated commercial formulas are available which deliver 1.5–2 kcal/mL, instead of the usual 1 kcal/mL. Calories may be added to the food using modular products (medium-chain triglycerides, glucose polymers) or oil, butter, and cream [25].

Some families may wish to try a homemade *blenderized* formula, which has been shown to decrease gastrointestinal symptoms in children who are gastrostomy tube fed and have had a Nissen fundoplication [26]. Contraindications to using a homemade blenderized formula are (1) acute illness or immunosuppression; (2) gastrostomy tube size less than 14 French; (3) continuous drip feedings, as the blended formula must be refrigerated; and (4) lack of resources for the family including electricity, refrigeration, hot water, and other needed supplies [27]. Using a homemade blenderized formula requires extensive education for the caregivers to ensure that the diet contains appropriate nutrients and that the formula is free from contamination [28].

31.6 Summary

The most important concept in the nutritional management of patients with CP is that there must be ongoing reevaluation of the individual patient's status, including weight, rate of growth, fat stores, and tolerance of the regimen. Changes will be made throughout the patient's life to maintain optimum nutrition and health. The best nutritional management is accomplished through an active partnership between the patient, family, and care team.

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Long-Term Prognosis

32

Harald Bode

Abstract

In children with cerebral palsy (CP) prognosis regarding unaided walking, need for walking aids or wheelchair is possible already at the age of 3 years. Gross motor function decreases in many adolescents and adults with CP due to pain, contractures, weight gain or burnout syndrome.

Chronic diseases and behavioural and emotional problems are more prevalent in adults with CP as compared to those without. Secondary musculoskeletal problems occur frequently. Especially pain becomes an important topic.

More than 90% of children with CP survive into adulthood. Life expectancy depends on GMFCS level and swallowing problems.

Transition from child- and family-centred services into those for adults remains a difficult topic, especially for severely handicapped individuals. Health and social services are used less often by adults with CP.

Health-related quality of life remains rather stable over the years; lower scores are found in severely affected persons. Participation strongly relates to the intellectual and social capacities of the individuals and may increase with improvements in rehabilitation technique, domestic assistance and legislation.

Happiness in life in individuals with CP is promoted by acceptance, trust placed in themselves by others and by means of confidence by themselves.

32.1 Introduction

Relatively little attention has been awarded in the past to the long-term prognosis of cerebral palsy (*CP*). This is rather regrettable as therapeutic measures and aims have to be evaluated not only on short-term but also within a long-term context. The information gained on long-term prognosis

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can be resorted not only to counselling of parents but also in therapeutics and on the therapy concepts in infancy. Here we discuss the long-term prognosis of motility and some pertinent aspects (morbidity, mortality, service use, quality of life and participation) of the essentially highly complex concept of cerebral palsy.

32.2 Walking and Hand Function

Endeavours of parents are primarily directed towards the *unaided walking* of their children afflicted with *CP*, this being consequently the aim of sometimes highly intensive therapeutic efforts. Depending on the type and severity of cerebral palsy and the accompanying functional disturbances, five different motor developmental clusters have been described. Children with severe motor handicaps (*Level V*) have achieved 90% of their motor capabilities measured on the GMFM at an age of 3 years, children with minor motor deficiency (*Level 1*) at about 5 years (see Chap. 22). A substantial individual variability has however to be recognised within the developmental profiles.

Based on the general clinical experience, all of the children with *spastic hemiparesis* achieve the ability of unaided walking without additional major problems [1]. All children with spastic diplegia or triplegia, normal visual ability and normal developmental quotients at an age of 9–18 months acquire the ability of unaided walking at an age of 36–54 months (2).

The ability to support their own weight on their hands in a prone position, and to roll from a prone in rear position within 18 months or to sit unaided within 24 months, must be regarded as closely correlated with the ability of unaided walking between 36 and 54 months [2].

It could be retrospectively demonstrated on 272 patients with cerebral palsy that the control of the head position prior to the 9th month can be regarded as a positive prognostic sign, while gaining head control after the 20th month is regarded to indicate a negative prognosis for learning of unaided walking. Regarded also as promising sign in this respect is an unaided sitting at 24 months and/or an alternating crawling within 30 months [3]. At an age of 3 years, *three motor* developmental profiles are differentiated for children with CP:

1. Children without adequate trunk control. They will hardly ever gain a persistent unaided walking ability. Adequate aids including (electric) wheelchair will be required.
2. Children with adequate trunk control not yet able to walk freely. These children may acquire the ability of free walking after being subject to intensive physiotherapy, being provided with ortheses and possibly orthopaedic operations (see Chap. 22). Walking will, however, frequently demand the utilisation of aids.
3. Children who have already acquired the ability of free walking. They will retain this ability over extended periods and shall receive regular medical attention preferably in physiotherapeutic blocks [1].

Children with *spastic tetraplegia* not being able to walk unaided at an age of 4 years will not acquire the ability up to an age of 7 years and later [4]. Prognosis may be more favourable in individual cases due to intensive therapeutic measures and adequate aids.

In to age, environment influences the method of mobility in children and adolescents with cerebral palsy. The method in one setting may be walking; wheel mobility may be preferred in the other [5].

Hand function within 18 months in children with spastic diplegia has a prognostic value for the child's future hand function [6]. Function of the paretic hand remains stable for many years if there has been adequate function primarily during early childhood [7]. However, we often observe a decreasing use of the paretic hand during early school age in hemiplegia.

32.3 Motor Functions of Adults with CP

Motor function takes a turn for the worse in many adults with cerebral palsy [1, 8, 9]. Ando and Ueda [9] noted a functional deterioration in 35%

of 686 adult patients with cerebral palsy, especially in those with involuntary movements and in those with workplaces not adapted to their motor disturbance.

Bottos et al. [1] examined 72 adults born between 1934 and 1980 in *Italian rehabilitation* centres. They also reported a loss of motor abilities at adult age. In many people the motor ability of unaided or even aided walking was lost or curtailed. Walking function was practically retained in all patients with *hemiplegia.* Adults demonstrated orthopaedic deformities in many cases, also in the cases of slight or medium motor disturbances, being attributed to excessive stress on joints during walking. During adult age contacts to health and rehabilitation service decreased radically. Frequently a physical "burnout syndrome" after years and decades of intensive therapy and motor stresses is described. In view of this long-term result, the authors come to the conclusion that the therapeutic aim of unaided walking should be reconsidered and a combination of motility possibilities including mechanical aids should be contemplated at an early stage. Independence training should be accorded a high priority [1]. These deliberations apply certainly not to all children with CP yet are convincing for certain degrees of severity.

In a *Swedish* study, 363 adult persons with CP but without intellectual deficiencies were questioned as to their motor and associated abilities and problems. 77% questioned reported problems with their spasticity, 80% had contractures, 64% could walk with or without aids, 35% complained of a decreasing motor ability, 9% had a loss of walking ability, 54% reported an unrestricted motility, 60% were physically active on a regular basis, 84% lived in their own residence, 33% were together with a partner, 24% worked full time, and 18% received a disability pension [8].

After a follow-up period of 7 years, a population of 149 adults with CP (mean age 40 years) showed deteriorated walking in 71% of patients with bilateral and in 34% of patients with unilateral CP. Deterioration was associated with greater frequency and intensity of pain, physical fatigue and reduced balance [10].

A few recent studies point out that aimed intensive training for adult and adolescent patients with CP can result in persistent functional improvements. Strength training of 2 × 1 h weekly over 10 weeks for 10 adults of 23–44 years of age with spastic diplegia significantly increased muscle strength and walking ability in comparison to a control group. Spasticity did not increase in those who underwent strength training [11].

Bates and Wilson [12] applied a forced motility training to nine hemiplegic adolescents of 13–18 years of age. It took place on 7 h a day and 5 days a week for a total of 2 weeks. The healthy hand was "degraded" to an assistant hand by a glove-like splint. The afflicted hand was intensively used according to the concept of motor learning within the scope of leisure activities (e.g., fine motor games, preparation of food, eating, rinsing) and special manipulative exercises. The patients improved their skills significantly in nearly all sectors and to a relevant degree. This was evidenced by the test criteria as well as by the impression of the patients themselves. These effects persisted still 5 months after termination of the intensive therapy [12].

Muscle strengthening programs in patients with CP may improve muscular reserve in the short term and muscle mass above critical thresholds in the long term. This may allow maintenance of functions for a longer span of life [13].

The long-term effects of various operative procedures depend on the individual problems of the children, the type of operation and the outcome measures. For example, single-event multilevel surgery showed the best results in children aged 10–12 years with GMFCS Level III [14]. Selective dorsal rhizotomy seems to have positive long-term effect on lower limb muscle tone, whereas functional improvements are mainly observed in GMFCS Levels II and III with a gradual decline during long-term follow-up [15]; see Chap. 26.

32.4 Morbidity

Chronic diseases associated with lifestyle behaviours appear to be more prevalent in adults with CP as compared to those without CP: diabetes (9.2% vs. 6.3%), asthma (20.7% vs. 9.4%),

hypertension (30% vs. 22.1%), other heart conditions (15.1% vs. 9.1%), stroke (4.6% vs. 2.3%), joint pain (43.6% vs. 28%), arthritis (31.4% vs. 17.4%) and obesity (41.4% vs. 29.7%). Good health, good mental health and regular physical activity were less frequent in adults with CP [16].

Behavioural and emotional problems are reported frequently, both in children and adults with CP. Caregivers reported attention problems (36%), social interaction problems (33%), abnormal prosocial behaviour (42%) and abnormal rates of communication (88%) in adults with CP; however another report denies increased prevalence of ADHD, depression, obsessive-compulsive disorder and autism spectrum disorder in adolescents with CP as compared to controls without CP [17].

Adult people with CP suffer, depending on severity and kind of their motor disturbances on various secondary musculoskeletal problems [18]; see Chap. 34. Contractures involving the ankle, knee and hip joints and also the upper extremities are frequently seen. Extremities may also be completely or partially shortened in length and/or circumference. In *spastic tetraparesis* progressive scoliosis is often encountered. It is demanding frequently for conservative and operative therapy [19, 20]; see Chap. 22.

As consequence of reduced exposure to gravitational load, possibly also due to malnutrition or inadequate nutrition, the bone mineral density may be reduced (see Chap. 23). Between 77 and 97% of adults with medium to severe CP are affected [21]. As a consequence, about 26% of the above-mentioned 10-year-old patients have already suffered fractures. A systematic review revealed an incidence of fractures in children with moderate-to-severe CP of 4% per year [21]. The prevalence of low bone mineral density, secondary osteoporosis and fractures increases in adolescence and adulthood, preferable in case of mobility limitations. Dual-energy X-ray absorptiometry is feasible to monitor bone density [22]. Vitamin D alone or with bisphosphonate increases bone mineral density and should be considered in CP patients taking antiepileptic drugs [23].

Dislocations of the hip appear, but rarely in patients with CP capable of walking, however, about 20–47% suffer from hip pains [24]; see Chap. 19.

Pain may be a consequence of degenerative arthritis. Further orthopaedic problems of adults with CP are patella alta, spondylolysis with progress to spondylolisthesis in ambulant patients and cervical stenosis in athetoid CP and spastic tetrapareses, often associated with myelomalacia or radiculopathy [25].

Pain has been reported in 30–80% of adult patients with CP. The back, the neck, the hip and the lower extremities are the most frequent locations. Pain may result from contractures, spasticity, deformities, fractures, poor nutrition, sitting on bony prominences, weakness and fatigue [18, 26]. Other common causes are dental problems, constipation or oesophagitis [27].

Fatigue is being reported as a main problem in adults with CP. It is unrelated to type or severity of cerebral palsy and may be associated with pain. Consequences may be deterioration of functions, activities and quality of life [26].

Other secondary disease characteristic for CP in adults appears especially in badly affected patients, concerning mainly the respiratory system (bronchitis and pneumonia) and the nutrition (disturbed eating habits, subcaloric nutrition, chronical constipation). The comorbidities already known from the children's age (subnormal height and weight, reduced intelligence, disturbed vision, epilepsy, possibly emotional disturbances) remain.

Neurogenic lower urinary tract dysfunction is frequent in adults with CP, especially with higher grades of cognitive and motor impairment (GMFCS Levels III–V). Storage symptoms are more common than voiding problems due to the high prevalence of neurogenic detrusor hyperactivity. Hydronephrosis, persistent urinary retention and urolithiasis are observed [28].

32.5 Mortality

The life expectancy of people with CP is dependent on the severity and on the disturbance of motor function, on the comorbidities, on the socioeconomic status of the patient's family and on the resources of the regional health-care system [29].

The standardised mortality rate (*SMR*) for people with severe CP of all ages is clearly higher than that of mild cerebral palsy. The SMR during

the initial 14 years of age was almost ten times higher than that afterwards [30]; see Chap. 34. Noted were high *SMR*s in reference to that of the normal population in reference to cardiac-circulatory diseases, for diseases of the digestive system and accidents. Surprisingly a high death rate for diseases not in connection with the cerebral palsy, such as for breast cancer (*SMR 3,0*) and brain tumours (*SMR 24*) as compared to the normal population, could also be ascertained. The underuse of preventive medicine facilities, difficult or less consequent diagnostics and/or treatment, communication difficulties, physical limitations, psychological barriers and staff attitudes might induce barriers to more successful outcomes [31]. A causal interrelation with CP appears to be speculative [30].

The life expectancy of children suffering from CP has been determined for 581 children born between 1980 and 1986 in *south-east England*. In 1995, i.e. at an age of 10–15 years, 92% of these 581 children were still alive. Of 165 children with *tetraparesis*, 85% were still alive; of those with *tetraplegia* and additional aetiological relevant diagnoses, 75% were still alive [32].

An evaluation of the West Australian register for people with CP born between 1985 and 1994 displayed 225 cases of death among a total of 2014 cases (approximate 11%). The annual mortality during the age of 0–5 years surpassed 1%, declined up to age 15 years and amounted subsequently to 0.35% annually. No case of death attributed to this affliction was reported after the age of 25 years—despite severe motor handicaps. The survival of children with CP was most reliably predicted by the intelligence quotient (*IQ*) or the developmental quotient (*DQ*) of the children, respectively. 50% of children with an IQ/DQ below 20, 76% with an IQ/DQ of 20–34 and 92% with an IQ/DQ of above 34 reached adult age. No improvement as to this survival rates was noted over the entire observation period [33].

The life expectancy of adult people with CP was investigated in *California* between 1980 and 1995. Data of 24,786 individuals over the age of 15 years with CP were acquired and scrutinised. Life expectancy of these patients proved to depend on the basic functionality, their mobility and eating habits. The data were analysed for the mortality risk and life expectancy. The mean survival rate during the 15 years of observation was between 95% (people able to feed themselves, capable of turning around and sitting unsupported) and 30% (people lying on their belly, unable to raise their heads who had to be fed) [34].

Out of a UK birth cohort of 1940–1950, 85% of people with CP surviving to the age of 20 survived to the age of 50 years as compared to 96% in the general population. More deaths occurred from diseases of the respiratory system, fewer deaths from injuries and accidents [35].

A Japanese cohort of children with CP born between 1988 and 2005 showed a 5- and 18-year survival rate of 98 and 89%, respectively. GMFCS Level V was the only significant predictor variable [36].

32.6 Transition and Service Use of Adults with CP

Transition to adult-oriented health care for people with chronic conditions is an underdeveloped topic in all countries. This refers also to adolescents with cerebral palsy. Only few transitional programs exist [37]. Main components of such programs should be collaboration of services, building capacities, a medical home or a case manager/navigator, spread of all information concerning disease, resources and services, education of the health providers, patients and caregivers and research [38]. As main barriers for successful transition to adult care, settings in multidisciplinary adult-focused clinics are reported: limited adult provider's willingness to accept CP patients, concern about the level of care in the adult system and lack of financial resources [39]. In our experience no significant problems in medical transition occur in adolescents with CP and GMFCS Levels I–II, without epilepsy and without intellectual disability (see Chap. 34). Many unsolved problems still remain in those with GMFCS Levels IV–V, with moderate or severe intellectual disability, severe visual disturbances or difficult-to-treat epilepsy.

Empirical experiences and various studies demonstrated that adolescents and especially

adults with CP utilise to a lesser degree than children on the resources offered by the health and social services. In cases of a nonindependent person with CP, this results in elevated temporal, physical and psychic demands of the relatives, frustrations and anxieties about the future.

In the majority of countries, there is a *lack of adequate structures* for the care of adults with CP. Caring relatives and afflicted patients criticise the bureaucratic structures and the attitude of those offering services [40, 41]. The expert knowledge of the medical personnel concerning the specific problems and requirements of adult persons with cerebral palsy are also limited [42]. The health and well-being of caregivers is strongly influenced by the patient behaviour, caregiving demands, family function and social support. Strategies for optimising caregivers' physical and psychological health should include supports for behavioural management, daily functional activities, stress management and self-efficacy techniques [43].

The estimated lifetime direct and indirect economic costs were calculated as to 11.5 billion dollars for persons with cerebral palsy in the United States in 2003 [44]. This underscores the need for effective prevention which so far is difficult.

32.7 Quality of Life and Participation

Children with CP seem to have a fairly similar quality of life as compared to their healthy peers [45]. However, they have fewer reciprocal friendships, exhibit fewer sociable/leadership behaviours, are more isolated and victimised by their peers than classmates without a disability already at an age of 10 [46].

Health-related quality of life remains rather stable in children and adolescents over the years. Adolescents and young adults with CP seem to have lower scores of quality of life, if people with severe cerebral palsy and intellectual disability are included. Severity of cerebral palsy explained 45% of the variance in quality of life scores [47].

Participation in home, extracurricular and community activities was higher in children as compared to young people with cerebral palsy. Participation was highest in *GMFCS,* Level I, and lowest in GMFCS, Levels IV and V [48]. In individuals without intellectual disability, the degree of social participation increased with age and stabilised at about 18 years being on the same level as in individuals without CP [49].

In children and adolescents with cerebral palsy, developmental trajectories of mobility performance depend on the level on gross motor function, whereas the trajectories of daily activities mainly relate to intellectual ability [50]. Adults with cerebral palsy without mental handicaps generally master the daily activities, the mobility and the communication by themselves. However, problems in daily life have been reported by 70% of young adults. These problems were referred to self-care (59%), productivity (52%) and leisure activities (37%) [51]. Adults with cerebral palsy experienced great difficulties with regard to their social integration. They encounter problems in professional training and finding appropriate jobs. This applies also to suitable leisure activities, e.g. in sports [8, 52, 53].

The *Danish* Cerebral Palsy Registry revealed the long-term social prognosis of children born between 1965 and 1978. 33% of adults with cerebral palsy vs. 77% of controls had an education beyond lower secondary school; 29% vs. 82% of controls were competitively employed. The odds ratios for not being competitively employed were 1.9 for *diplegia* vs. *hemiplegia*, 22.5 for a developmental quotient 50–85 vs. >85 and 3.7 for those with epilepsy vs. those without epilepsy [54]. Unfortunately, no sign of increased social integration was observed over the past two decades in adults with cerebral palsy. Only 28% had a partner, and 19% had children [55].

Those adults with CP which have a regular school education and walking abilities have obviously better prospects on the occupational market [56]. For many afflicted with CP, the problems of decreasing motor ability and various morbidities greatly impair their quality of life in adult age.

Improvements of rehabilitation techniques, *domestic* assistance and the *legislation* pertaining to training and employment of handicapped and a barrier-free access improve the situation

of people with cerebral palsy and help to maintain independence (Murphy et al. 2000; [57]). Essential claims as to demands and aids also for people living in Germany with cerebral palsy are covered by the German social law (Social Law Code IX of 2001). Realisation of the code is, however, difficult in times of financial bottlenecks.

However, success *in life* is appraised by people with cerebral palsy not only in economical but also in medical and other aspects. Adolescents with cerebral palsy define success in life for themselves as "being happy in their life". Essential factors are the trust and confidence placed in them by others, the acceptance enjoyed and the confidence in themselves [58].

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Quality of Life

33

Anna McCormick

Abstract

The concept of quality of life (*QoL*) is very personal for each individual and requires careful consideration when providing care. It may, in fact, be the most important consideration when providing care for individuals with childhood-acquired disabilities. These conditions quite often have long-term impacts on physical health, cognition, and/or behavior with resultant alterations in function and participation. It is therefore critical that care providers understand the definition of QoL, know the options for measuring this concept, and be aware of the goal-focused tools that may be used to incorporate each person's wants and needs into care plans. This knowledge allows care providers to facilitate care that keeps QoL as a priority.

Although indicators of quality of life have been deemed variable and individual, pain is the single most common element throughout all domains to negatively impact quality of life. Investigation and treatment of pain appears essential for improvement in life quality. Many studies also highlight the need for societal change to maximize inclusion and limit social isolation. It is also of note that with aging, there is an increased link between independence and QoL. Essentially people should feel physically well, socially connected and have optimal independence. These factors appear to enhance positive feelings regarding current life situation and hope for the future, thus adding quality to one's life.

33.1 Introduction

The World Health Organization (WHO) defines quality of life (QoL) as "the individual's perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards, and concerns" [1]. This concept is very personal for each living individual and requires careful

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consideration when providing care. In lifelong conditions with high variability of presentation, as is the case with cerebral palsy, assessment of this broad concept with multiple dimensions presents significant challenge.

To work toward greater understanding of this concept, the clinician must become knowledgeable about ways to assess and quantify QoL, common indicators of QoL that have been recognized in research to date, the role of the proxy when self-report is not possible, and care models that can provide significant positive impact in this area.

33.2 Quantifying Quality of Life

Over time the number of outcome measures has increased exponentially. The literature now reports over 90 instruments that have been utilized in children and adolescents to assess quality of life [2]. Authors have endeavored to define meaningful outcomes for the majority of individuals. When one uses the WHO International Classification of Functioning, Disability and Health (ICF) framework [3] to help conceptualize QoL, the reason for the very high degree of variability becomes quite apparent. It is easy to imagine the number of personal factors and environmental factors which must be taken into consideration. Layered on this is the variation in presentation of the clinical condition known as cerebral palsy. The important dimensions for assessment may be quite diverse, and measurement often requires a personalized approach based on needs and wants of each individual.

It is also important to understand the difference between quality of life and health-related quality of life (HRQoL). Both these terms are often used interchangeably. In general however quality of life is a much more general concept which takes all facets of life experience into consideration. Health-related quality of life focuses more on how one's health impacts on life experience. As one considers measurement, outcomes may be very different depending on the number of dimensions of the tool focused on health, the condition, and body function.

Some tools that are more commonly utilized in cerebral palsy are outlined in Table 33.1. The

Table 33.1 Common tools utilized to assess quality of life in cerebral palsy

Tool	Age range	Number of domains	Self-report and proxy Y = Both	Condition specific (CS) vs. generic (G)	Focus/differences
CP QOL-Child	4–18	7	Y	CS	Focus on well-being: How child/youth feels about aspects of life
CHQ	5–18	12	Y	G	Developed as measure of general health status and well-being
					Some questions not appropriate in CP
KIDSCREEN	8–18	10	Y	G	Measures QoL of healthy and chronically ill children
					Generic tool designed with children's input
PedsQL	2–18	5	Y	G CS module	Assesses physical, emotional, social, and school function
					Focus on what the child can do
HUI	3–adult	8	Y	G	Structured around the WHO paradigm of disability with physical systems focus
					General and applicable to most individuals
PODCI	2–18	5	Y	G	Focus on physical function
					Sensitive to detect change in physical function
CPCHILD	5–19	6	Proxy	CS	Developed for children and youth with severe impact from CP focused on caregiver perspectives/priorities

majority of these tools are more generic and offer the ability to compare between diagnostic groups, while two tools and one module are specific to CP. A number have been used in multiple countries with large sample sizes. All tools have the option of proxy reporting if for some reason the individual cannot self-report.

33.2.1 Specific Measurement Tools

The **CP QOL-Child** questionnaire [4] offers a CP-specific multidimensional tool with focus on well-being. It has seven domains including social well-being and acceptance, feelings about functioning, participation and physical health, emotional well-being, access to services, pain, and feelings about disability and family health.

The Child Health Questionnaire (CHQ) [5] was developed to measure functional health and well-being. It measures 14 unique QoL domains. It has been used in studies of children with CP but when used for this population had an introductory sentence indicating that some questions might not be appropriate in this condition. There are two lengths of parent questionnaires with 50 (CHQ-PF50) or 28 (CHQ-PF28) items and an 87-item child self-reported version designed for children over 10 years of age.

The KIDSCREEN QoL measure for children and adolescents [6] was developed to measure general HRQoL. It involved a sample of 22,827 children and adolescents from 13 European countries. There is a long (original) version with 52 items covering 10 dimensions, a 27 item with 5 dimensions, and a 10-item index version [7]. Only one domain represents physical well-being. This tool has been utilized in epidemiologic public health surveys, clinical intervention studies, and multiple research settings.

The PedsQL measurement model [8] has a modular approach. There are generic core scales with 23 items to measure the dimensions of health as delineated by the WHO. It assesses four domains including physical, emotional, social, and school function. A disease-specific module for CP was created. The generic core scale of the PedsQL differentiated HRQoL between healthy children and children with CP. It has been suggested that the CP module and generic core scales would provide an integrated measurement model with the advantages of both generic and condition-specific instruments.

The Health Utilities Index (HUI) [9] is a generic health-related quality of life instrument structured around the WHO paradigm of disability [3]. This allows factors to be compartmentalized in a way that is intuitive for rehabilitation healthcare providers. There are a large number of general population surveys utilizing this tool. This provides significant reference data. It has also been utilized in looking at QoL in youth and adults with CP [10].

The HUI has eight attributes: five are physically based and two are hearing and vision. Individuals with higher physical involvement score lower by the nature of the scale. There is also positive and negative scoring. Negative scoring is said to represent conditions being "worse than death." This is a judgment that can be questioned.

The Pediatric Outcomes Data Collection Instrument (PODCI) [11] assesses upper extremity function, transfers and mobility, physical function and sports, happiness and satisfaction, and expectations for treatment. It was developed and is endorsed by the American Academy of Orthopaedic Surgeons®. The tool has a focus on activity and participation. Sensitivity to change has been reported. Calculation requires formulae and recoding of some items. This tool may be time-consuming.

Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD©) questionnaire [12] was developed for children and youth with severe impact from CP. It is a condition-specific, valid, reliable tool. The domains include activity limitations, health status, well-being, and ease of care. Items are rated on degree of difficulty and level of assistance. Its focus is on caregiver perspectives and priorities. It may be used in evaluating interventions using outcomes that are meaningful to patients and their caregivers.

Deciding on which tool to use can be difficult; however by clarifying one's research question, the right tool can be selected. The focus of the tool, need for proxy vs self-report, age range of

population, specific domains of interest, time for completion, psychometric properties, and previous use of the tool should all be considered [13]. As well combining a general tool with more specific individualized outcome measures may give added quality to research in this area.

33.3 Is Quality of Life Different in Individuals with Cerebral Palsy?

Quality of life may be looked at from many perspectives. It is multidimensional and dynamic. With so many different ways to measure QoL, the reports are variable depending on tools used. There is also variability based on age at the time of assessment. Regardless to clear variability for many reasons, there are a number of determinants of QoL that the evidence supports.

33.3.1 Focus of Tool

Measures focusing on physical aspects, function, and health have reported lower scores in individuals with CP [8, 14]. When the tools emphasize an individual's interpretation of more general aspects of their life, QoL scores are higher and tend to be similar to the general population [15, 16].

33.3.2 Age and QoL

Assessment of QoL in infants and young children is reported by proxy. This information, though very relevant, is focused through a different lens (Sect. 33.4).

Self-reported QoL of 8–12-year-old children with CP has been studied in 743 children from six European countries. Overall children with CP indicated similar QoL as the general population of children [15]. Similar findings were reported from an American study in youth from 10–13 years of age [16]. Although one must remember the focus of the tool and the individual, dynamic multidimensional nature of QoL, this information may be quite reassuring and helpful in counseling families following a new diagnosis.

There is also *evidence* supporting the fact that young adults aged 18–25 have good psychosocial well-being with scores for social relationship and environmental context domains being similar to the general population. Scores were however lower for physical health, psychological well-being, and role function domains [17]. This *concept* is supported by low HUI scores, prolonged hospital stays for reasons of mental health [10], and low rates of employment in this population [18].

No clear association has been found between physical indicators and psychosocial well-being [17]. Individuals with significant physical involvement may be quite successful from a psychosocial perspective. There is therefore support for limiting physical barriers, optimizing techniques to maximize independence, and promoting inclusion to meet the needs of individuals aging with CP.

33.3.3 Individual Determinants of QoL

Pain has repeatedly been documented as the single most common element throughout all domains to negatively impact quality of life [11, 15]. The link between pain and QoL is so strong that each individual should be asked by their healthcare provider about pain and its impact on their life. This information can be used to guide care and target treatment to decrease pain and improve quality of life.

Although there is convincing evidence that *impairments* are not significantly associated with many domains measured in QoL tools [15], it is helpful to assess how certain impairments may have impact on individual domains of interest. In the domain of physical well-being, severe limitation of self-mobility has been associated with low scores. Speech difficulties appear to have negative impact on relationships with parents. Evidence of intellectual impairment is related to low score in mood and emotions and reduced autonomy. Although individuals may have population comparable scores for overall QoL, looking

at specific domains may help us glean how promotion of independent mobility, maximizing communication strategies, and assessment/treatment of mood disorders may have significant impact on important aspects of life.

Given the limited impact of impairment when assessing the broad concept of QoL, psychosocial and environmental factors have greater importance. Building inclusive, accessible, supportive communities appears to be crucial to optimizing life experience.

33.4 Proxy Data

Communication difficulties and cognitive involvement in cerebral palsy result in increased challenge in assessing quality of life. In some instances the only way to assess QoL is by asking the person who has the closest relationship with the individual. This person is termed *the proxy*. The difficulty with information collected in this way is that there is an added layer of complexity.

Data has suggested that proxy-reported quality of life for children with cerebral palsy is related to parental psychosocial distress [19]. Parental distress has been found to be negatively correlated with the domains of parent proxy-reported QoL. There also may be lower scoring in domains related to social support and higher rating in psychological domains when parent proxy is compared to health professionals [20].

Whenever possible data is collected directly from the individual, they are the person living with the condition, and it is their personal experience that is sought when looking at quality of life. When this is not possible, there are a number of tools which have proxy data collection options. When proxy information is utilized, the person asking the questions must be quite aware of the limitations reflected in the data.

33.5 Quality of Life in Caregivers

The impact of a lifelong condition such as cerebral palsy is widespread, and the impact on lives of others is extremely important [21–24]. Stress and QoL have been an ongoing concern for care providers. Coping with the news related to a health concern and a subsequent diagnosis of cerebral palsy has been related to parental grieving and stress [21, 22]. There is evidence of high levels of depression in this population of care providers [21, 23]. There has also been report of social isolation, impact on family dynamics, physical strain, sleep disturbance, and decreased ability to maintain employment [24].

Behavioral challenges including high level of activity, aggression, emotional symptoms, and peer interaction problems are common in cerebral palsy [25]. These challenges may limit therapeutic intervention, decrease ability to socially integrate, and limit participation [26]. These difficulties are also related to parental distress [27]. This information reminds care providers of the importance of incorporating screening questions regarding physical, cognitive, and behavioral function and well-being in clinical interaction with clients. Designing treatment and support plans with close links to team members specializing in emotional support starting at the time of diagnosis and dual diagnosis treatment programs hold hope for limiting morbidity, maximizing integration and participation and subsequently improvement in QoL. Individual goals can then be set in these areas with improvement of QoL as a general overarching goal.

33.6 Patient-Focused Tools

Many recently developed QoL measures are formulated from qualitative data based on client and family interview. They are therefore reflective of the priorities for individuals with CP. These tools are however very general and may not reflect specific issues which are important to individuals' QoL. These general tools can therefore be used along with flexible, individualized patient-focused tools to ensure the person's voice is being heard.

There are a number of goal-focused tools such as the COPM [28] and the Goal Attainment Scale [29] which can guide discussion around an individual's priorities in their life and circumstance.

This allows formulation of an individualized plan with the person's wants and needs being addressed as the primary concern.

The COPM includes a discussion between the therapist and individual regarding the individual's wants and needs. The individual may choose their most important problems or areas of concern. There is a rating scale that includes performance and satisfaction. Following a rehabilitative intervention, the goals are reassessed and rescored to see if a significant improvement in function has occurred.

When utilizing the Goal Attainment Scale, each patient defines their own goals. The therapist assists the client to rate each goal on a 5-point scale. Ratings range from much greater than expected to much less than expected. Goals may be weighted by the patient for importance or difficulty.

Combining focused goal assessment with a wider scan of QoL allows for care plans and models of care that not only have a positive impact but also clearly have the individual's goals as a priority.

33.7 The Future

The general population may be surprised by the similarity in subjective QoL measurement in children with CP and the general population. This reminds us that QoL is an individual, personal experience. Self-report is essential but when this is not possible, proxy reporting may be considered. Interpretation of the proxy report must be identified and assessed accordingly.

It is clear that QoL should be central in assessment and provision of care. It is often the most important outcome of treatment for chronic conditions [30]. Goals should be individualized based on a person's priorities. Utilizing a combination of individualized goal outcomes and more general QoL measures pre- and post-interventions may assist in maximizing general health and well-being.

It is clear that when pain is present, investigation and treatment of pain is essential to improve QoL. Societal change for inclusion and limitation of social isolation also appears to be essential to many domains or facets of this multidimensional concept. Newer measurement tools have incorporated these domains, and facilitation of societal change is the focus of many programs, such as the "Just say Hi" campaign of the Cerebral Palsy Foundation [31].

New constructs are on the horizons that are pushing us to consider lifelong developmental conditions from a social ecological perspective. The six F-words for CP is such a construct based on the WHO International Classification of Functioning, Disability and Health (ICF) [32]. With this construct in mind, we are asked to consider and discuss function, family, fitness, friends, fun, and the future. Moving forward this construct may be quite useful in studying QoL in a practical holistic manner with life quality at the center of patient care.

As one studies QoL in individuals with CP, it is important to remember the 17 million people in the world living with CP. Further study is required, but for now the literature informs us that living with minimal pain, maximal inclusion, and having lives that each individual perceives as high in quality are key areas for consideration going forward.

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Rehabilitation Principles of Adults with Cerebral Palsy

34

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Abstract

Cerebral palsy (CP) is a nonprogressive condition as to its etiology and neuropathogenesis. However, health and function may deteriorate as patients with CP grow older. Problems secondary to "growing" may develop in muscle tone, motor, and postural control. Movements or postures adopted to compensate for these abnormalities may result in further disturbances affecting health and functional state. Although appropriate medical management, rehabilitation, adaptive strategies, recreational activities, and assistive technology allow most persons with CP to participate to social events, develop skills, find jobs, and live an independent and active life, many need more assistance and care in adulthood. Aging and CP can be a difficult combination where collaboration is strongly needed between disciplines in order to generate evidence for guiding clinical practice and establish appropriate systems for care.

34.1 Introduction

"Whoever is born grows": this popular Turkish saying reflects the hope and expectations of parents for their offspring. However, growth is under the influence of many biological and environmental factors both in the healthy child and in the child with cerebral palsy (CP). The limitations associated with CP continue from childhood till elderly years. The transitional periods from childhood to adolescence and adulthood and later to old age carry particular risk for potential medical and social complications. Changing social needs; decreased motivation in the patient and family; psychological problems; increasing difficulty in balance, strength, coordination, and postural

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control; skeletal deformities due to the adverse effect of gravity; hypertonia; and dystonia all might further limit ambulation and physical independence over time [1]. The factor of "growing," a normal process for other individuals, represents a struggle against secondary problems for physicians and physiotherapists treating CP patients during the transition period [2]. Elderly CP patients also need specific management: their condition amplifies the physiological and psychological results of aging, often causing "premature aging." As they grow older, many adults with CP are in danger of other health problems such as osteoarthritis, fatigue, loss of balance, and pain, which are often more serious than those of healthy elderly people. The extent of secondary problems varies according to the type and severity of CP [3]. It is important to maintain elderly CP patients' ability to walk independently in order to continue their participation. For such a multidimensional situation, the multidisciplinary team caring for the child with CP needs to be enlarged to include adult specialists in order to manage the transition and try to improve the quality of life in adults with CP.

In this chapter, we will examine growing up with CP especially in terms of physical and motor functions through the principles of rehabilitation.

34.2 Cerebral Palsy and Age

Most children with CP survive into adulthood: 80% live to their 20s and 80% of adults with CP live to 55—although this rate is lower than the approximately 90% in the non-CP population, individuals with CP who are able to walk are known to have a relatively normal lifespan [4]. For this reason the adult life of individuals with CP has been gathering more interest in recent years [5]. Physicians and physiotherapists should be aware of changes in mobility, strength, and endurance to be expected during the maturation process of persons with CP.

The particular problems of aging with CP stem from alterations in existing motor and other impairments: the natural decline due to aging is steeper in persons with CP due to associated secondary problems [6]. Significant deterioration in the ability to walk with or without aids was reported in 40% of adults with CP [3]. The possibility of losing independent walking ability in adulthood seems to be higher for individuals with choreoathetosis or quadriplegic spastic CP than for those with hemiplegic and diplegic forms [7]. Adults with CP are also at significantly higher odds for chronic disorders like arthritis, premature aging, pain, fatigue, and cardiopulmonary problems resulting in reduced independence, a sedentary lifestyle, and social isolation [8]. The presence of sensory and cognitive problems increases the severity of limitations [9].

34.3 Reduction in Mobility

Walking is one of the most important functions: during all the physiotherapy applied in childhood, the greatest hope of the family and the child is to ambulate independently. However, adults with CP, especially those with poor gait function who required the use of aids during childhood (GMFCS level III), are likely to report deterioration in their walking ability over time and may stop walking entirely [10]. This possibility increases with age: Jahnsen et al. [11] reported progressive risk of deterioration from age 25 to 45 years, and more than 70% of CP patients over 45 years old report a decline in walking ability. The age of deterioration also appears to be associated with the distribution of motor impairment and muscle weakness: median 37 years in bilateral CP vs. 52 years in hemiplegic CP [1]. Walking may cease altogether in the early 20s and 30s [7]. Sometimes this is due to personal choices in response to current or changing symptoms, environment, activities of daily life, or vocation. Previously ambulant adults with CP may decide to use walking aids or a wheelchair to save energy for other activities, to prevent falling, and to feel safer [12]. However, losing the ability to walk affects patients' symptoms; their social, educational, and professional life; and the level of assistance needed with activities of daily life like personal hygiene or getting dressed [8].

Spasticity may appear more pronounced in adulthood, frequently related to pain, fatigue, and secondary muscle and skeletal problems.

Balance is one of the most commonly reported problem areas, with more than 60% of adults affected; progressive postural instability can be due to factors associated with aging, like weight gain and diminishing vision, hearing, and vestibular functions, and also to factors associated with CP itself, namely, spasticity, poor muscle strength, and joint limitations. Falls or other negative experiences may discourage the older adult with CP [10, 11].

Physical fitness In addition to the natural decrease associated with aging, the tendency to reduce energy loss leads to gradual reduction in physical activity and fitness [13].

*Musculoskeletal deformitie*s Relatively common are dislocations of the hip, skeletal abnormalities, and contractions of some muscle groups [14]. They result from muscle hypo- or hyper-tone; asymmetrical strength of the pelvic, hip, and leg muscles; weakness of trunk muscles; or problems in bone alignment and asymmetrical weight-bearing. Hip dislocation is an acquired condition that affects individuals with CP. Patella alta and ankle deformities resulting from spasticity and weak antigravity muscles are among other common musculoskeletal disorders reported to affect 18–59% of adults with CP [15].

Joint degeneration Insufficient joint loading in childhood due to delayed weight-bearing, asymmetrical muscle activity, abnormal muscle tone, insufficient strength, and abnormal postural control and postural alignment may lead to poor joint integrity and irreversible damage to the articular cartilage of the joint surface. This leads to an early onset of osteoarthritis, a common cause of pain, predominantly affecting the hips, knees, and feet. Studies report osteoarthritis is more frequent, more severe, and earlier in individuals with CP: approximately 25% of young adults with CP between the ages of 15 and 25 are at risk of osteoarthritis. The incidence is reported to be higher in ambulatory individuals due to postural control and impaired movement [16]. The affected joints vary according to the form of impairment and therefore to the clinical type of CP. The hip deserves special consideration: the incidence of hip osteoarthritis is reported to exceed 50% in ambulatory adults with CP [17]. Moreover, the rate of complications after surgical intervention is higher in CP compared to non-CP patients. Nevertheless, surgery for hip joint misalignment and degeneration improves pain and walking function. The timing of the operation is very important and requires close follow-up by the orthopedic surgeon, the physiotherapist, and the caregivers. Physiotherapists should start strengthening the hip and trunk muscles, standing up, and ambulation in the early postoperative period.

Patella alta or a high-riding patella is another relatively frequent condition in ambulatory adults with CP, often associated with chronic anterior knee pain or a crouched gait pattern especially in diplegic CP [18].

Pain is a very common, if not the most common, physical symptom which is directly proportional to age and inactivity in CP. Approximately one-third of adults with CP suffer from chronic pain which contributes to the decline in motor functional capacity [19]. Pain is often experienced in more than one part of the body, most commonly the neck, back, hips, knees, and feet. It is worse after fatigue, maintenance of a certain position for extended periods, and on early morning hours. It improves with rest, physical therapy, and exercise. Some studies recommend physiotherapy programs to focus on pain-reducing exercises [20].

The pathogenesis of pain varies: it is frequently presumed to be caused by "arthritis," but other causes to be considered are deconditioning; narrowing of the spinal canal; soft tissue injuries in muscles, tendons, or ligaments; and entrapment or compression of peripheral nerves, all likely to result from posture and activity patterns that involve repetitive movements, poor alignment, and poor postural control [21].

Chronic pain is significantly associated with deterioration of functional skills. Preventive treatment aimed at correcting skeletal and muscle abnormalities early in life may help to avoid progressive deterioration.

34.4 Rehabilitation Approaches in Adults with CP

Rehabilitation should help the patient reach their full functioning potential at home, school, recreation, and community settings. For the sake of clarity, the problems of adults with CP who require physiotherapy and rehabilitation management can be listed in the following order: limitation in physical activity and functional mobility, pain and fatigue, musculoskeletal disorders and deformities, arthritis, osteoporosis and fractures, and premature aging [22].

Physiotherapy plays a central role in managing these conditions. In most settings the physiotherapist applies the therapeutic program, recommends equipment, plans for home life, and provides an interface with the occupation of the individual. Preventing further disabilities and secondary disorders and minimizing functional limitations and impairments that may develop over time are also within the physiotherapist's scope.

Physiotherapy and rehabilitation programs in CP vary based on the individual's age and functional status. Their spectrum covers daily life activities and specific training schedules. In principle, the dynamic motor control approach based on changing motor patterns and tasks is used for a realistic assessment of the individual (rather than the hierarchical model of neurological motor development): it focuses on improving and maintaining existing skills and capabilities, particularly gross motor function, movement, and functional mobility by working on positioning, sitting, transition from sitting to standing, and walking with or without assistive aiding devices and orthoses, wheelchair use, and transfers.

Therapy can be applied at home, in clinics and hospitals as outpatients, in rehabilitation hospitals as inpatients, or even at the workplace of the patient. Physiotherapy and rehabilitation plans should include specific goals, objectives, and measurable short-term priorities. These short-term goals allow therapists and patients to have a clear understanding of the process. Adolescent physiotherapy programs should be supported by recreational activities to provide motivation for new skills [23].

Physiotherapy involves evidence-based practice whenever possible. However, guidelines for people with CP and research on the effects of physical activity in adults with CP are limited. Some studies report benefit from strength training and improvement in cardiorespiratory fitness with physical endurance training which may contribute to reaching higher levels of physical activity. Besides studies focusing on health issues such as medical and functional status, research has addressed the effectiveness of various physiotherapy interventions such as neurodevelopmental treatment, strength training, and orthotic management [24]. Biofeedback, electrical stimulation, and behavioral approaches may be included into the physiotherapy program [25].

Functional exercises combining aerobic and anaerobic capacity and strength training significantly improve physical fitness, the intensity of activities, and quality of life in ambulatory individuals. Isotonic, isometric, and isokinetic exercises can be used to increase muscle strength and improve motor functions. Training programs on static bicycles or treadmills can be beneficial for gait and gross motor development without improving spasticity levels and abnormal movement patterns [26]. The treadmill is a functional training method that may help the patient to learn to walk at higher speeds and for longer distances. For non-ambulatory CP patients, treadmills that support body weight can be used.

Recommendations on the type, frequency, and duration of exercise are tailored for the adult with CP taking into account muscle tone, coordination, and pulmonary capacity. Exercise improves strength, flexibility, posture and balance, and consequently functional activities such as walking, running, and activities of daily life. Another important and proven effect is on reducing depression and anxiety that accompany aging.

Strengthening exercises are to be emphasized as studies demonstrate the relationship between muscle strength and activity. Methods widely used in all age groups include functional activities and the use of gravity as well as body weight. These methods require a sufficient level of loading in order to increase muscle strength: the patient needs to apply more effort against pro-

gressive resistance. This is highly emphasized to increase power generation capacity and improve muscle performance, motor skills, and range of motion [27, 28]. Such exercises applied to upper and lower extremities increase strength without increasing spasticity in adults with spastic CP.

Exercises that do not include weight-bearing do not easily transfer to weight-bearing situations, which use diverse and more complicated muscle patterns. Better improvement in functional motor performance is achieved when strengthening exercises contain closed kinetic chain exercises associated with functions. In these exercises, the person puts weight on the legs and raises the body mass using concentric and eccentric activation of the muscles of the lower extremity. Manual resistance, gym equipment, free weights, gym balls, thera-bands, treadmills, static bikes, leg presses, and isokinetic devices are some other examples of progressive resistance exercises [29]. Electrical stimulation is proposed as a useful modality when selective muscle control is required for specific strengthening programs.

Muscle strength training is most commonly used for patients especially at GMFCS levels I–III who have better selective control and less co-activation than others. Muscle strengthening for individuals in level IV and V is controversial because of problems related to motor control: although strengthening develops motor skills, its positive influence on functional capacity has not been proven; it is significant only when it is aimed to improve a specific motor skill or function. At these levels, hydrotherapy may be preferable to muscle strengthening. Any pain before or during the exercise should prompt modification of the strengthening training program, such as working different muscle groups on different days.

Some other interventions applied during childhood such as muscle tendon lengthening, selective dorsal rhizotomy, botulinum toxin injections, and intrathecal baclofen pump implantation can help to improve postural and motor control, preserve functional capacity, and, especially, maintain joint mobility and muscle strength in adulthood [30]. However, the long-term effects of treatment received in childhood raise concerns for two reasons. The first is a possible deleterious effect of these interventions in the long run related to the stress created by weight-bearing on poorly aligned joints and by uncontrolled movements on joints and muscle tendons. The second is about late effects of surgical interventions on functionality and personal and social well-being.

Some CP patients reaching late adolescence or young adulthood decide to discontinue therapy, even including those who had achieved mobility with or without aid. Reasons are multiple. Sometimes, parents' encouragement, urging, and assistance lose their effect at later ages. Therapy meeting the goals of the parent or caregiver, such as the use of a mobility aid rather than a wheelchair, or a position facilitating the care of the patient might not result in satisfaction and comfort from the patient's part [31]. Moreover, as the patient gets older, decreased motivation, increased body weight, and secondary problems may further reduce the functional capacity, resulting in loss of functional mobility and even in a totally dependent state. Another important reason is the lack of continuity in maintenance or prevention programs.

34.5 Summary

As adult CP patients live longer and grow older, the need for more specialized care becomes evident. CP is a lifelong condition that cannot be cured; long-term rehabilitation requires health practitioners to be aware of and prepared for problems arising in adulthood, expecting and preventing functional decline with increasing age. Adults with CP need specific information in order to make their own choices. They also require age-appropriate physical training to deal with decreased mobility and balance, management of pain and fatigue, treatment for secondary osteoarthritis, and support and guidance for challenges faced in the workplace and at home. Because many people with CP outlive their caregivers, planning for long-term care is of crucial importance for health and social services.

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