Cerebral Palsy

From Childhood to Adulthood

Christos P. Panteliadis
Editor

Fourth Edition

Springer

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Preface to the Fourth Edition

Seven years have passed since the release of the third edition of the book *Cerebral Palsy: A Multidisciplinary Approach.* As a result of the readership's good response and the quick expanding knowledge in neuropathology, genetics, ultrasound, early markers, epilepsy in children and adults, muscle biology, comorbidities, long-term prognosis and transition to adulthood, the editor was encouraged to publish a new edition. The title of the new fourth edition is *Cerebral Palsy: From Childhood to Adulthood*.

New distinguished authors from around the world, along with many of the authors of the third edition, have provided sharper and more acute dimensions in this upgraded version of the book. All the chapters have been revised and updated. The addition of new chapters, such as Epilepsy in Children, Epilepsy in Adulthood, Genetics, Comorbidities, Long-Term Prognosis, Young Adults with CP and Their Transition and Orthopaedic Care in Adults with CP, and the inclusion of up-to-date evidence-based therapies have enhanced the multifaceted subjects of the book.

The editor would like to thank all the expert authors for their invaluable input, cooperation and patience towards the successful realization of this project. Thanks also to my friend and co-worker Christian Hagel for his help. Many thanks to the publisher Springer Medicine Books, Springer Nature, for their unwavering commitment in disseminating medical knowledge, and above all the contents' appearance and book design. Special thanks to my wife, Eli, for her patience and support.

Thessaloniki, Greece — Christos P. Panteliadis

Preface to the Third Edition

Six years have 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 and the 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 have 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 this 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*) constitutes 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 neurologists, orthopaedists 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 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 Documentation

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. One of the oldest and probably well-known examples of CP is the mummy of the Pharaoh Siptah (1196–1190 B.C). The first conceptions of CP and our knowledge about etiology and pathogeny allow us to assume that CP existed in the Ancient World. Although there is lack of detailed medical descriptions from before the nineteenth century. Mentions to CP can be found in representational art, literary sources, and paleopathology.

In the Ancient World, the first medical description of CP was made by *Hippocrates* in his work *Corpus Hippocraticum*. Concrete examples and definitions of CP, however, did not emerge until the early nineteenth century with observations by William John Little. Toward the end of the nineteenth century, four more personalities emerged, adding to the historical hallmarks of CP: William Osler, Sigmund Freud, Sarah McNutt, and William Richard Gowers. The significant developments that have followed since then are all due to the contributions of these five personalities in the field of CP. The chapter is in all historical fields up to this day revised.

Keywords

History of cerebral palsy · History of medicine · Ancient world · Historical documents · Historical review · Documents · Little · Freud · Osler

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 disease" 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 8 month of pregnancy, and also that "pregnant women who have fever or lost too much weight, without any obvious cause, gave

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birth to their child with difficulty and dangerously, or they would abort dangerously" (Fig. 1.1) [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. Soranos described the first time the Scoring components of clinical examination of newborns [2] (Table 1.1).

Concrete examples and definitions of CP, however, did not emerge until the early nineteenth century with observations by William John Little. Toward the end of the nineteenth century,

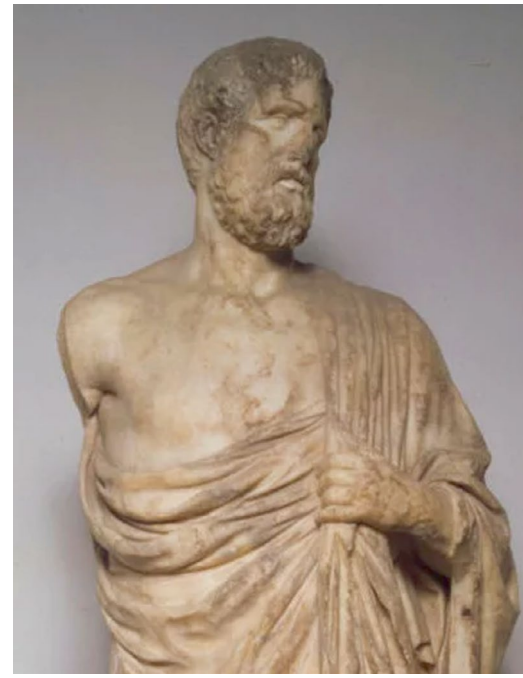


Fig. 1.1 Hippokratis (island Kos), the father of science medicine

Table 1.1 Important chronological history and terminology of cerebral palsy

Period	Name	Comments
1196–1190 B.C	Egyptian monuments and mummies	Pharaoh Siptah with deformity probably due to congenital abnormality rather than to poliomyelitis
Fifth-fourth century B.C	Hippokrates, Ploutarchos	Role of prematurity, congenital infections, and prenatal stress
10 B.C–4 A.C 70–130 A.D 98–138 A.D 130–199 A.D	Emperor Tiberius Claudius Nero Roman historian Suetonius Soranos from Ephesos Galinos	In the manuscript *The Twelve Caesars* it is described that the emperor suffered from multiple physical and behavioral problems
1729–1799 1812–1820 1820–1830 1830–1831	Lazzaro Spallanzani Reil, Cazauviehl, Lallemand, de Kergaradec Andrey, von Heine, Billard, Cruveilhier, Breschet, Rokitansky	In 1794, performed the first time studies on bats that concluded they could navigate using sound rather than sight. Today known as echolocation, medical sonography Reported *cerebral atrophy* in adults Reported cerebral atrophy in children
1842–1861	Henoch, Little, Strommeyer	Noted an association between prematurity, prolonged labor, asphyxia, neonatal convulsions, and the use of obstetrical forceps with later spastic diplegia in children
1888–1889	Osler	First two introduced the term *cerebral palsy* and provided the first classification of CP, treatment in the early stage
1891–1897	Freud, Wallenberg	Included prenatal factors in pathogenesis of CP. Provided the most comprehensive classification for spastic diplegia

(continued)

Table 1.1 (continued)

Period	Name	Comments
1885–1888	Mc Nutt, Gower	Described *birth palsies* and identified 'first born' children as being at risk for CP
1955	Apgar Soranos scoring components	Set a score describing an infant's condition at birth Soranos score for newborns examination in years (98–138 A.D)
1960	Bobath, Vojta	Need to correct abnormal postural reflexes, especially in very early life
1970–1980	Sonography, imaging	Use of brain CT/ MRI (*see text*)
1990	Botulinum toxin	Management of spasticity with botulinum toxin
2000	Functional MRI, PET	Use of MRI, SPECT, and PET
From 2000–till today	Gross Motor Function Classification System (GMFCS) , Bimanual Fine Motor Function (BFMF), Manual Ability Classification System (MACS), Comprehensive Therapy (CT), Constraint-induced Movement Therapy (CIMT), Hand-Arm Bimanual Therapy (HABIT), HABIT-ILE including the Lower Extremity, Hippotherapy, Hydrotherapy, Rhythmic Auditory Stimulation (RAS), HINE, SINDA	GMFCS as a classification system for gross motor function in children with CP. BFMF is a scale that classifies the fine motor function in children with CP (Level I–V). MACS as a standard classification for children with CP on the basis of manual abilities used for children between 4 and 18 years and adults between 18 and 24 years. CT as multidisciplinary physiotherapies. CIMT focused in children with hemiplegic CP and adults with stroke. HABIT for improving bimanual coordination in children with hemiplegic CP. HABIT-ILE including therapy in lower extremities in children with CP. Therapy with horses on posture and body function by children with CP. Hydrotherapy for motion, proprioception, strength, neuromotor control, pain. RAS in neurorehabilitation of children and adults with CP, SINDA (Standardized Infant Neuro Developmental Assessment), HINE (Hammersmith Infant Neurological Examination)

four more personalities emerged, adding to the historical hallmarks of CP: William Osler, Sigmund Freud, Sarah McNutt, and William Richard Gowers.

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 entitled *Egyptian Mummies* (first published in 1924) [5]. 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 stated that "we cannot be certain whether these defects

were neurological impairments due to poliomyelitis, spastic paresis or a post-mortem artefact" [7]. 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 illustrates 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…." 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 [10].

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 [11].

An example of cerebral palsy from Hellenistic art has been provided by Temple S. Fay (1895–1963) 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 D. Grmek, a pioneer of medical history and paleopathologist [12] and Martha L. 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, 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 JMS [18], in his article *The emperor with the shaking head*, diagnosed the Emperor with the athetoid variant (*dystonia*) of cerebral palsy and further noted that the Emperor's high intelligence is consistent with this variation of CP. A secondary form of dystonia consequent to a CNS infection or head injury in childhood seems tenable hypothesis. In a more recent article entitled *A neurological mystery from history: the case of Claudius Caesar*, Murad reexamines ancient his-



Fig. 1.2 Matthias Grunewald (about 1470–1528) painted Saint Cyriacus who was depicted as "exorcizing" the Emperor Diocletian's daughter



Fig. 1.3 J. De Ribera (1591–1652). The young child with the clubfoot. Left spastic hemiparesis (Louvre, Paris)

torical sources and concludes that along with CP, 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. 1.2). 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. 1.3). In the monasteries of Mount Athos, there are several icons on exhibit that depict paralyzed persons (Fig. 1.4).



Fig. 1.4 Icon "The Paralytiker" from monk Merkurius (about 1613–1620) in monastery Holy Dionysios, Mount Athos/Greece

1.4 The First Half of the Nineteenth Century

The history of CP in the early to middle nineteenth century began with publications by Johann Christian Reil (1759–1813) and Claude Francois Lallemand (1790–1854). Reil born in Rhaude (Ostfriesland/Germany), graduated 1782, and since 1788 was a professor at *Hallenser klinik Institute* and from 1810–1813 was a professor of anatomy and therapy at University Berlin. Since 1795, Reil has been undertaking intensive studies of brain anatomy and makes important contributions to the function of the autonomic nervous system, the basal ganglia, and the topographical relationships of the cerebral cortex (the later term *Insula Reilii* goes back to his work). In Leipzig in 1813, Reil contracted typhus and died shortly thereafter [20]. Lallemand, born in Metz (France) studied medicine in Paris in 1815, he was admitted to the Hôtel Dieu (*the Parisian hospital*), and he became the assistant to the famous surgeon Guillaume Dupuytren (1777–1835). In 1818, he became a doctor of medicine and early in 1819, on the recommendation of Dupuytren, Prof. of surgery in Montpellier. Between 1820 and 1834, his last three-volume work *Recherches anatomico-pathologiques sur l'encéphale et ses dépendances* was published in Paris [21]. In 1794, Lazzaro Spallanzani (1729–1799) born in Reggio Emilia, Prof. of physics and mathematics, in an article he analyzed opinions and performed studies on bats that concluded they could navigate using sound rather than sight (see Table 1.1). He was the first to study the ability on bats of fertility that blazed the trail for future investigators [22].

In 1827, Jean-Baptiste Cazauvieilh (1802–1849), born in near Bordeaux (France) reported cerebral atrophy in individuals with congenital paralysis and tried to distinguish lesions in the developing brain with those related to trauma. He described the anatomical-clinical picture on *cerebral agenesis* and *paralyse congeniale* [23]. One year later in 1828, Charles-Michel Billard [24] described pathological changes in the infant brain; however, it was the works of Jean Cruveilhier [25] and Carl von Rokitansky [26] 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 [27].

William John Little (1810–1894), the founder of orthopaedic surgery in England, was the first personality to intensely engage cerebral palsy. At the age of 16, he worked as an apothecary's apprentice (Fig. 1.5) [28]. 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, surgeon, and orthopedist, 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 [29]. Little, then, undertook the same procedure on 30 patients with clubfoot, detailing the results in his doctoral thesis in 1837.

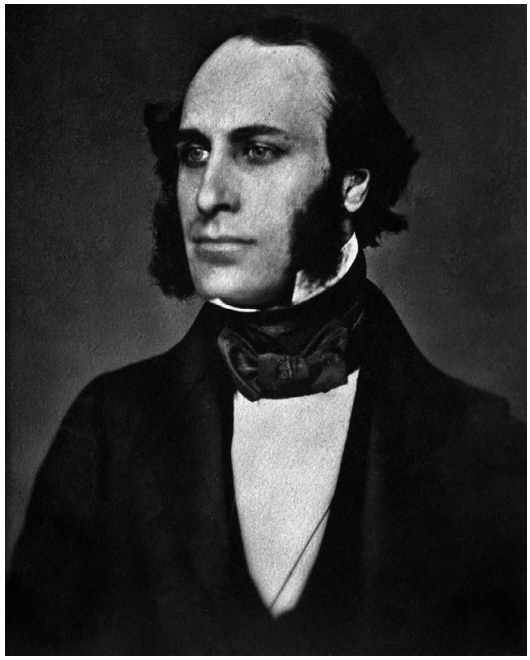


Fig. 1.5 William John Little (1810–1894)

In 1843, Little delivered nine lectures entitled 'Deformities of the Human Frame,' which were published in the Lancet between the 1843 and 1844 [2, 30–33]. 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; the mechanical injury to the fetus 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" [30–33]. 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 [34].

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, Alois Bednar (1816–1888) from Pottenstein (now Czech Republic) described leukomalacia as a distinct disorder of the newborn [35]. 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* [34] (see Chap. 12).

1.5 The Second Half of the Nineteenth Century

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 an interruption of the proper placental relation of the fetus 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* [34, 36].

Little's work appeared at about the same time as that of Jakob von Heine (1800–1879), a German scientist and physician. He was the first to recognize poliomyelitis as a clinical disease entity. In the second edition of his book *Spinale Kinderlähmung*, he reported that the symmetrical paralyses of the lower extremities resulted from spinal, rather than cerebral, disease [37]. In 1867, Virchow described white, softened areas around the ventricles of infants examined postmortem [38]. Parrot [39] 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" [40].

In 1868, Jules Louis Cotard (1840–1889), under the guidance of Jean-Martin Charcot (1825–1893), a French neurologist and psychiatrist, analyzed the different etiologies of cerebral paralysis (especially trauma) and described partial atrophy of the brain in these conditions [41]. These were documented in his dissertation *Etude sur l'atrophie cerebrale* and coined the term *cerebral sclerosis* in children. In 1889, Cotard contracted diphtheria and diet. After his death, the mental phenomena he described in 1880 are incorporated into medical terminology *Cotard syndrome*) a rare mental illness of varying severity, in which the affected persons hold the delusional belief that they are dead (*do not exist*), is an elusive condition, rarely reported, and poorly researched [41]. In 1885, Jendrasik and Marie described the *hemiatrophie cerebrale par sclerose lobaire* [42].

A large series of cases of porencephaly were reported in 1882 by Hans Kundrat (1845–1893) an eminent pathologo-anatom in Vienna, from Carl von Rokitansky school (1804–1878) [43]; 103 cases by Jean Audry (1858–1950) internist in 'Hôpital de la Charité de Lyon' between 1888 and 1892, became known in 1892 through his publication about *Athétose double et les chorées chroniques de l'enfance: étude de pathologie nerveuse* [44]. The first description of athetosis was in 1871 from the American neurologist William Alexander Hammond (1828–1900) and described in his book *Diseases of the Nervous System*. Since the first description of athetosis in 1871, the disorder has been a source of controversy, as were many aspects of Hammond's career [40], 80 cases by Ernest Gaudard Ernest (1858–1936), born in Westsuize, promotion in 1884 with title *Contribution á l'étude de l'hemiplégie cérébrale infantile* (on infantile hemiplegia) is quoted several times [45], and 160 cases by Adolf Wallenberg on pediatric cerebral paralysis in 1886 [46]. Joseph Parrot an historian, in 1873 and Victor Henri Hutinel in 1887 suggested that congenital hemiplegia might result from localized encephalomalacia, which is secondary to venous congestion, stasis, thrombosis, and hemorrhage. Hutinel (1849–1933) born in Châtillon-sur-Seine is a France internist and pediatrician, 1877 graduation and 1879 medical in *Hospice des Enfants Assistés*. and from 1897 *Prof. de pathologique medical*, and in 1907 director in *Hôpital des Enfants malades in Paris.* In 1909, he published in Paris his 5-volume book *Les maladies des enfants* [36, 47].

In 1882, James Ross (1837–1892) born in Kingussie (Schottland), a pathologo-anatom with emphasis in neurology and psychiatry, 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": and his forgotten neurology textbook two-volume: *A Treatise on the Diseases of the Nervous System* (1881 and 1883) [48]. In 1887, he published with Judson S. Bury a monography *On peripheral neuritis* and in 1893, the monography *On the spasmodic paralyses of infancy*, and a small monography *On aphasia* [49].

In 1885, Ernst Adolf Strümpell (1853–1925) a German internist and neurologist, born in Neu-Autz (today Lettland), provided a fresh impetus to the study of these disorders by claiming that they were a form of CNS infection, which he termed polioencephalitis [50]. Strümpel is among others an eponymous for Morbus Bechterew-Strümpell-Marie, Marie-Strüpell-Encephalitis, Strümpell-Leichtenstern-Encephalitis, Morbus Strümpell-Lorrain. The same year, William Richard Gowers (1885–1888) of England men-

tioned 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 [51]. In France, Jules Joseph Dejerine (1849–1917) a Swiss-French neurologist, used the term 'Maladie de Little.' In 1885, Sarah McNutt (1839–-1930) a physician, born in NY, continued to raise the profile of the risks of long-term disability arising from birth trauma [52].

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 [30]. This hypothesis was also supported by Sir Thomas More's statement that King Richard was born in the breech position 'feet forward' [53]. Gower and Little found that more extensive motor involvement was correlated with greater intellectual deficiency. Erratic learning, short attention span, irritability, destructiveness, aggression, habitudes, 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 [54–56]. 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. 1.6). Many of these cases were from the Pennsylvania Institution for Feeble-Minded Children, where patients showed severe mental retardations. Osler credited Strümpell'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 [54–56]. Osler believed that



Fig. 1.6 First photography of a child with the symptoms of spastic diplegia by Osler

Strümpell's theory of polio encephalitis (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.

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" [57–60].

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 Zerebrallähmung' 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 [61].

Freud established that all diplegias that originated from birth and had been attributed to birth abnormalities actually had their pathological origin during intrauterine life [62]. James Stansfield Collier (1870–1935), born in Cranford (England) was the most important of his time neurologist and epileptologist in St. George Hospital. In 1899, he published *Cerebral diplegia* and in 1900, with JSR Russel and FE Batten *Subacute combined degeneration of the spinal cord* and other publications, such as *hydrocephalus, seizures, amyotonia congenita und aphasie*. Collier had a deep interest in cerebral diplegia, referred to Freud's 1897 [63] 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." Collier contracted pneumonia and died in London (see Chap. 12) [63, 64].

Bernard (Barney) Sachs (1858–1944), the great New York neurologist and former student of Freud, characterized Freud's book as *masterly* and *exhaustive.* Sachs, born in Baltimore, in 1882 graduated by Rudolf Virchow, continuation in neurology in Vienna by neuro-anatom Theodor Meynart, in Paris by Jean Martin Charcot, by John Hughlings Jackson, and in 1894, President of American Neurologic Association [65]. 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 or 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" [66]. Fliess born in Arnswalde (today Poland) worked in clinic "Jean Martin Charcot in Vienna meet through Josef Breuer (1842–1925) an Austrian physiologist and psychoanalyst develops a friendship and worked in *psychoanalysis*," one speaks of the *Fliess period* of psychoanalysis in the years 1887–1902. Other points of Breuers medical work were the temperature regulation of the body, the control of respiration by the vagus nerve (the mechanism is known as the Hering-Breuer reflex), and the physiology of the inner ear [66].

In 1890, Sachs and Peterson F (1859–1938) admitted to a persistent confusion between cerebral palsy and poliomyelitis anterior acuta. This study based upon an analysis of 140 cases, and described the difference between infantile spinal paralysis (*paraplegia*) and several forms of cerebral palsy such diplegia, hemiplegia, epileptic seizures, et cetera [67]. Osler and Freud (as well as Sachs) debated whether convulsions by themselves could cause CP. Freud in his 1891 mono-

graph 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 [68, 69]. He believed that diplegia was due to prematurity and a lack of postnatal development of the pyramidal system. Édouard Brissaud (1852–1909), a French physician and pathologist, 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). Brissaud had interests in a number of medical disciplines including motion disturbances, anatomy, neurology (e.g., Bourneville-Brissaud disease) and psychiatry. Freud argued against Brissaud's theory that diplegia was due to a form of developmental arrest that occurs with prematurity.

1.6 The First Half of the 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 [70, 71] described ataxia as a type of cerebral palsy, which was later corroborated *by Forster's* work in 1913, *Der Anatomische Astatiche Typus der Infantilen Zerebrallähmung* [72]. In 1917, the Austrian mathematician Johann Radon (1887–1956) had an idea today called the *Radon transform* for the first time, considered two or three-dimensional systems (called the *X-ray* transform); the theory since then been generalized to arbitrary Euclidean spaces (*fundamental space of geometry*) in ancient Hellenistic times. Radon transform is conceptually very simple once one has realized the fundamental role played in quantum mechanics by the metaplectic representation of the symplectic group [73]. Following Osler's footsteps, Winthrop Phelps (1894–1971), born in Bound Brook, New Jersey, an orthopaedic 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 [74]. 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 [75]. In 1928, Dorothy Klenke Nash (1898–1976), born in New Jersey, was the first female neurosurgeon in USA, and maintained her status as the country's only female neurosurgeon until 1960 [76]. In 1941, Phelps published an impressive paper entitled *The management of cerebral palsy* [77] (see Chap. 12).

Normal motor development had been described in great detail by Schaltenbrand [78], McGraw [79], Gesell and Amatruda [80], Illingworth [75], and others [81]. The abnormal postural reactions of the body during CP are attributed to the tonic reflexes described by Walshe and Magnus [82]. In 1947, Strauss and Lehtinen noticed (for the first time) that behavioral and emotional abnormalities are common in children with cerebral palsy [83]. 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 [84, 85]. According to Perlstein and Shere, about 75% of children with CP were found to have speech defects and, of those, 50–75% wanted/required speech therapy [86, 87]. According MacNamara in 1949, an early intervention in the first few months of life is possible [88].

1.7 The Second Half of the 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 [89]. 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. Carl Delacato and Glenn Doman [90, 91], in Philadelphia, and Vaclav Vojta [92], 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" [92].

Marie Killilea (1913–1991) is the mother of Karen Killilea (1940–2020). Karen was 3 months premature and weighed less than two pounds and spent her first months of life in a neonatal intensive care unit. Marie Killilea wrote in 1952 a book titled *Karen*, a novel about her daughter's life with CP. By her early teenage years, she was walking with crutches, swimming, typing, and going to school. Karen was an example of everything she made him live, traveled to Rome twice and met with Pabst Paul VI and wrote about you see what kids or adults can do with CP. The book which is still in print today hit the New York Times bestseller list in 1952.

In 1955, Virginia Apgar (1909–1974), born in USA, elected to do anesthesiology generated a scoring system that forced obstetricians to examine the condition of newborns at birth and assess the need for treatment [93]. 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 [94]. 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 RC and Polani PE [95] 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. The memorandum gives a definition of CP notes the need for definition of clinical terms and suggests that at the present, time clinical features offer the most useful basis for classification. Banker BQ and Larroche JC [96] coined the term 'periventricular leukomalacia' and in 1967, Christensen E and Melchior JC published the first book on CP, which concentrated on clinical and neuropathological studies [97]. As pointed out by Alberman and Goldstein already in 1970 [98], the earliest possible diagnosis and treatment are essential to minimize the effects of the insult on the CNS.

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 (see Chaps. 20, 24, and 25). In the 1980s, medical researchers and clinical studies prove Freud's theory that CP can happen before birth or can also be caused by birth injuries. Marie Killilea (1913–1991) is the mother of Karen Killilea. Karen was 3 months premature and weighed less than two pounds and spent her first months of life in a neonatal intensive care unit. Marie Killilea wrote a book, titled *Karen*, a novel about her daughter's life with CP. The book which is still in print today hit the New York Times bestseller list in 1952. Historically, the first indication of therapy for strabismus was performed by Alan B Scott in 1981 (Research Foundation, Eye muscles and motor control). In 2006, a consensus was developed on the best practice for the treatment of CP using the botulinum toxin [99].

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 Vicomte de Kergaradec (1787–1877). 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?" [100].

1.8 The Late Twentieth Century

Crothers B and Paine RS were pioneers that used a multidisciplinary approach for the evaluation and treatment of children with CP [94]. Crothers was a pediatric neurologistand Paine a pediatric neurologist in an institute which offered advanced diagnostics, surgery, treatment, and rehabilitation. Both from USA, they have published many papers in all fields of cerebral palsy based on a unique study of some 1800 individuals with *CP* examined between 1930 and 1950. Their childhood and in more cases their early adult life were closely scrutinized in order to explain and illustrate the ways in which the relevant types of brain disorder affect growth and development [94].

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. HINE (Hammersmith Infant Neurological Examination) is a relatively new method and was first developed in 1999–2000 (for more see Chaps. 19, 20, 22, and 24–26). SINDA (Standardized Infant Neuro Developmental Assessment), published before 10–13 years, is a new neurodevelopmental scale applicable in the first year of life after the neonatal period, that is in the age range of 6 weeks to 12 months.

The gross motor function classification system (*GMFCS*) developed by *Palisano* and his colleagues [101] 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 they incorporate 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 (see Chap. 25). Marie Joan Lyons Killilea (1913–1991) is the mother of Karen Killilea and an American author, activist, and lobbyist for the rights of people with CP. Her work culminated in the formation of the cerebral palsy. Karen Killilea born in 1940, she was 3 months premature and weighed less than two pounds and spent her first 9 months in a neonatal intensive care unit.

1.9 Early Twenty-First Century

In 1998, the group for the Surveillance of Cerebral Palsy in Europe [102] 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*) [103], 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. 20 and 25). In the 2007 consensus definition, the term *cerebral palsy* was defined as: a group of permanent disorders of the development of *move-*

ment and *posture*, causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain.

The advent of new imaging techniques signaled a revolutionary approach in the diagnosis of CP (see Chaps. 10, 13, and 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. Since 2005 and in follow years up to 2022, the CP community has increased its focus on the need for federally funded cerebral palsy research. This advocates that health care professionals provide strong support for advancing the science of the profession and also improve the well-being of the patient [100]. In the last 12–23 years, two new methods (SINDA and HINE, see Table 1.1 and text) have published for early neurodevelopmental diagnosis and intervention. In 2021, a new classification has been developed by the International League Against Epilepsy (ILAE 2021) to classify the semiology [104]. Panteliadis (2021), in two recent publications, epileptic therapy and neurosurgical methods are described until the end of the twentieth century [105, 106].

New methods and technologies of intrauterine monitoring of newborns have made great progress. Thus, from very early on, we have the possibility to follow all the stages of intrauterine life. Obstetrics has made great progress and the intensive care units for premature newborns, as well as newborns with respiratory problems.

Gross Motor Function Classification System, Bimanual Fine Motor Function, Manual Ability Classification System, Comprehensive Therapy, Constraint-induced Movement Therapy, Hand-Arm Bimanual Therapy, HABIT-ILE including the Lower Extremity, Hippotherapy, Hydrotherapy, Rhythmic Auditory Stimulation, HINE, SINDA (see Table 1.1). GMFCS as a classification system for gross motor function in children with CP. BFMF is a scale that classifies the fine motor function in children with CP (*Level* I-V). MACS as a standard classification for children with CP on the basis of manual abilities used for children between 4 and 18 years and adults between 18 and 24 years. Comprehensive Therapy as a multidisciplinary physiotherapies. CIMT focused in children with hemiplegic CP and adults with stroke. HABIT for improving bimanual coordination in children with hemiplegic CP. HABIT-ILE including therapy in lower extremities in children with CP. Therapy with Horses on posture and body function by children with CP. Hydrotherapy for motion, proprioception, strength, neuromotor control, pain. RAS in neurorehabilitation of children and adults with CP, SINDA (Standardized Infant NeuroDevelopmental Assessment), HINE (Hammersmith Infant Neurological Examination).

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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, primarily affecting posture and mobility. 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. Hippocrates (fifth to fourth century B.C.) was the first to discuss the association of prematurity, congenital infection, and prenatal stress in relation to the pathogenesis of brain damage. William John Little (1810–1894), the founder of orthopaedic surgery in England, was the first personality to intensely engage cerebral palsy. In recent years, scientists have reached a broad consensus on the definition of cerebral palsy. For the fourth edition, the chapter has been reviewed/revised by the Book Editor.

Keywords

Definition · Inclusion criteria · Characteristics · Diagnosis

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2.1 Introduction

Cerebral palsy (CP) is the term applied to a group of children with motor impairment and related service requirements, and primarily affecting posture and mobility. 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 [2, 3].

Over the last centuries, since ancient times it has occupied scientists. *Hippokrates.*

is the first to describe the definition of cerebral palsy. William John Little, the founder of orthopaedic surgery in England, was the first personality to intensely engage cerebral palsy [1]. In 1888, William Osler 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 [3]. Osler noted the association between difficulties during delivery, asphyxia,

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prolonged resuscitation, and seizures (see Chap. 1). Freud was the third major personality to have a historical contribution to cerebral palsy in the nineteenth century. Sigmund Freud wrote several volumes entitled *Cerebral Palsy*. He developed a classification system that is still in use today and essentially unchanged (for more see Chap. 1).

In England, Mac Keith RC and Polani PE 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 [4]. The Little Club classification uses the term 'Spastic,' with sub-categories of *hemiplegia, double hemiplegia*, and *diplegia.* The other categories were: dystonic, choreo-athetoid, mixed, ataxic, and atonic CP. Little described the spastic deformities of 47 cases of children with CP into hemiplegic rigidity, affecting one side more than the other, paraplegia, affecting both legs more than the arms, and generalised rigidity. At the time this spastic rigidity was known as *Little*'s *disease* but is now known to be synonymous with cerebral palsy [5, 6].

Between 1950 and 2000, several authors published rather similar definitions of CP [7, 8]. The Mutch et al. [9] 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 [10] 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. https://ec.europa.eu/health/indicators-_data/. Arnaud et al. [11] in a new publication described population-based registries and provide useful data for generating health indicators. The sharing of Public health indicators play an increasingly important role in health policy decision for CP and could already help people with disabilities in Europe and to increase public awareness of this complex condition. In recent years, scientists have reached a broad consensus on the definition of cerebral palsy, and thus made communication more uniform and easier in many points.

2.2 Definitions

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 unique, well-recognised and understood search term. Following this workshop, Rosenbaum et al. [12] 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 CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems.

The differences between the SCPE [10] and Rosenbaum [12] 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. In a review from 2016 [13], a similar definition is given for Cerebral Palsy. CP has always been known as a disorder of movement and posture resulting from a non-progressive injury to the developing brain; however, more recent definitions allow clinicians to appreciate additional handicaps than just the movement disorder. Moreover, the authors propose to control the methods applied, in order to improve quality of life and career opportunities for people with CP. A last publication from 2020

[14] does not provide anything new about definition, epidemiology, and classification of cerebral palsy. The well-known representations are shown again.

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 (see Chap. 5).

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. In recent years, scientists have reached a broad consensus on the definition of cerebral palsy.

2.3 Elements Varying Between Sets of Inclusion Criteria for CP

Consensus with Freud's phenomenological approach that CP is defined exclusively by clinical description [15] is gaining greater acceptance [16] (see Chap. 1). 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 [17]. 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?,' which tried to define which diagnoses were and were not included [18]. 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 CP Register birth year 1999, Perth/Australia].

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 [10, 16], but controversy remains concerning a few issues.

2.3.1 Type of Disorder of Movement or Posture

Spasticity, dyskinesia, and ataxia are always included but the rarely encountered isolated hypotonia is excluded by European workers 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 [19]. According Vitrikas et al. [20], the movement disorders associated with CP are in following categories: spasticity, dyskinesia, ataxia, or mixed/other. *Spasticity* is the most common movement disor-

der, occurring in 80% of children with CP. Movement disorders of CP can result in secondary problems, including hip pain or dislocation, balance problems, hand dysfunction, and equinus deformity (see Chaps. 20 and 22). Patients with CP often also experience problems unrelated to movement that need to be managed into adulthood, including cognitive dysfunction, seizures, pressure ulcers, osteoporosis, behavioural or emotional problems, speech and hearing impairment.

The European collaborative study of the Surveillance of Cerebral Palsy based registries can provide useful data for generating health indicators [21]. Sharing PHIs (Public health indicators) for CP helps to improve public health policies for people with disabilities in Europe and to increase public awareness of this complex condition https://ec.europa.eu/health/indicators_data/. In his doctoral thesis [22], Casey concluded that power mobility should be considered earlier, and that it is important to reduce postural asymmetries for children with CP to reduce the risk of developing scoliosis, windswept hip deformity, contractures and pain.

2.3.2 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 [23]. Four *programmes* required *activity limitation* clarified as 'difficulties an individual may have in executing activities' [12] 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 [24] 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 (Table 2.1).

In 2008, the GMFCS was revised and extended to children aged 12 years or less on the basis of functional abilities and limitations [25]. The GMFCS includes five levels and four age bands, and the GMFCS-E&R developed for older youth (12- to 18-year) and contains many additional parameters, such communication and making management decisions, the dynamics of communication and others. In 2009, in a new publication, the GMFCS was revised and expanded to include youth adults [26]. 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 (see Chap. 20 and 25).

Table 2.1 Early signs of cerebral palsy (see Chap. 9)

Muscle tone alterations	Examination of muscle tone, Hypotonia, floppiness, scissoring, fisting, stiffness, opisthotonic posturing, passive resistance to stress, dystonia
Persistence of primitive reflexes	Moro, asymmetric tonic neck reflex, crossed extensor reflex, persisting support reflex (lags), placement reflex, palmar reflex
Asymmetric neurological signs	Tone, parachute reflex, hand preference before 12 months, asymmetric placing reaction, asymmetry of upper-lower limbs
Deep tendon reflexes	Sustained clonus, persistent crossed abductor reflex

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

The diagnosis of CP is *primarily* clinical. Early diagnosis begins with a medical history and involves using neuroimaging, standardized neurological, and standardized motor assessments that indicate congruent abnormal findings indicative of cerebral palsy (see Chap. 9). 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 post-term age by trained observers in high-risk infants either born very preterm or with neonatal neurological signs [27, 28], (Table 2.1). 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 post-term 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 [19]. 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*'. Secondary complications such as contractures and deformities may affect their seating or lying posture, their ability to move around independently and cause pain.

2.3.4 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 (see Chap. 9). With *increased* diagnostic capabilities, aetiological diagnoses for children with the CP label are now identified more frequently; 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 [29] National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, *Germany*-wide networking + European reference works for rare disease (see also Chap. 7). 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 [16].

2.4 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, and it affects about 10–12% of all newborns. 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 post-neonatally. 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 [19]. However since most post-neonatally acquired CP is acquired by 2 years of age [30], variations in upper age limit have little effect on estimations of prevalence.

Pham et al. [31] in a recent systematic review including a meta-analyses emphasize the inconsistency of phenotypic definition of CP. The authors found that diagnosis of CP was ascertained by a good clinical report only in a minority of genetic studies from 1990 to 2019. Further, compliance with the 2000 and 2014 SCPE guidelines was limited to a minority of the studies (18 out of 57; 32%). Archana et al. [30] found a prevalence of 26% for epilepsy in the studied population of children with CP. The highest incidence of seizures (30.4%) was found in children with *spastic hemiplegia*, and the extent of cortical injury correlated with the risk to develop epilepsy. The prevalence of congenital hemiplegia is estimated to be about 0.41–0.79/1000 live births. Panteliadis et al. [32] examined 223 children (122 boys and 101 girls) suffering from *congenital hemiplegia* at the age of 3 months to 12 years. Epileptic seizures developed in more than one third of patients with *spastic hemiplegia*, although EEG abnormalities were evident in the majority of them.

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 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. In *recent years*, scientists from all over the world have reached a broad consensus on the definition of cerebral palsy and thus made communication more uniform and easier in many points.

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3 Epidemiology of the Cerebral Palsies

Eve Blair, Christine Cans, and Elodier Sellier

Abstract

Epidemiology of cerebral palsy (CP) aims to describe the frequency of the condition in a population and to monitor its changes over time, and a guide to the management of patients. 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, associated impairments, severity of the clinical pattern and on the neuroimaging findings. Caution should be paid when interpreting changes in prevalence rates since factors that may influence these estimates are numerous. The *diagnosis* may be made in infants as early as 4 months of age through a combination of neurological examination, prenatal findings, recognition of clinical risk factors and neuroimaging findings. Over *the last* 20 years, various other screening tests, developmental and neurological examination methods have been developed. For the fourth edition, the *chapter* has been reviewed/revised by the Book Editor.

Keywords

Epidemiology · Prevalence · Trend · Classification · Impairment · Register · Risk factors

3.1 Introduction

The first medical description of CP was made by Hippocrates in his work *Corpus Hippocraticum*. Since then, many centuries passed until the first scientific publications for CP definition from William John Little. In 1853, Little described the condition of spastic diplegia (*Little's Disease*) which he ascribed to prematurity and birth asphyxia. Four more personalities emerged, adding to the historical hallmarks of CP: William Osler, Sigmund Freud, Sarah McNutt and William Richard Gowers [1] (see Chap. 1).

Epidemiology is the study of the determinants, occurrence, and distribution of health and disease in a defined population. In human disease, *epidemiology* is the most common type of study, often used to identity risk factors for a disease whose causative agent has not been identified. Aetiology and epidemiology of CP are

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programmes developed to prevent cerebral palsy and plan health services to meet the needs of the affected children. The changes in the epidemiology and aetiology of CP in the gynaecology and neonatal intensive care units have improved significantly over the last 40 years, and are completed.

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]. *Thirdly,* it seeks specific risk factors and combinations of risk factors associated with CP or different subtypes of CP. In recent years, scientists have reached a broad consensus on the definition and epidemiology of cerebral palsy and thus made communication more uniform and easier in many points. CP *describes* a group of permanent disorders of the development of movement and posture and are non-progressive disturbances or injuries in the developing fetal or newborn brain. 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 (see Chap. 2). 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 Chaps. 2 and 4). Children and adults included under the CP umbrella have very heterogeneous clinical presentations, with many well-recognised risk factors in the prenatal perinatal and early postnatal periods. The temporal distribution of *risk factors* for cerebral palsy is as follows: prenatal 21%, perinatal 30.5%, postnatal 17.1%, unidentified 31.4%. 85–91% of patients present with spasticity. Already in the first days of the newborn's life, an experienced neonatologist or children neurologist can point to CP, based on the neurological examination, the medical anamneses and the existing prenatal (*preconception*), perinatal and postnatal risk findings [3].

Graham et al. [4] describe in detail all fields of cerebral palsy, such as classification, epidemiology, aetiology, diagnosis, pathophysiology, the muscles from children with CP, management of comorbidities, screening and prevention, physiotherapy, rehabilitation, management of non-motors symptoms, quality of life of young people and adults; farther, therapies management strategies, prognose and future studies, the role of stem cell therapy and the topographical description in CP: in unilateral and bilateral CP (*see definitions*).

- In monoplegia: is one limb affected and it is more often the lower limb.
- In hemiplegia: is one side of the body affected.
- In diplegia: the lower limbs are much more affected than the upper limbs.
- In triplegia: the usual pattern is unilateral upper limb involvement and bilateral (asymmetrical) lower limb involvement.
- In quadriplegia or tetraplegia: all four limbs are involved diplegia, triplegia and quadriplegia are covered by the term bilateral cerebral palsy according to SCPE terminology.

In *addition* to motor impairments, they may also have impairments of 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.

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. In *recent* years, scientists have reached a broad consensus on the definition and epidemiology of cerebral palsy. Over the last 20 years, the prevalence of CP has shown a *downward trend* due to advances in gynaecology, prenatal diagnosis, and improved intensive care units. The gynaecologists are well prepared for complicated births, such as underweight premature babies, multiple births or placental problems (see Chap. 5).

3.2 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 [5]. 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 which typically exist in developed countries where neonatal and infant mortality is low.

3.3 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 [6]. 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 [7]. 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 [8] 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 [9]. In the USA, the Autism and Developmental Disabilities Monitoring Network (*ADDM*) [10] 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.

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. [9]	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. [10]	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. [11]	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]	Quebec, Canada	9–11 years old	228	1999–2001	Per 1000 children living in surveillance areas	1.8
Oztürk et al. [16]	Turkey	2–16 years old	102	1990–2004	Per 1000 live births	1.1
Banerjee et al. [17]	Metropolis of Kolkata, India	<19 years old	48	1984–2003	Sample of 16,979 children <19 years old	2.8

Registers are population databases utilising information from multiple sources, relying on a clear definition and inclusion and exclusion criteria of CP [11]. 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 valid data comparisons and research collaborations [12–17]. 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*.

3.4 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. According to Odding et al. [18], the most important risk factors for CP are low birthweight, intrauterine infections, multiple gestation and in some cases are often multifactorial; the majority of patients with CP have the spastic type, of which the diplegic group is the smallest, 25–80% have additional problems. In a *review* article, Gulati et al. [19] discussed the diagnosis and the management of comorbidities, such as epilepsy, cognition, vision, hearing, and gastrointestinal function by children with CP. A recent review [20] by a multidisciplinary, international group of CP experts focused on the following tools with the best predictive validity for detection of CP before 5 months of age: neonatal MRI (86%–89% sensitivity), the Prechtl Qualitative Assessment of General Movements (98% sensitivity) and the *Hammersmith* Infant Neurologic Examination (90% sensitivity), (See Chaps.1 and 11).

Epilepsy is present by 20–40% and is most common among the spastic hemi- and tetraplegics. Archana et al. [21] found a prevalence of 26% for seizures in the studied population of children with CP. The highest incidence of seizures (30.4%) was found in children with *spastic hemiplegia*, and the extent of cortical injury correlated with the risk to develop epilepsy. Panteliadis et al. [22] examined 223 children (122 boys and 101 girls) suffering from *congenital hemiplegia* at the age of 3 months to 12 years. Epileptic seizures developed in more than one third of patients with *spastic hemiplegia*, although EEG abnormalities were evident in the majority of them.

3.4.1 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 [4]. 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 [4, 22] (see Chap. 12). 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 [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. *Aetiology* and *epidemiology* of CP are programmes developed to prevent cerebral palsy and plan health services to meet the needs of the affected children. The changes in the *epidemiology* and *aetiology* of CP in the gynaecology and neonatal intensive care units have improved significantly over the last 40 years. Neonatal intensive care units are completed. Upadhyay et al. [24] in a last review provide a brief explanation about the various aetiological factors, pathophysiology and recent therapeutic approaches in the treatment of CP. CP is the most common *neuromotor* disability with a prevalence of 2–3/1000 live births. According to epidemiological studies on the possible risk factors associated with CP, the highest contributing risk factor is prematurity and being underweight [25]. Another review paper [26] summarises aetiology, epidemiology, the risk factors associated with CP and the advances in its treatment. A recent review [27] shows that the prevalence of CP in high-income countries, as 1.4 per 1000 live births in the most recent international reports. This represents a 35% reduction in birth prevalence over a 15-year period, and that's mostly what you owe interrogation of pre-

ventive strategies, improvements in clinical care from conception into childhood, earlier detection of CP and implementation of early intervention strategies. Diplegia is the most common form of CP in diverse studies with a prevalence of (30–40%), followed by hemiplegia (20–30%) and quadriplegia (10–15%).

Diagnosis *approaches* were based on clinical investigation, neurological examinations (*experience*), the prenatal cranial ultrasound, MRI and biomarkers. 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 the 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.

The European collaborative study of the Surveillance of Cerebral Palsy based registries can provide useful data for generating health indicators. Sharing PHIs (Public health indicators) for CP helps to improve public health policies for people with disabilities in Europe and to increase public awareness of this complex condition. https://ec.europa.eu/-health/indicators_data/.

In his doctoral thesis [28], Casey reviewed a total of 2328 children in the *Study I*, aged 0–11 years, of whom 58% were boys and 984 girls 42%. No child used a manual wheelchair before 1 year, and none used a power wheelchair before 3 years of age. The *Study II* included 2735 children with CP aged 0–18 years (59.5% boys and 40.5% girls). Most children aged 0–11 years could not self-propel their manual wheelchair; whilst more children could independently drive a power wheelchair. Further, windswept hip deformity presented earlier than scoliosis. The author *concluded* that power mobility should be considered earlier, and that it is important to reduce postural asymmetries for children with CP to reduce the risk of developing scoliosis, windswept hip deformity, contractures and pain.

3.4.2 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 [29]. 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 Chaps. 20 and 25) was proposed and validated by the Canadian research group Can Child [30], www.canchild.ca. It was subsequently extended and revised [31]. 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. 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 (see Chaps. 24 and 25).

GMFCS	Evaluates the gross motor function of the individual with CP
MACS	Evaluates functions of upper limb
CFCS	Evaluates everyday communication
EDACS	Emergency department detection of chest pain score
BFMF	Bimanual fine motor function
CIMT	Constraint-induced movement therapy
HABIT	Hand-arm bimanual therapy

The European collaborative study of the Surveillance of Cerebral Palsy based registries can provide useful data for generating health indicators. Sharing PHIs (Public health indicators) for CP helps to improve public health policies for people with disabilities in Europe and to increase public awareness of this complex condition. https://ec.europa.eu/health/indicators_data/.

Surveillance of cerebral palsy in Europe: A collaboration of cerebral palsy surveys and registers. https://doi.org/10.1101/2023.09.01.23294913 [32]. These population-based CP registries can provide data that are relevant for generating key outcomes of interest at the population level, thus potentially contributing to improving public health policies for children with disabilities. 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 (see Chaps. 20, 24, and 25). 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. The MFCS was developed to provide a simple method for classifying children with CP aged 12 years or less on the basis of functional abilities and limitations. The *GMFCS* includes five levels and four age bands. The GMFCS-E&R was developed with the intent that a 12- to 18-year, including communication between youth, families and professionals for goal setting and making management decisions. A recent *review* [33] identified 41 studies discussing the effects of functional gait training on walking ability in children and young adults with CP. The *Meta-analysis* showed that gait training to be a safe, feasible and effective intervention to improve walking ability. Furthermore, gait training showed a better effect than standard physical therapy.

3.4.3 Classification Based on Associated Impairments, Including Epilepsy

As mentioned in the most recent *CP* definition [34], 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 (Chaps. 37 and 38) on comorbidities. For some, such as communication and speech disorders and feeding problems, standardised assessment tools have only very recently been proposed [22, 34, 35], 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 (see Chaps 37 and 38).

Intellectual is the *first* most commonly associated impairment encountered among children with *CP*. It occurs in 30–40% when restricted to severe intellectual impairment (IQ level < 50) [36] 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 [36].

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 [34, 35]. Some will require continuous long-term treatment in order to avoid repeated fits compounding the original cerebral anomaly. Archana et al. [37] found a prevalence of 26% for epilepsy in the studied population of children with CP. The highest incidence of seizures (30.4%) was found in children with spastic hemiplegia, and the extent of cortical injury correlated with the risk to develop epilepsy 38% had focal epilepsies, 57% generalised epilepsies and 3% had combined focal and generalised epilepsy (see Chap. 12).

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) (see Chap. 33).

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* [10].

3.5 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; such as physician, surgical specialist, physiotherapist, occupational therapist. Clinicians usually consider severity in terms of loss of motor ability, possibly in combination with type of motor disorder, and the widespread use of GMFCS, BFMF and MACS have greatly increased the comparability of results between centres. In Australia, the Australian Spasticity Assessment Scale is used to categorise the severity of spastic impairment (see Chap. 25). Another scale has been developed for dyskinesia based on the *Barry-Albright Dystonia* (BD) scale [38]. 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 [39]. 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.

3.6 Classification Based on Neuroimaging Results

Following recent recommendations, [40] 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. [41, 42]. 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 [41]. 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 [42] (see Chap. 10). 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% [41, 42]. Harmonisation of *neuroimaging* classifications and international consensus are important for the future [42], and training tools based on web imaging will be very helpful for the physicians and students. Quantitative aspect may also be taken into account for neuroimaging classifica-

tions, and several have been proposed recently including one for unilateral spastic lesion [43] and a semi-quantitative one for all children with CP [44]; however these should currently be considered as research tools rather than tools for clinical practice. In a last [45] systematic *analysis* in 41 countries from 5 continents, the prevalence showed a decreasing trend in well-organised third units centres. The birth *prevalence* estimate of CP in these centres declined to 1.6/1000 live births.

3.7 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, 42]. Prevalence is higher in males than female (rate ratio of 1.35) [46]. 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 (see Chap. 5).

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. 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 [47]. The prevalence of CP of post-neonatal 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) with a decrease over the period [48].

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 [49]. In more recent years, SCPE has shown a decrease in CP prevalence for children born between 1980 and 2003 in Europe [10, 15] 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 [8]. 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 [10, 11, 15]. Moreover, studies on the different subtypes of CP suggest different time trends according to subtype. A decrease of bilateral spastic CP [50, 51] and an increase of unilateral CP were described for children born between 1983 and 1998. Prevalence of children with dyskinetic CP has also risen between birth years 1976 and 1996 [51].

3.8 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. 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 (see Chap. 5).

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 *post-neonatally* 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. In recent years, several authors and scientists have dealt with the complex problem of epidemiology, aetiology and the changing faces in the onset of cerebral palsy. Much progress has certainly been made in the understanding of the disease, the pathology of its appearance and the degree of heritability. However, science does not stop here and in the coming years we will know even more about the problem of CP, which has been known since ancient times [19, 20, 25, 42, 52–54].

3.9 Conclusion

The concept of CP 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. Over the last 20 years, the prevalence of CP has shown a *downward* trend due to advances in gynaecology, prenatal diagnosis and improved intensive care units. The gynaecologists are well prepared for complicated births, such as underweight premature infants, multiple births or placental problems.

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Neuropathology of Cerebral Palsy

4

Christian Hagel

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 present chapter focuses on pathophysiological aspects and the neuropathological alterations observed in CP. The pathologies described comprise: (a) *periventricular leukoencephalopathy*, (b) *germinal/ventricular haemorrhage*, (c) *por−/hydranencephaly*, (d) *pontosubicular neuronal apoptotic necrosis*, (e) *cortical border zone infarction/ulegyria*, (f) *territorial infarction*, (g) *marbled state*, (h) *multicystic encephalopathy*, i) *hyperbilirubinaemia* and (j) *infections*. The neuropathological findings particularly underline the importance of localisation, extent and timing of brain injury for the clinical picture, whereas data on brain development may indicate possible time windows for therapeutic intervention.

Keywords

Cerebral palsy · Paediatric neuropathology · Brain development · Brain infarction · Intraventricular haemorrhage

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4.1 Introduction

The diagnosis cerebral palsy (CP) refers to motor disturbances resulting from a static brain lesion in the pre-, peri- or postnatal period. The aetiologies of CP are manifold, comprising developmental defects, trauma, infection, toxic agents, vascular insults, etc. (see Chap. 5). Despite considerable progress in obstetrics, the prevalence of CP has almost 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 morphological findings particularly underline the importance of localisation, extent and timing of brain injury for the clinical picture, whereas data on brain development may indicate possible time windows for therapeutic intervention (see Chaps. 5 and 6).

4.2 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 alter-

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Table 4.1 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

ations. Table 4.1 gives an overview of the ontogenesis of the brain.

As depicted in Table 4.1, 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].

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 such as patent ductus arteriosus, pulmonary valve atresia, etc. alterations in composition of the blood, e.g. 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 (see Chap. 5).

The border zones or *watershed regions* between the main basal cerebral arteries play an important role in perinatal hypotensive brain injury. 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]. Patients with parasagittal cortical border zone infarctions may clinically present with mental retardation, motor deficits and epilepsy [5].

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 [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 Chap. 6) 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. The affected neurons 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].

Extreme neonatal hyperbilirubinaemia associated with kernicterus is another possible cause for CP (see Chap. 5). In an Australian prospective cohort study, kernicterus led to CP in combination with other neurodevelopmental deficiencies in 2/26 children [24].

Prenatal infections constitute a major cause for neurodevelopmental disabilities and neonatal deaths. Whereas cardiovascular aetiologies of CP are linked to the developmental stage of the fetal brain, infections may hit the foetus at any time in gestation and often result in a diffuse damage of the central nervous system (see Chap. 5). This may include a subsequent deranged development leading to a multitude of neurological deficiencies. Moreover, there is a considerable overlap in the course of the infections and in their neuropathology. In *viral infections* for example, CP may be encountered in Rubella, Cytomegalovirus (CMV), Human immunodeficiency virus (HIV), Herpes simplex virus (HSV) and Zika virus [25].

CP is not exclusively a disorder of the brain but consecutively 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 accordance, a magnetic resonance imaging (MRI) study of adults with CP revealed a significantly decreased proportion of spinal grey matter in 16 adult CP-patients compared to 16 controls [26].

4.3 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 [27] 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 non-obligatory 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, such 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 [27] speculated that the damage might in part result from abnormal excitatory inputs to these neurons. 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. [28] 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. [29] 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. Post-haemorrhagically 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. [28], the work of Chua et al. [29] 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 [30]. 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 (21% oxygen) 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.

4.4 Morphology of Brain Lesion Associated with Cerebral Palsy

4.4.1 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 [31]. In an autoptic study by Leech et al. [32] 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 [33]. On autopsy fresh lesions are readily identified macroscopically and impress as masses of erythrocytes on histological examination (Fig. 4.1a). 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 was demonstrated by MR imaging in seven infants [34]. 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.

4.4.2 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 is one of the pathogenic factors for this type of neuronal necrosis [35]. The alterations are related to asphyxia at birth and are frequently associated with subependymal haemorrhage or infarcts [36].

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. 4.1b). The damage in the subiculum diminishes towards the hippocampal CA regions and towards the parahippocampal gyrus. 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 mineralise. Since the glial elements persist, the lesion does not impress as a defect, but the parenchyma may focally show a spongy texture.

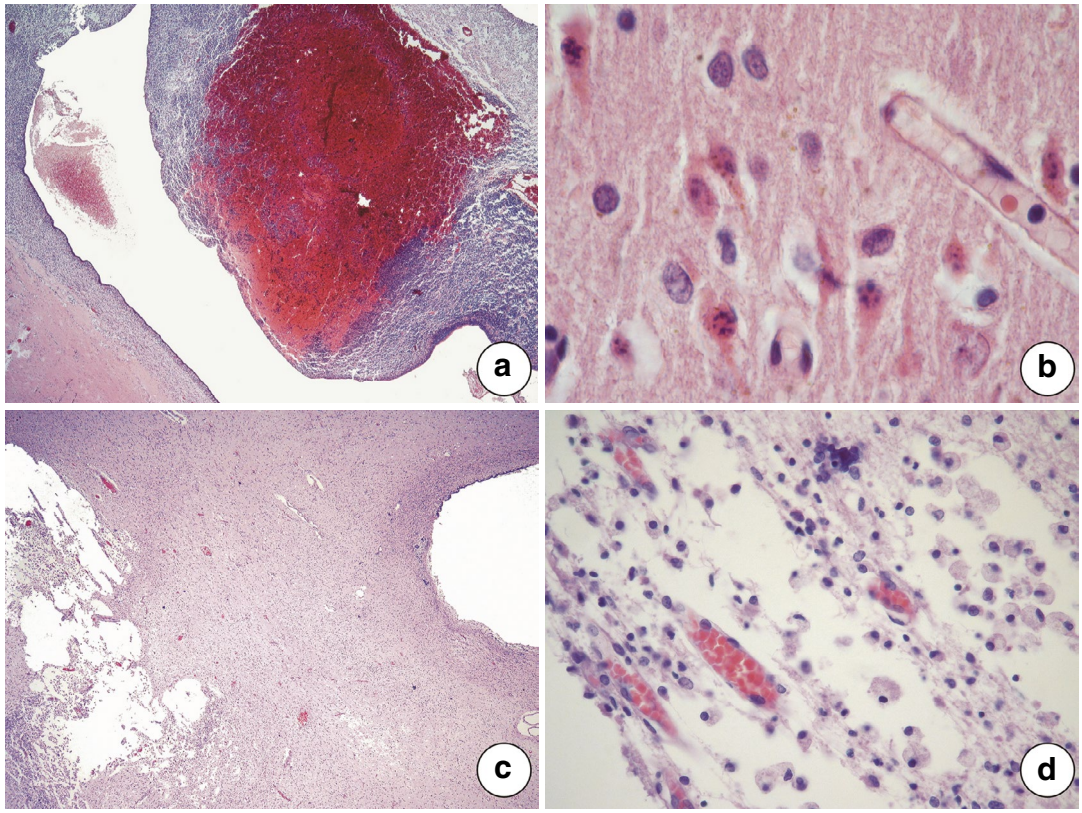


Fig. 4.1 Pathology of pre- and perinatal brain lesions. (**a**) Fresh haemorrhage in the germinal layer in a female foetus with a malformation of the heard, 2fifth gestational week (H&E, original magnification ×5); (**b**) fresh neuronal necrosis presenting as eosinophilic neurons with karyorrhectic 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)

Karyorrhexis is a feature of programmed cell death, and accordingly previous studies have demonstrated fragmentation of DNA as indicator of apoptosis in pontosubicular necrosis [37] as well as expression of apoptosis-related protease caspase-3 and poly-ADP-ribosylated proteins [38].

4.4.3 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 Chap. 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. 4.1c, 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 [39]. PVL may occur in association with status marmoratus of the basal ganglia [40] or cortical infarction [41]. 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.

4.4.4 Cortical Infarction

Upon autopsy, acute *border zone infarctions* 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. A radial gliosis in the form of small gliotic scars extending from the bottom of the lesion towards the pia mater may be observed resulting in an irregular granular appearance of the cortical surface (granular atrophy). An explanation for this peculiar morphology referred to as *ulegyria* was given by Norman [42]. He presented a case of a premature infant born at 30 weeks of gestation who suffered from cardiac arrest 3 days after birth and died 8 days later. Upon autopsy, ulegyria was observed in which viable neurons were found along cortical arteries descending from the leptomeninges interspersed by stripes of neuronal necrosis. The author concluded that 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.

4.4.5 Status Marmoratus

Marbled state of the basal ganglia was first described by Anton [43] 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] (see Chap. 12), 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 (no data in 25%).

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 [44]. Late lesions, by 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 (Fig. 4.2). 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 [45]. However, Friede and Schachenmayr [44] exclusively observed myelinated nerve fibres in marbled state. The findings of Friede and Schachenmayr [44] 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 [46]. 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 4.3). Upon scarring, a disorientation of fibres occurs which sprout through the lesion. The deviant fibres are abnormally myelinated. 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.

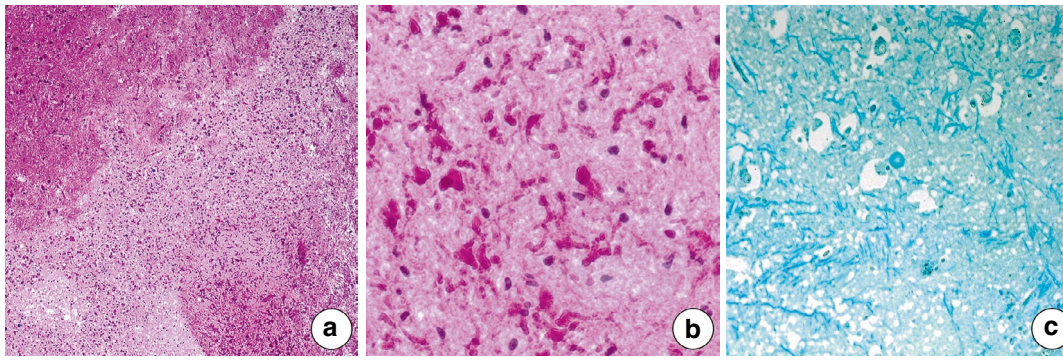


Fig. 4.2 Status marmoratus in a 64 year old man who suffered from early childhood brain damage. Upon autopsy, no neuropathology was noted macroscopically. However, microscopic examination of the thalamus revealed very old patchy microinfarctions. (**a**) upper left part: normal white matter; middle: spongy rarefication of tissue and focal loss of nuclei; lower right: massive astrogliosis with abundant Rosenthal fibres (H&E, original magnification ×25); (**b**) close up of the Rosenthal fibres shown in (a) (H&E, original magnification ×250); (**c**) Myelin stain demonstrating rarefication and derangement of myelinated nerve fibres in the infarcted area (Luxol blue, original magnification ×100)

4.4.6 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 [47]. 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 [48]. 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. [49], 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. 4.3a–d). The basal ganglia and the structures supplied by the vertebrobasilar circulation are often spared [50]. 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 [51].

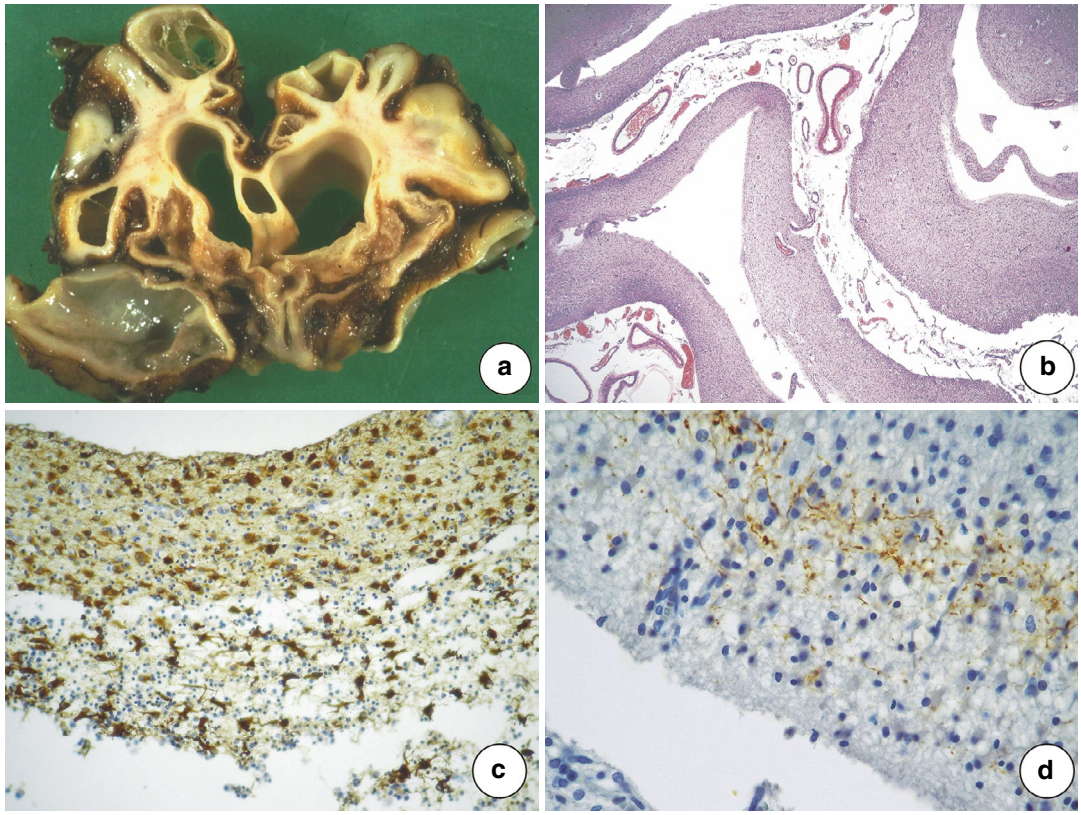


Fig. 4.3 Pathology of multicystic encephalopathy. (**a**) macroscopic findings in of a female full-term infant with perinatal asphyxia born by caesarian section; (**b**) same case as in **a**, histological overview showing gliotic remnants of the cortex (H&E, original magnification ×5); (**c**) immunohistochemical labelling of reactive astroglia at the border of the necrosis, same case as in **a** (GFAP, counterstain haemalum, original magnification ×100); (**d**) immunohistochemical labelling of residual axons and axonal swelling in the cortex of multicystic encephalopathy, same case as in **a** (neurofilament, counterstain haemalum, original magnification ×100)

As an underlying cause for the infarction, meningitis [52] and systemic infections (see Sect. 4.4.8) have been reported. Furthermore, thromboembolic infarction and hyperviscosity of the blood due to *polycythaemia* may cause gross necrosis of brain tissue [53]. Ford et al. [54] 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 the affected 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 4.2.

Table 4.2 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	Preterm/perinatal
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

4.4.7 Hyperbilirubinaemia

Extremely high levels of unconjugated bilirubin may result in a toxic encephalopathy macroscopically appearing as symmetrical yellow-green discolouration (icterus) of deep nuclei (kernel), i.e. the pallidum and subthalamic nucleus. Histologically, *kernicterus* presents with prominent, so-called protoplasmic astrocytes (Alzheimer II glia, Fig. 4.4a) which may also be seen in deep cortical layers, the cranial nerve nuclei of the tegmentum, and in the dentate nucleus of the cerebellum. The toxic damage is accompanied by oedema that may lead to herniation of the lower brainstem. Chronic progression eventually results in neuronal cell death and a spongy appearance of the neuropil in the affected areas with some scattered macrophages. Total tissue necrosis with consecutive formation of cysts is not a feature of kernicterus. Although hyperbilirubinaemia is in principle treatable, neonates continue to die from it. López-Corella et al. [55] reported a male neonate who suffered from ornithine transcarbamylase deficiency, which typically is associated with severe hyperammonaemia. The boy died on the sixth day of life despite intensive care. At autopsy, the brain showed a yellowish discoloration, which was also detectable in the thalami, basal ganglia, hippocampi, dentate nuclei, and grey matter of the brainstem on dissection. Histologically, the typical changes of kernicterus with Alzheimer II glia, gliosis, edema, and neuronal necrosis were found.

4.4.8 Infections

Prenatal *Cytomegalovirus* (CMV) infection is the most common congenital infection in most regions of the world. It may cause different inflammatory lesions presenting as meningoencephalites, developmental alterations like microcephaly, lissencephaly and polymicrogyria, and/or asphyxic damage presenting as periventricular leukomalacia, porencephaly and ventricular dilatation [56]. Infected cells are preferentially found in the olfactory bulb and the walls of the lateral ventricles of the newborn. Histologically, cells bearing viral inclusions are greatly enlarged (cytomegaly, Fig. 4.4b). The viral inclusions are observed in astrocytes, microglia and ependymal cells, leptomeninges, vessels and rarely in neurons.

Neonatal *Herpes simplex virus* (HSV) infection of the CNS presents as a diffuse meningoencephalitis with necroses and microcephaly. Histologically, the lesions comprise necrosis with cellular debris and macrophages, mononuclear inflammatory cells, reactive astrocytes and calcifications.

Fetal *Rubella* infection leads to malformations in 10–12% of the cases with highest risk during the first 4 weeks of gestation. CNS pathology consists of a chronic meningitis which infiltrates the brain via the perivascular spaces, also affecting the vessel walls. Subsequently mineralisation, necrosis and thrombosis of vessels may develop with risk of asphyxic damage to the brain. Postnatal progression of the infection may

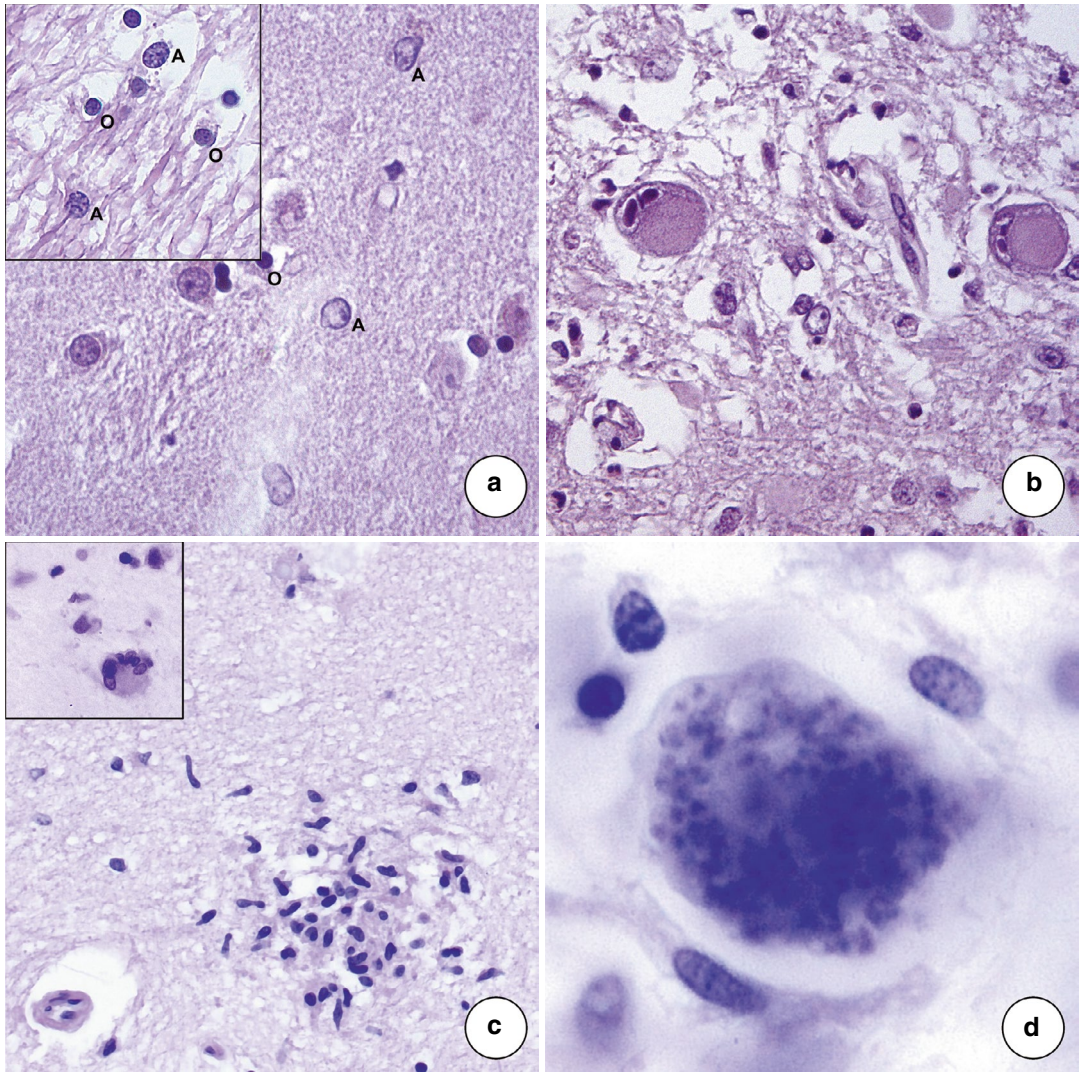


Fig. 4.4 Pathology of pre- and perinatal toxic/infectious brain lesions. (**a**) Alzheimer II glia in hyperbilirubinemia presenting as astrocytes with clear bloated nuclei, insert: normal brain tissue (*A* astrocytes, *O* oligodendrocytes, H&E, original magnification ×250); (**b**) Cytomegalic cells with viral nuclear inclusions in CMV infection (H&E, original magnification ×250); (**c**) Microglial nodule in HIV infection, insert: multinucleated giant cell (H&E, original magnification ×100); (**d**) Pseudocyst in Toxoplasma gondii (H&E, original magnification ×500)

lead to panencephalitis with diffuse destruction of the white matter [6].

Most infants with maternally transmitted *Human immunodeficiency virus* (HIV) infection develop neurologic symptoms in their first year of life characteristic for a white matter disorder. Symptoms comprise amongst others, failure of brain growth, ataxia, seizures, and spastic paresis [56]. Brain autopsy reveals changes similar to adult AIDS patients including atrophy, microglial nodules, and multinucleated giant cells (Fig. 4.4c). A characteristic pathologic change has been termed calcific vasculopathy. In 8/12 children aged 5 months to 10 years who died of AIDS, Belman et al. observed calcifications in small- to medium-sized vessels in the basal ganglia, predominantly in the putamen and outer segment of the globus pallidus [57]. The deposits contained both, calcium salts and iron.

Fetal *Zika virus* infection is frequently associated with *microcephaly*. Chimelli et al. described the neuropathological lesions in 10 autopsy cases of stillborn or newborn babies [58]. The findings corresponded to a severe mixed pathology of tissue destruction and developmental disorder including thin neocortex with calcification and focal agyria, malformed or ill-defined hippocampi, absent or thin corpus callosum, small basal ganglia and thalami, cerebellar hypoplasia, and small brain stem. Upon histologic examination mild lymphohistiocytic infiltrates were noted. The pallium was thin, in some cases only consisting of remnants of germinal matrix and leptomeninges. In other cases, neurons were detected in the cortex by NeuN immunohistochemistry. Occasionally, siderophages were observed. Disturbed neuronal migration was detected in the cerebrum, cerebellum and brain stem presenting as polymicrogyria, meningeal glioneuronal heterotopia and cerebellar cortical dysplasia. In one case, siderophages were found indicating an old subependymal haemorrhage. Oligodendrocytes were detected only in one case with infection in late gestation. Wallerian degeneration and axonal spheroids were observed in particular in midbrain and brainstem. Consecutively to disruption of descending tracts, the brain stem was small and the spinal cord was abnormally shaped. The cerebellum showed neuronal heterotopia and the neurons of the dentate nucleus were disorganised.

Toxoplasmosis is a protozoan infection transmitted by a wide range of hosts, most frequently by cats. Congenital infection is observed with an incidence of 1 in 1000–3500 live births. CNS manifestations mainly comprise meningoencephalitis causing hydrocephalus, microcephaly, calcifications, porencephaly or hydranencephaly [56]. A typical finding at autopsy are multifocal abscesses, often with extensive necrosis. Preferably, the lesions are located in the basal ganglia and at the cortico-medullary junction in the cerebral hemispheres. Histologically, pseudocysts of Toxoplasma gondii (Fig. 4.4d) and sometimes free tachyzoites are seen in the vital tissue. Astrogliosis and activation of microglia are found, and microglial nodules may also be present in some cases. Involvement of the vessels may lead to vasculitis with thrombosis and fibrinoid necrosis. Cortical malformations are not observed in toxoplasmosis.

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Aetiological Factors

5

Christos P. Panteliadis, Martin Häusler, and Mary Jane Platt

Abstract

The aetiology of cerebral palsy (CP) is heterogeneous, multifactorial, and complex, with diverse risk factors, and is only partially understood. *Development* of the nervous system starts with neurulation on days 17–19 of gestation and continues during the first years of life. CP can result from brain injury occurring at any point during this time, i.e. during the prenatal, perinatal, or postnatal periods. While the *relationship* between *damage* and *clinical* disease is mostly clear, the contribution of different risk factors to the damage and clinical phenotype often remains obscure. Here are reviewed and discussed the risk factors and aetiological mechanisms that underpin the development of CP, including intrauterine exposure to toxic agents, preterm labour, hypoxia, asphyxia, neonatal encephalopathy, and multiple pregnancies. In all these *fields*, the aetiological factors are reviewed.

Keywords

Aetiology · Prenatal factors · Perinatal ischaemic stroke · Prematurity · Multiple pregnancies

5.1 Introduction

Already in *ancient times*, Hippocrates (460–390 B.C) discussed the association of prematurity, congenital infection, and prenatal stress in relation to the pathogenesis of brain damage. He referred to children with *intrauterine disease* as having increased morbidity and mortality [1] (see Chap. 1).

Currently, cerebral palsy is the commonest physical lifelong motor impairment, usually starting in childhood, and occurring in 1.0 to 2.5–3 per 1000 live births. It is *not progressive* and is characterized by an aberrant control of movement and posture. The *last* 15 years have seen a significant reduction of CP in well-organized countries. This reduction is due to better monitoring of pregnancies, better organized intensive care units, greater availability of neonatal neurologists, and to earlier interventions (see Chap. 9) [2].

In 1961, *Courville* assumed intrauterine hypoxia to be the most important cause of CP,

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producing lesions of the cortex, the basal ganglia, and the cerebellum [3]. The aetiology of cerebral palsy (CP), however, is much more heterogeneous, multifactorial, and complex with mechanisms still only partially understood. The *most common* aetiological risk factors are various and frequently classified according to the assumed timing of exposure: i.e. prenatal, perinatal, or post-neonatal, because the resulting spectrum of cerebral damage is strongly influenced by the patients' age, with different brain structures showing different susceptibilities towards damage at different ages of gestation (see Chaps. 4 and 9). These *risk factors* include prematurity, in utero or perinatal stroke, anoxia, hypoxic-ischaemic encephalopathy, maternal disorders of clotting, maternal migraine mostly in the first trimester, multiple birth, placental infarcts or abnormalities, neonatal sepsis including meningitis, and post-neonatal traumatic brain injury. These are summarised in Table 5.1.

The causal pathways to the development of CP are also *complex* in pathophysiology with various aetiological factors (see Chaps. 4 and 9). While CP may result from exposure to a single aetiological factor producing irreversible brain injury, perinatal asphyxia in the preterm neonate may be followed by circulatory failure and neonatal infection which can amplify the brain damage [4, 5] (see Chap. 6).

Table 5.1 Risk factors and aetiology of cerebral palsy. (Adapted from [4])

	Prenatal	Perinatal	Postnatal
Maternal	Hypoxic-ischaemic encephalopathy, vascular thrombosis), maternal epilepsy and cognitive impairment, cervical or third-trimester bleeding, maternal trauma and infection during pregnancy, antiphospholipid autoantibodies, fertilisation problems, pre-pregnancy obesity	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, genetic susceptibility, 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 (gestations), low birthweight, maternal disorders of clotting, congenital brain malformations, intrauterine death of a co-twin	Cerebral infarction, venous sinus thrombosis	Near drowning, suffocation, cardiac arrest, post-neonatal traumatic brain injury, acquired thrombophilia, infarction, child abuse, neonatal seizures

The resulting neuropathological correlates of CP include white matter injury, *such as periventricular leukomalacia*, germinal matrix haemorrhage, and injury to the cortex, basal ganglia, and thalamus. Even with modern *diagnostic* techniques, a specific aetiological factor can be identified in no more than 50–75% of all CP cases. The frequently risk factors are prenatal, perinatal and postnatal. Ultrasound and MRI can be helpful for the condition of the foetus in all stages of the pregnancy [5]. The gas analysis (acid/base) in umbilical cord blood (*Apgar score*) can be very helpful diagnostically about the condition of the infant as well as perinatal and postnatal [6]. Himmelmann et al. [7] studied a group of 3818 children with postneonatal MRI. The distribution of CP type, motor, and associated impairments differed by neuro-imaging patterns, showed that bilateral findings were associated with a more severe outcome, than unilateral compromise. The long-held view that a 'difficult *birth*' is responsible for the origins of CP is not supported by evidence. Little uses information from 47 case studies to support his stance that abnormal births oftentimes cause deformities. One of the conditions *Little* described throughout the article involved adverse neurological symptoms as a result of partial suffocation during delivery [8]. Odding et al. [9] suggested that among children with tetraplegic CP, a prenatal aetiology was likely to be responsible for 50–55% of the children, a perinatal aetiology for 30%, and a postnatal aetiology for 15–20% for the remainder.

Sellier et al. [10] 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, the *risk* of CP is lowest in babies who are of above-average weight for gestation at birth but increases when weight is well above normal or is well below normal [5, 9]. In a review, Korzeniewski et al. [11] describe the *epidemiological* evidence for risk factors, such as preterm delivery and foetal growth restriction, genetics, pregnancy infection, and other exposures. They also *discuss* the role of magnesium sulfate in preterm labour (see Chap. 8) and therapeutic hypothermia for birth-asphyxiated infants and their role in the development of strategies for the prevention of CP.

5.2 Intrauterine Exposure to Toxic and Other Agents

Iodine is an essential micronutrient for thyroid hormone synthesis. Iodine deficiency during pregnancy is associated with neurological endemic cretinism, and hypothyroidism-related CP is common in areas of severe iodine deficiency [12, 13]. Brain *imaging* findings in affected children are very similar to those seen in children with non-iodine-related CP [13]. Further effects of severe iodine deficiency during pregnancy include adverse obstetric outcomes, low birthweight (*small for gestational age*), and impairments of cognition, motor function, hearing, and speech [12]. According to Lee [13], children born to mothers with TSH (Thyroid-Stimulating Hormone) levels >4.0 mIU/L in pregnancy had a twofold higher risk of LBW compared to those born to mothers with TSH 0.1–2.5 mIU/L, regardless of TPO (*Thyroid Peroxidase*) antibody status. The American thyroid association, the European thyroid association, and the Endocrine society recommend supplementation with 150 μg/day of iodine in women who are planning to become pregnant or are pregnant [13].

Furthermore, in a study on pregnant women without overt thyroid disease, women with subclinical hypothyroidism, isolated hypothyroxinaemia, or TPO antibody-positivity were at significantly higher risk of preterm birth [14]. These *findings* lead the authors to suggest a need to optimizing clinical decision-making strategies regarding levothyroxine treatment during pregnancy or iodine supplementation [14] as treatment of at-risk mothers with iodised oil supplements have been shown to decrease the prevalence of CP. Additional causes of

maternal *hypothyroidism* other than iodine deficiency may also contribute to the aetiology of CP [12–14]. Whether primary congenital hypothyroidism in the child is also associated with an increased risk of cerebral palsy is still a matter of discussion. However, newborn screening tests for *congenital* hypothyroidism should be performed in all infants to enable timely substitution.

Further intrauterine *risk factors* increasing the risk of CP are maternal use of alcohol during pregnancy (2.5-fold increase of the risk- pre/perinatally acquired) [15], methylmercury exposition, 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 [16]. *Nutritional* protein (macro- and micronutrients) is of special significance in the synthesis of all known neurotransmitters, brain and neuronal myelination [17].

An adequate intake of *vitamins* during pregnancy is also important. According to Adams et al. (2022), when providing evidence-based recommendations for *prenatal* vitamin supplementation, the levels of most vitamins decrease significantly during pregnancy, including vitamins A, C, D, K, B1, B3, B5, B6, folate, biotin, and B12. As this may *affect* a wide range of pregnancy- and infant health issues, vita-min supplementation may also be important during pregnancy [18]. However, there is currently *no* international standards for the compo-sition of prenatal supplements, vitamin preparations vary widely in their contents and often contain only a few vitamins.

For distinct toxic agents, *meconium* analysis is an effective method for identifying in utero exposure of infants to xenobiotics to detect licit and illicit drug abuse as a risk factor for adverse pregnancy outcome (Fig. 5.1).



Fig. 5.1 Vitro figure symbolic of scientific methods and the contemporary achievements of paediatrics in the protection of the child, which you calmly accept in the stoic cares of Mother-Science. Work of Dr. Antonis Filippopoulos (*Mixed Technique*)

5.3 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 5.1) and various pathologic processes may contribute to the clinical features [19]. Pluripara have a three- to fourfold higher incidence of CP (*mainly spastic diplegia*), and children born after in vitro fertilisation (IVF) also have an increased risk of CP, probably due to the high frequency of twin pregnancies [20]. Although much of this *risk* is

attributed to prematurity and low birth weight—the two most important risk factors in twin births—it is not entirely so [21]. 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 [22], (see Chap. 7). 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 foetal 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 is a hypothesis (see Chap. 7). Newton et al. [23], in contrast, suggested that the vanishing twin syndrome was unlikely to account for a high proportion of cases of CP.

Studies from *different* countries have found that the rate of multiple births has increased through the most recent decades. This *increase* may relate to rapid developments in fertility treatment, and higher maternal age at first pregnancy, two important factors associated with multiple pregnancies. According to Sebghati and Khalil (2021), in the last *decades*, the incidence of multiple pregnancies may have risen due to older maternal age at conception. The authors describe the risks associated with *multiple* pregnancies and discuss the problems and risks of intrauterine foetal reduction [24].

In 2000, a network of 14 CP registers and surveys from 8 countries was formed across Europe, known as '*Surveillance* of Cerebral Palsy in Europe or SCPE'. The larger number of cases in this multi center collaboration provides the possibility to study trends over time, to estimate risk more precisely in different subgroups, and to describe the clinical picture of multiples with CP in a European context [25]. In all *multiple* pregnancies, delivery should be performed by an experienced team competent in multiple pregnancy deliveries [26].

5.4 Preterm Labour and CP

The risk of CP is *higher* in infants born preterm than in infants born at term and increases with decreasing gestational age. Two major pathologies associated with CP and preterm labour are *periventricular* leukomalacia (PVL) and intraventricular haemorrhage (IVH). 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 (Fig. 5.1).

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 [27, 28]. 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. 4).

There are no specific *signs* or *symptoms* for developing PVL. The diagnosis is commonly established during routine brain ultrasound studies and advanced neuroimaging techniques. 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 [28, 29]. Prolonged CO2 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 [4, 5] and neonatal infectious diseases (see Chap. 6) [30].

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, such persistent ductus arteriosus, acidosis, airway suctioning; a high cerebral venous *pressure*, e.g. pneumothorax, high ventilation pressure; abnormal arterial blood pressure, such as hypotension, hypertension, septicaemia; and impaired cerebral autoregulation in extreme prematurity [31, 32].

In *addition* to the mass effect of a 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 [33]. *Moreover*, bleeding into the *stem cell* layer may result in reduced cortical grey matter volume (see Chap. 4). This *intraventricular* parenchymatous-haemorrhage in the preterm child should be distinguished from subdural, subarachnoid, and intraparenchymal haemorrhages in the term-born neonate.

A recent publication [34] on extremely preterm infants born in 2013–2018 and treated in academic medical centers, found that 78.3% survived to discharge which was an improvement compared to earlier periods of time, of whom 8.4% showed moderate to severe cerebral palsy. *Among* infants born at less than 27 weeks gestational age, rehospitalization and severe neurodevelopmental impairment were common at 2 years. *However*, as the authors note, the 2-year-outcome is dynamic because the complexity of developmental and cognitive milestones, and engagement with quality-of-life oppor-tunities will also impact on function in later life (see Chaps. 31 and 38).

5.5 Hypoxia and Neonatal Encephalopathy

Intrauterine *hypoxia* of the foetal brain is a common prenatal and perinatal risk factor associated with CP, remaining a major cause of death or lifelong disability. 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 (Table 5.1).

A *genetic* contribution to the aetiology of placental abruption, pre-eclampsia, and chorioamnionitis has also been suggested [35]. Placental abruption (Pa) is a partial or total separation of the placenta from its normal implantation. Pa starts with necrosis (*ischaemic changes*) and rupture (*bleeding*) of maternal blood vessels in the decidua. This is followed by haematoma formation and can lead to acute vital risk for the mother and the fetus, [36, 37]. The *differential* diagnosis of interuterine hypoxia includes infections, vascular stroke, seizures, genetic/congenital charges (load), metabolic problems, and toxic causes.

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 foetal heart rate and contractions of the uterus, and the analysis of maternal blood hormones (such as *oestradiols*). Signs of foetal circulation deficit include low heart rate and metabolic acidosis of the foetal blood. Both *methods* are sensitive, but their specificity is low; a transiently abnormal CTG result can be observed in about 30% of all pregnancies.

Foetal tachycardia or abnormal reactions of heart rate to exogenous stress like uterus contractions may be the only evidence of subacute or chronic hypoxia but can also occur transiently without causing damage. Chronic *hypoxia*, that is impaired cerebral oxygen supply of the fetus over an extended period of the pregnancy, is associated with adverse mental-cognitive development. However, *chronic* intrauterine hypoxia with onset after the 34th week of gestation is only rarely associated with PVL or sub-ependymal cerebral haemorrhage, and 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 (see Chap. 9). In 1955, Virginia Apgar (1909–1974),

generated this *scoring* system that forced obstetricians to examine the condition of newborns at birth and to assess the need for immediate treatment. The APGAR score was the first to standardize the *language of asphyxia*: Newborns with low scores would have a lower chance of no brain damage later in life. In Ancient Greece, this topic was described by Soranos from Ephesos (98–138 A.D) already using terms such as paralysis or paresis.

During *labour*, in turn, many specific physiological mechanisms protect the normal (*healthy*) fetus from repeated mild hypoxic episodes, so that only severe hypoxia or prolonged anoxia causes neurological deterioration. *Accordingly*, the role of perinatal asphyxia as an aetiological factor should not be overestimated. 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 definition of *birth asphyxia*, of the outcome CP, and 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].

Acute intra- or peripartum asphyxia nevertheless exists. Examples of such events *include* premature detachment of the placenta, reduced utero-placental blood flow, etc. causing cerebral lesions due to hypoxia and/or ischaemia [40] (see Chap. 4). 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.

According to *criteria* of the American College of Obstetricians and Gynaecologists Task Force on Neonatal Encephalopathy [41], the following signs are consistent with acute intrapartum or peripartum asphyxia:

- APGAR score of <5 at 5 and 10 min.
- Foetal umbilical artery acidosis, with pH <7.0 and/or base deficit of ≥12 mmol/L.
- Multisystem organ failure (dysfunction) consistent with a hypoxic-ischaemic event.
- A sentinel hypoxic or ischaemic event occurring immediately before or during labour, with foetal 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 also suggests that only severe cerebral palsy, e.g. *spastic* quadriplegia or *dyskinetic* CP, is associated with hypoxic-ischaemic encephalopathy (HIE) which is not the same as perinatal hypoxia. Neonatal *encephalopathy* affects term-born, and late preterm newborns and affected children are known to show a high risk of perinatal problems (*neurological morbidity*) [30] and for long-term disabilities (cerebral palsy, epilepsy, cognitive impairment). However, it is still difficult to predict long term outcome for the individual child from perinatal data, including MRI images [41] (see Chap. 13). A more detailed discussion of the topics HIE and neonatal encephalopathy is provided by the review of Russ et al. (2021) [42] who compare postnatal clinical and *radiological* findings (*ultrasound*, *MRI*) with prenatal findings (see Chap. 10).

5.6 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, circu-latory failure, and hypoxia and may need aggressive artificial ventilation or even *extracorporeal* membrane oxygenation, 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]. The

presence of meconium in the *amniotic fluid* (AF) is also a gestational age-independent risk factor for cerebral palsy among preterm infants. Meconium in the AF may sometimes initiate vasoconstriction that leads to hypoxic-ischaemic cerebral palsy. Simultaneously, foetal defecation throughout gestation appears to be a physiologic phaenomenon [43], but only a minority of children with meconium- stained amniotic fluid develops meconium aspiration syndrome.

5.7 Perinatal Stroke

Perinatal stroke (PS) can be defined as a disruption to cerebral blood flow (*vascular brain injury*) between the 20th week of foetal life and the 28th postnatal day. The two most common types of PS are arterial ischaemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) [44]. The third clinical entity is haemorrhagic stroke in the term born neonate (see next section). AIS *comprises* a group of arterial ischaemic injuries that can occur in the prenatal, perinatal, and postnatal periods in term and preterm infants, each with different clinical presentations and risk factors [5, 36, 44] (Table 5.1, Fig. 5.2).

According to Fluss et al. [45], the aetiology of AIS frequently remains speculative, e.g. thrombosis in the carotid artery, and rarely by carotid occlusion through thromboembolic processes in the placenta. The *middle* cerebral artery is the most common site of AIS and the majority affect the left hemisphere. *Perinatal* stroke has an incidence between 1:1300 and 1:3500 live births with CSVT being much less common at 1–2 per 1,000,000 births; together they ac count for about 15% of the children with hemiplegic CP [45].

Birth-related risk factors for *perinatal* stroke are similar to risk *factors* for complicated birth in general so that those do not necessarily indicate a specific risk for venous or arterial occlusion: Such as emergency caesarean section need for resuscitation, foetal heart rate abnormalities, meconium-stained amniotic fluid, prolonged labour, low 5 min *Apgar* scores, intrauterine growth restriction, small for gestational age, male gender, maternal prothrombotic risk factors, and delayed presentation. Blood-gas analyses address the timing and possible causation for the development of foetal/newborn hypoxaemia and acidosis [46]. *Further* risk factors include maternal pre-eclampsia, a history of impaired maternal fertility, small and large for gestational age, trac-

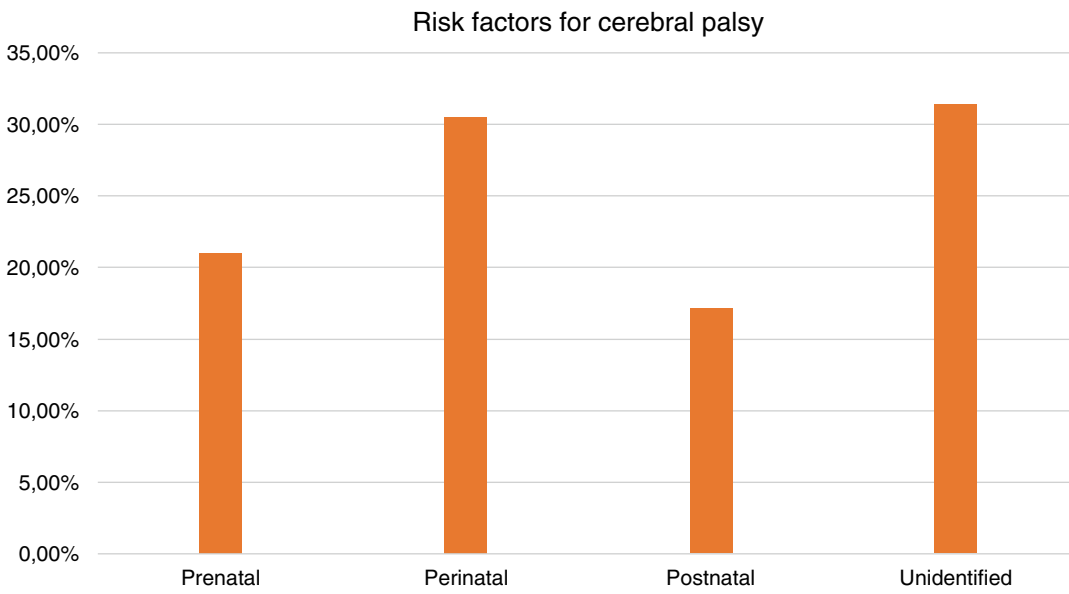


Fig. 5.2 Risk factors for cerebral palsy in % of prenatal, perinatal and postnatal period

tion on neck vessels during delivery, perinatal infections, dehydration and hypotension of the newborn, the use of intravascular catheters, placental thrombotic lesions, and hereditary thrombophilia [5, 35, 40].

Furthermore, 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 arterious duct 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 lead 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 [46]. Only some infants with PS are symptomatic in the first days of life; in others, symptoms develop gradually during the first year of life or later [47]. *Most* children, however, develop CP, frequently combined with behavioural abnormalities, and/or deficiencies in cognition and attention (see Chaps. 31 and 38).

5.8 Subdural, Subarachnoid, and Intraparenchymal Haemorrhage

Much less common than intraventricular haemorrhage (*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 foetal head include cephalopelvic disproportion, rigidity of the bony pelvis, prolonged duration of labour, unusual presentations or the need for prolonged manipulation, or forceps application [48].

Blood may reach the *subarachnoid* space by different ways: after haemorrhage in the cerebral parenchyma or in the periventricular region, or after disruption of superficial *leptomeningeal* arteries or fragile vessels bridging the subarachnoid space. Primary subarachnoid haemorrhage commonly occurs after hypoxic-ischaemic brain insults and after foetal 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 secondary to 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 intra-cranial haemorrhage within the first weeks of life. In the *absence* of recognised coagulation or anatomic abnormalities, cerebral hemi-spheric IPH is usually 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 [5, 49]. For the treatment of intraparenchymal haemorrhages resulting from the application of antithrombotic agents see reference [5, 31, 32]. This *guideline* provides

evidence-based recommendations to assist employed medical personnel in the care of patients with antithrombotic-associated intracranial haemorrhage [48].

5.9 Post-neonatal Risk Factors for CP

Post-neonatal CP is much less common, with about 1.20–2.0 cases per 10,000 population [50, 51]. 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 (see Table 5.1). The *most* common causes are infections, usually originating in the CNS, and accidents, for example, head injury due to accidents or child abuse (see Chap. 6) [52].

Other *causes include* heart failure or cardiac arrest leading to generalised anoxia with anoxic encephalopathy, 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 [53]. Prognosis is similar for acquired as for congenital CP, although children with *post-neonatal* CP are more likely to develop spastic hemiplegic CP or spastic quadriplegic/dyskinetic CP than children with non-postneo-natal CP [54].

5.10 Genetic Factors in CP (See Chap. 7)

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 5.1), and studies in small communities have shown that CP is more frequent in populations where marriages between relatives take place. 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 [50]. In *addition* to these monogenic diseas-es, candidate genes that may influence various processes critical in the pathogenesis of lesional CP in a polygenic fashion are increasingly recognised [55] (see Chap. 7).

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) [5]. 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, and implications for genetic testing [56]. Mutations of many different genetic loci can produce a CP-like phenotype (see Chap. 7).

5.11 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. Both promote the occurrence of neonatal thrombotic disease and placental abnormalities, resulting in preterm birth or spontaneous abortions [5, 49]. Moreover, there is a causal relationship *between* the presence of immune thrombocy-topenia, vitamin K deficiency and secondary coagulation defects due to maternal drug intake (*anti-seizure medications*), and neonatal cerebral haemorrhage.

5.12 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 5.1). Also, an *immaturity* of the endome-

trial environment and undiagnosed chromosomal abnormal-lities may increase the risk of CP. There may also be an association of CP with *maternal* cognitive impairment, motor impairments in a sibling, maternal epilepsy, maternal obesity, and a history of two or more foetal deaths in the family (see Chap. 6).

5.13 Infections

Infections may contribute to CP during all developmental phases, including the classical intrauterine infections: e.g. *TORCH* toxoplasmosis, rubella, cytomegalovirus, and herpes which typically cause *chronic* CNS inflammation, maternal chorioamnionitis or intrauterine inflammation (*microorganisms* are frequently associated with *chorioamnionitis*) [11, 35]. The associated *destruction* of nervous tissue is caused by various mechanisms, including direct destructive actions by the infectious agents, bacterial toxins, viral virulence factors, the host's inflammatory reaction, vascular thrombosis and inflammation or systemic cardiovascular failure. While the *infection* is the key mechanism leading to CP in classical meningitis, systemic infection may exacerbate known damaging mechanisms, as for example seen with hypoxia-related periventricular leukomalacia [11].

Clinical *chorioamnionitis* has been defined as a broad clinical syndrome with any combination of fever, maternal or foetal tachycardia, uterine tenderness, foul-smelling amniotic fluid, or elevated white blood cell count. The *presence* of one or more of these signs and symptoms, however, does not necessarily indicate intra-uterine/intra-amniotic inflammation—or that histopathologic chorioamnionitis is present [35]. Intrauterine inflammation can also occur as *sterile* intra-amniotic inflammation in the absence of demonstrable microorganisms but may have been induced by infectious agents including neonatal *septicaemia* (group B streptococci, listeria, *E. coli*) with or without meningitis.

5.14 Early Recognition

New methods of intrauterine newborn monitoring have made great progress and, from early on, allow all stages of intrauterine life to be followed. *Obstetrics* and *neonatal care* has also made great progress, and in every difficult or high-risk delivery, the paediatric and obstetric teams must be prepared for complications. Immediately after delivery, a first assessment of the newborn's condition is performed.

During the *early neonatal* period, clinical reexamination of the primitive reflex status and cranial ultrasound will provide initial information on the presence of brain lesions. More detailed data may derive from MRI studies. *Earliest* possible identification, diagnosis and treatment are essential and possible through a neurological and neurodevelopmental examination in the first month of life [57]. *Such* clinical examinations are important and should be carried out in a timely manner and focus on muscle tone, reflexes, assessment of the findings from prenatal brain ultrasound and in a thorough neurologi-cal examination by experienced neuropaediatricians (see Chaps. 9, 11, and 17).

5.15 Conclusion

The *aetiology* of cerebral palsy (CP) is heterogeneous, multifactorial, and complex, with diverse risk factors, and is *only* partially understood. In *ancient times*, Hippocrates (460–390 B.C) discussed the association of prematurity, congenital infection, and prenatal stress in relation to the pathogenesis of brain damage. Here are *discussed* the risk factors and aetiological mechanisms that underpin the development of CP, *including* intrauterine exposure to toxic agents, preterm labour, hypoxia, asphyxia, neonatal encephalopathy, and multiple pregnancies.

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Intrauterine Infection and Cerebral Palsy

6

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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.

Keywords

Etiopathogenesis · Preclinical models · Infection

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6.1 Introduction

The development and maturation of the human brain in utero occurs throughout the fetal period and is orchestrated by a set of complex interactions amongst 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:

- 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. 4). The fastest rate of growth occurs in the immediate *neonatal* period. Anomalous development in any of the aforementioned stages constitutes cerebral 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 neurula-

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tion can lead to neural tube defects, while abnormalities of neuronal organization can lead to developmental delay 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.

6.2 Etiopathogenesis 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 (see Chap. 2). 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 5). 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. 5).

6.3 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 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, IL-13. Additionally, the Treg axis includes IL-1 antagonist, 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 [7] 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 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 et al. [8] showed that elevated levels of IL-6, 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. These studies suggest that maternal infection in pregnancy is inextricably linked to fetal outcome and prevalence of CP.

6.4 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 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 intraamniotic infection (see Chap. 5). 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 overarching pathway is associated with the development of known precursors of CP such as periventricular leukomalacia (PVL) [10, 11] (see Chap. 16).

6.5 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 is through animal models. Smith et al. [12] 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 level 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 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 [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 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, white matter damage and inhibit the regeneration of *microglia*. The lack of microglial proliferation exacerbates cerebral hypoxia-ischemia, predisposing to the development of CP [20].

6.6 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. 5). In fact, the very low birth weight (<1500 gm) cohort sees higher rates of CP ranging from 5 to 15% secondary to PVL, intraventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD) [21]. The combination of preterm birth, IVH, and inflammation associated with hypoxia-ischemia have 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. 5). 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, PVL, 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 [25]. 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].

More recently, common perinatal *infections* such as congenital CMV have been associated with CP. In a systemic review by Ong and Fan, the pooled prevalence of CP in patients who had confirmed congenital CMV was a staggering 26% [29]. The various intracranial anatomic anomalies of congenital CMV can be detected by antenatal sonographic assessment. The meta-analysis suggests that among the vast array of clinical phenotypes of congenital CMV, assess-

ment for CP needs to be included in the follow up for these children.

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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The Genetics of Cerebral Palsy

7

Marije Meuwissen and Katrien Janssens

Abstract

This chapter describes the recent insights into the contribution of genetics to cerebral palsy (CP). Epidemiological studies on familial recurrence of CP and the higher incidence of congenital anomalies in CP patients have long been suggesting a contribution of genetic factors to the aetiology of CP. Recent large-scale *genetic studies* have now proven that both chromosomal copy number variants and monogenic disorders play an important role in CP aetiology. *Describes* the history of genetic discoveries in CP up to today, *describes* the currently available genetic tests in the diagnostic setting and proposes a genetic testing strategy in CP cases.

Furthermore, it reflects on the relevance of a genetic diagnosis for clinical management and counselling of families, e.g. regarding recurrence risks and family planning. *Finally*, it provides some future perspectives on the identification of novel CP-related genes and potential therapeutic targets, as well as on methods to improve diagnostic yield.

Keywords

Cerebral palsy · Genetics · Copy number variants · Monogenetic variants · Chromosomal microarray analysis

7.1 Introduction and Definitions

Cerebral palsy is a clinical descriptive term that was defined by the International Working Group on the Definition and Classification of CP in 2004 as 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. It is *commonly* accompanied by other clinical comorbidities, including intellectual disability (ID), speech and language deficits, epilepsy, autism spectrum disorder (ASD) and impairment of vision or hearing [1], rendering the phenotypic spectrum that can be seen in a CP patient broad and variable.

Similar to other neurodevelopmental disorders (NDD) as ID and ASD, the clinical diagnosis of CP is made based on signs and symptoms

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rather than underlying pathology of aetiology. The *timing* of clinical diagnosis is key: Symptoms in a very young child may fit the clinical diagnosis of CP, while long-term follow-up may show, e.g. slow disease progression, strictly speaking no longer fitting a CP diagnosis. With this in mind, genetic diagnostics in CP should study disorders associated with '*typical*' CP, but should also include disorders that may present as CP, but with a slightly different, slowly progressive course, the so-called CP-mimics (see Chaps. 5 and 17). Examples are early-onset hereditary spastic paraplegias and neuro-metabolic disorders [2].

7.2 Could CP Be of Genetic Origin? First Hints from Epidemiological Studies

Historically, inadequate oxygen delivery to the brain during birth due to brain injury, trauma or prematurity was thought to be the leading cause of CP. Large population-based, controlled studies have shown however that birth asphyxia is a rather uncommon cause and accounts for less than 10% of CP cases. This insight has contributed to an increased interest in genetic studies to elucidate its additional causes (see Chap. 4 and 5).

The contribution of *genetic factors* to CP was initially suggested by epidemiological studies. (a) First, several population-based studies show familial aggregation of CP cases. In families with an affected child, the risk is increased 9.2 (6.4 to 13)-fold in a subsequent full sibling and 3.0 (1.1 to 8.6)-fold in a half sibling [3]. (b) Second, a significantly higher concordance rate for CP is seen in monozygotic twins when compared to dizygotic twin pairs [4]. (c) Third, the risk of CP in consanguineous families is approximately 2.5 times higher than in outbred families [5], pointing to possible autosomal recessive genetic factors underlying CP. Lastly, siblings of CP patients have an increased risk of other neurodevelopmental conditions such as ID, ASD, ADHD, epilepsy and schizophrenia, even in the absence of CP [6]. All these findings show that genetic factors may contribute to the occurrence of CP and/or NDDs in sibs.

Apart from the *epidemiological* evidence in sibs of CP patients, further evidence comes from the significantly higher prevalence of congenital anomalies in individuals with CP as compared to the general population (12–32% vs. 2–3%) [7]. Most are cerebral malformations, including hydrocephaly and schizencephaly, but the prevalence of noncerebral malformations such as cardiac, musculoskeletal, urogenital abnormalities and dysmorphisms is also higher [8]. This strong association supports a role for genetic contributing factors, although an additional contribution of environmental factors such as congenital infection, malnutrition and/or teratogens may also be present [8] (see Chap. 10).

7.3 CP Can Be of Genetic Origin—Methods to Detect Genetic Causes

A '*genetic cause* of CP' refers to one major genetic factor that in itself can cause CP in a patient. We distinguish two of those major genetic factors, namely the chromosomal abnormalities, causing a numerical or structural alteration of a chromosome, and the monogenic disorders, caused by alterations in the nucleotide sequence of one gene (see Chap. 5). An overview of the organisation of genetic structures is depicted in Fig. 7.1.

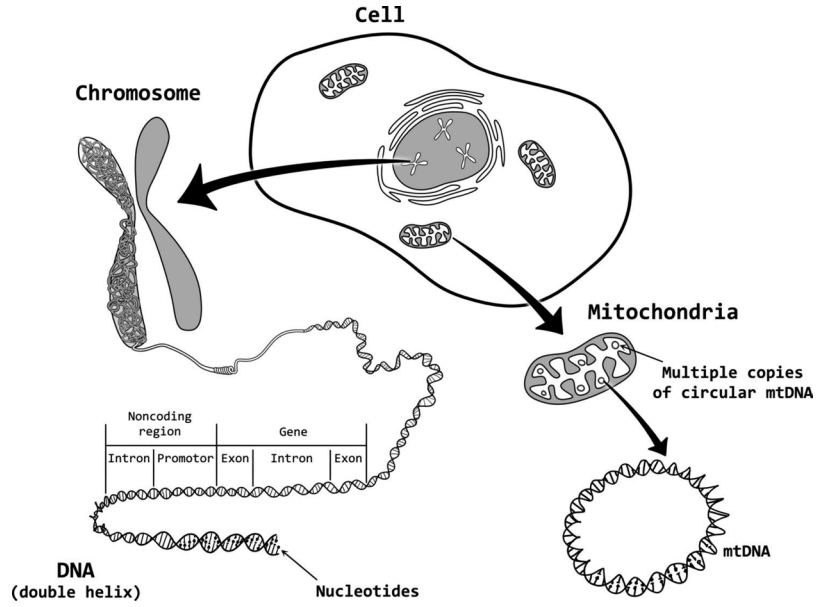


Fig. 7.1 An overview of the organisation of genetic structures (i.a. chromosomes, DNA, genes, exons, introns, nucleotides, mitochondria and mtDNA)

7.3.1 Detection of Chromosomal Abnormalities

Historically, microscopic cytogenetic analysis by *karyotyping* with G-banding was used to detect chromosomal abnormalities. This analysis allows the detection of subchromosomal deletions and duplications as well as balanced rearrangements including translocations and inversions with a resolution of at best 5 Mb [9]. Most disease-causing subchromosomal abnormalities in the context of CP however are cryptic, meaning they are too small to be detected by *karyotyping*; these cryptic aberrations are collectively called copy number variations (CNVs) or microdeletions/-duplications and can be as small as 1 kb. *Molecular* techniques to detect those aberrations are chromosomal microarray (CMA), with a resolution of approximately 50–200 kb [10], and more recently low-pass genome sequencing (also called shallow whole genome sequencing or *sWGS*), with a resolution that varies depending on the depth of sequencing, but is classically in the same range as CMA.

7.3.2 Detection of Nucleotide Sequence Alterations

Detection of alterations at the basepair level, single nucleotide variations (*SNVs*) or small insertions/deletions, needs a different approach. At *first*, starting from the 1990s, Sanger sequencing of single genes was applied, but this technique has been largely abrogated as a first-tier strategy and replaced by next generation sequencing. This latter *technology* enables the massive parallel sequencing of a panel of genes, of all protein-coding genes (collectively known as the *exome*, hence whole exome sequencing (ES) or even of the entirety of the genome (whole genome sequencing (GS) of several patients at the same time. *Nowadays*, many genetic labs have implemented ES in routine diagnostics, using a capture-based method to select only the protein-coding regions of the genome (Table 7.1).

Despite the a priori filtering out of 99% of the genome, the number of variants detected with ES in any given patient is still too high (*approximately* 80,000). A number of different criteria are utilised

Table 7.1 Diagnostic genetic testing methodologies. (Adapted from Emrick and DiCarlo et al. [15])

Genetic test	Advantages	Disadvantages/limitations
Karyotype	Detection of – Trisomies including mosaicism – Large chromosomal abnormalities – Balanced chromosomal rearrangements – Ring chromosomes	– Low resolution (5–10 Mb), hence no detection of CNVs or SNVs
Chromosomal microarray (CMA)/ shallow whole genome sequencing (sWGS)	– Detection of microdeletions/-duplications – SNP array: Detection of regions of homozygosity and uniparental disomy	– CNVs smaller than ±100 kb are undetected – Misses balanced chromosomal rearrangements – Misses low-grade mosaicism
Single gene analysis/targeted small gene panel	– May have better, more even coverage than WES	– Limited number of genes
Exome sequencing (ES)	– Broad coverage of genes, no selection bias – Possibility of novel gene discovery	– VUS detection – Incidental finding detection – Suboptimal for CNV detection – No detection of repeat expansions, non-coding variants
Genome sequencing (GS)	– Broad coverage of genes, no selection bias – Possibility of novel gene discovery – Enables detection of CNVs, repeat expansions and non-coding variants	– VUS detection – Incidental finding detection – Challenging interpretation of non-coding variants
mtDNA analysis (sanger/RFLP)	– Specific for mtDNA genome	– VUS detection
Repeat expansion panels (SCA2/3/6/7)	– Correct identification of the expansion number	– Limited number of genes

SNP single nucleotide polymorphism, *VUS* variant of unknown significance

when filtering and ultimately classifying these variants. First, *variants* are filtered based on their presence in the genes of a virtual panel, a specific subset of genes related to a specific disorder—for example, when searching for the cause of CP in a patient, a variant causing a late-onset heart condition is not of interest. Second, variant frequency in control populations is taken into account: If a variant is present in healthy people at a certain frequency, it is less likely to cause disease. The cut-off varies according to the type of disease, e.g. age of onset, penetrance, severity but is generally set at 0.1% for dominant and 2% for recessive diseases.

The gnomAD database (https://gnomad.broadinstitute.org/) is commonly used as a reference database, as it contains data on hundreds of thousands of control individuals, both from *exome* and *genome* sequencing. Third, the variant needs to comply to the expected mode of inheritance: A disease can be dominant or recessive, depending on whether only one or both copies of the gene need to be defective in order to cause disease. In dominant NDDs, an important contribution of de novo variants—variants that are absent in both parents and occurred as a new event in the patient—has been appreciated [11]; indeed, if inherited, the parent would be expected to be affected as well. In order to easily discriminate de novo from parentally inherited variants, trio ES is advised, as a pairwise comparison of all detected variants can be made between patient and parental DNA. For *recessive disorders*, this same trio strategy enables detection of variants that are homozygous (both parents carry the same variant and transmitted it to their affected child), compound heterozygous, e.g. two variants in the same gene with biparental inheritance or hemizygous (one variant on the single X-chromosome in males).

Fourth, in silico prediction programs can be used to predict the functional consequences of the variant; there are a myriad of programs available, but those like CADD and Revel, that are meta-scores taking into account a lot of different parameters, are the most informative [11, 12]. Lastly, the presence of the variant or variants of the same type (e.g. nonsense, missense, …) in disease databases or disease-specific literature can help to assess the *pathogenicity* of a variant.

Utilising the above filtering steps, the number of variants of interest is decreased to on average 0–20 per patient. Those remaining variants are classified in five different categories according to *internationally* implemented criteria set by the American College of Medical Genetics [13], namely pathogenic, likely pathogenic, uncertain significance, likely benign and benign. The first two categories comprise variants that are respectively certain or highly suspected to cause disease, the latter two variants that are probably/certainly not disease-causing. Variants of uncertain significance (VUS) are variants for which information is insufficient to classify them with any certainty.

While ES has caused a surge in newly-identified monogenic disorders, the technique has its drawbacks. Technical limitations *include* the inability to detect small insertions or deletions with a size in between the resolution of ES and CMA/sWGS (roughly any variant between 100 bp and 100 kb), balanced rearrangements, non-coding variants, repeat expansions and *low-grade mosaicism*. The technique of GS can overcome most of these hurdles, but while it is slowly adopted in routine diagnostics in some countries, the high cost of both the sequencing and of the labour-intensive '*sifting*' through the entire genome looking for that one disease-causing variant currently prevent its large-scale implementation.

7.3.3 Detection of mtDNA Variants or Repeat Expansion Disorders

The standard analysis of the mitochondrial DNA consists of Sanger sequencing, followed by restriction fragment length polymorphism (*RFLP*) for quantification of heteroplasmy [14]. ES and GS are expected to replace these techniques, with the caveat that, in case of ES, the probe set needs to contain probes targeting the mtDNA, which is often not the case for commercial kits. A further *complicating* factor, regardless of the technique applied, are the varying levels of heteroplasmy of mtDNA variants in different tissues, warranting not only testing in blood, but also in other tissues, e.g. muscle or skin [14].

Another *group* of disorders warranting a separate analysis since they can be missed using ES are repeat expansions. Repeat expansion disorders should especially be suspected in cases of ataxic CP. This hurdle will be overcome by the use of GS, that will enable repeat expansion detection.

7.4 CP Is of Genetic Origin—Results of Genetic Studies in CP

7.4.1 CNVs in CP

The first reports of CNVs contributing to NDDs like ID and ASD date from the 1980s and 1990s of the *twentieth century*, with a sharp increase after the introduction of CMA. On the contrary, the interest in the contribution of CNVs to the aetiology of CP is much more recent. This is most likely attributed to the persistent misconception that CP is always caused by brain injury, trauma or prematurity [1], but convincing data from genetic studies now prove otherwise.

The first report of CNV analysis in a cohort of 50 CP cases was published in 2014 [16]. Rare CNVs (population frequency <1%) with a potential relevance to CP were identified in 10 cases, but none of them were de novo, calling into question their validity as CP-causing variants.

In 2015, the findings of CNV analysis in a cohort of 115 CP cases were published, with a detection of de novo CNVs in eight (7%) cases [17]. In three of these, multiple de novo CNVs were seen, indicative of complex chromosomal rearrangements. Two of the CNVs were associated with known syndromes, namely *Angelman*

syndrome and *Wolf-Hirschhorn* syndrome. Rare inherited CNVs affecting known clinically relevant loci were detected in an additional three cases (2.6%), leading to (likely) pathogenic CNVs in ~10% of cases.

Another report from 2015 demonstrated clinically significant pathogenic (n = 10) or likely pathogenic (n = 6) CNVs in 16 out of 52 CP cases (~31%), with a single CNV in 11 cases and multiple CNVs in the remainder of the cases. Of these, nine were de novo and seven inherited. Genes of interest located in the CNVs annotated as pathogenic included *TSC1*, *SPAST*, *MEF2C*, *WDR45* and *NKX2–1*. The high *diagnostic* yield was hypothesised to be the result of the stringent definition of cryptogenic CP, thereby excluding identifiable acquired causes [18], but could also be the result of an overinterpretation of pathogenicity of the inherited variants, like in the case of a paternally inherited *KANK1* deletion. This *deletion* was deemed pathogenic as an overlapping deletion was previously reported in a four-generation family presenting with congenital hypotonia evolving into spastic quadriplegia [19]. In this family, maternal imprinting of the gene was presumed to explain the paternal non-penetrance (see Chap. 12). However, this theory could not be corroborated in a subsequent case report [20] and an additional report on a de novo *KANK1* deletion in a patient with genetically proven Wolf-Hirschhorn syndrome spoke against the pathogenicity of *KANK1* deletions [17]. *Finally*, in 2020, small CNVs including *KANK1* were classified as likely benign based on a non-consisting phenotype, the absence of a phenotype in carrier parents and similar frequencies of the CNVs in affected cases versus controls [21].

A study performing CNV analysis in a subgroup op 97 cases with hemiplegic CP showed a de novo CNV in 7 (7.2%) of cases [22]. An additional 18 (18.6%) of cases presented with rare inherited CNVs affecting loci associated with known genomic disorders or neurodevelopmental or muscular risk genes; however, all were annotated as VUS since evidence of relevance of the CNV to CP could not be demonstrated.

A *comprehensive* review of CNVs reported in CP was provided by Friedman et al. in 2022 [2], it underscores the genetic heterogeneity of CP. Recurrent CNVs in CP are the common 22q11.2 deletion (OMIM #188400) [18, 23–25] and 22q11.2 duplication (#608363) [22, 25]. Other *chromosomal* hotspots are less evident and the number of CP-associated CNVs is vast. However, again, it has to be noted that association between the reported CNV and CP was not proven for all CNVs; examples are a case of steroid sulfatase deficiency and a case of Klinefelter syndrome reported by Zarrei et al. [22], which are unlikely to be the cause of CP in the respective patients. Even for some of the CNVs containing genes associated with NDDs, a definite link with the phenotype awaits confirmation. Still, the contribution of CNVs to the aetiology of CP is substantial, warranting CNV detection by CMA/sWGS or in exome/genome sequencing data in the genetic workup of CP (see Chap. 5).

7.4.2 Monogenic Causes of CP

Some incidental case reports describing metabolic and/or genetic findings in CP patients, often with *familial* recurrence, have been reported in the literature since the mid-1990s. These studies led to the identification of several monogenic causes of CP or CP-mimics, including neurometabolic disorders [26–31].

In 2004, a *homozygous* missense variant in the *GAD1* gene was reported in four patients from two different consanguineous Pakistani families presenting with CP, developmental delay, ID and epilepsy. *GAD1* codes for glutamate decarboxylase 1, an enzyme responsible for the production of the neurotransmitter gamma-aminobutyric acid from L-glutamic acid [32].

In 2005 and 2006, heterozygous *COL4A1* variants were detected in several families presenting with hereditary porencephaly secondary to cerebral hemorrhage, causing a CP phenotype with spastic hemiparesis [33, 34]. *COL4A1* encodes procollagen IV alpha-1, that together with procollagen IV alpha-2 (encoded by *COL4A2*) assembles to form a heterotrimeric helix that gives stability to (i.e. vascular) basement membranes. Not unexpectedly, heterozy-

gous pathogenic variants in *COL4A2* were later also reported to cause hereditary porencephaly and CP with hemiparesis [35].

In 2009, a homozygous splice variant in *AP4M1* was identified in five sibs from a Moroccan consanguineous family presenting with congenital spastic tetraplegia, severe ID and neuroaxonal degeneration with white matter loss. *AP4M1* is one of the four subunits of the adaptor protein complex 4 (AP4). Biallelic pathogenic variants in the genes encoding the other subunits, *AP4B1*, *AP4S1* and *AP4E1*, were later also reported to be associated with CP [36, 37]. Characteristic findings of these AP4 deficiency syndromes are early-onset developmental delay, moderate to severe ID, infantile hypotonia followed by spastic di- or tetraplegia, postnatal microcephaly, foot deformities and epilepsy [38]. The AP4 complex mediates protein trafficking from the trans-Golgi network to early and late endosomes. An important cargo is ATG9A, an inducer of autophagy. ATG9A mislocalisation and altered autophagy have been demonstrated to be hallmarks in the pathomechanism of AP4 deficiency [38, 39].

In 2013, a *homozygous* variant in *ADD3* was discovered in four sibs from a consanguineous Jordanian family presenting with variable ID, spastic di- or quadriplegia and ocular movement disorders. *ADD3* encodes gamma-adducin, part of the adducin family of proteins with an actin-capping function that modulates the fast-growing end of actin filaments and controls actin molecule length [40].

Reports on multigene studies focused on the detection of monogenic causes of CP, both in sporadic cases and cohorts, appeared starting from 2014 to 2015 [41–44].

The *first larger study* reporting on a cohort of 98 unselected CP trios was published in 2015. The study demonstrated a predicted deleterious variant in a known NDD-associated gene in six cases (6%; *TUBA1A* (n = 2), *SCN8A*, *KDM5C*, *L1CAM* and *PAK3*) of which four arose de novo and two were inherited. In *addition*, eight (8%) potentially pathogenic variants were reported in novel CP candidate genes (*AGAP1*, *JHDM1D*, *MAST1*, *NAA35*, *RFX2*, *WIPI2, CD99L2* and *TENM1*) [42]. The same year, Schnekenberg reported a small study in four ataxic CP cases; in three cases, a diagnosis was made using ES or a gene panel with de novo variants in *KCNC3*, *ITPR1* and *SPTBN2* [44].

As of 2018, reports were published describing genetic results in even larger CP cohorts using either a gene panel or single/trio ES [23, 45–53]. As a consequence, the number of CP-associated genes increased exponentially. One of the *largest studies* of that period included 1526 patients, among which 1345 patients in a retrospective cohort—mostly children who also had developmental delay and/or ID—with a diagnostic yield of 32.7%, and 181 patients in a health care-based (adult) cohort of whom 10.5% carried a (likely) pathogenic variant [23].

Very *recently*, two large meta-analysis were recently published. One *included* 11 studies describing ES results in a total of 2419 individuals together with five study cohorts comprising 294 cases in which CMA was performed [51]; the second *included* 13 studies describing ES results in a total of 2612 individuals with CP [54, 55]. In the cohorts from the first meta-analysis, an average 23% diagnostic yield from ES was obtained; CMA led to a diagnosis in 5% of CP patients. The *second* identified an even higher yield of 31.1%. Of note, these results reflect the genetic contribution to CP in high-income countries, while results in low-income countries might point to a larger contribution of environmental risk factors such as birth asphyxia and maternal infection [1].

A recent review by Van Eyk et al. identified 190 recurrent CP genes; Table 7.2 shows a subset of 11 of these genes in which (*likely*) pathogenic variants were reported in at least 20 CP individuals. Of *interest*, many of these genes are also part of other gene panels for e.g. *ID*, *autism* and *epilepsy*, effectively demonstrating that CP is part of a spectrum of neurodevelopmental disorders. Also, an overlap of these genes with gene panels for movement disorders was noted, including hereditary spastic paraplegia, ataxia and dystonia [1]. This is not unexpected, as a CP phenotype may reflect the earliest-onset phenotype in the clinical spectrum of these disorders.

Table 7.2 The most frequently mutated genes in CP cases. (Adapted from Van Eyk et al. [1])

Gene	Associated disease (OMIM number)	Inheritance mode	CP subtype
ATL1	Spastic paraplegia 3A, autosomal dominant (182600)	AD	Spastic diplegic, triplegic or quadriplegic
ATM	Ataxia-telangiectasia (208900)	AR	Ataxic, dyskinetic
CACNA1A	Developmental and epileptic encephalopathy 42 (617106)	AD	Ataxic, spastic hemiplegic
COL4A1	Brain small vessel disease with or without ocular anomalies (175780)	AD	Spastic hemiplegic, diplegic, quadriplegic or choreoathetoid
CTNNB1	Neurodevelopmental disorder with spastic diplegia and visual defects (615075)	AD	Spastic diplegic, dystonic
GNAO1	Neurodevelopmental disorder with involuntary movements	AD	Variable and mixed; dyskinetic, dystonic, spastic hemi/quadriparesis
KCNQ2	Developmental and epileptic encephalopathy 7 (613720)	AD	Dystonic quadriparesis
PAFAH1B1 (LIS1)	Lissencephaly 1 (6074432)	AD	Spastic quadriparesis
SPAST	Spastic paraplegia 4, autosomal dominant (182601)	AD	Dystonic, spastic diplegic
SPR	Dopa-responsive dystonia owing to sepiapterine reductase deficiency (612716)	AR	Hypotonic, dystonic
TUBB4A	Hypomyelinating leukodystrophy (612438)	AD	Spastic dystonic diplegia, dystonic

AD autosomal dominant, *AR* autosomal recessive
For each of these genes, at least 20 individuals with CP have been reported with a pathogenic or likely pathogenic variant

No large studies have been performed on the contribution of *mtDNA mutations* or repeat expansion disorders to CP. However, case reports indicate that mtDNA variants can give rise to a CP phenotype [28, 56, 57]. Furthermore, cases of ataxic CP-mimics have sporadically been reported in several autosomal dominant spinocerebellar ataxias caused by extreme repeat expansions (SCA2, SCA3, SCA6, SCA7) [58–62]. These disorders should therefore be considered in ES negative cases.

Based on current knowledge, we propose a genetic testing strategy in individuals with CP that is depicted in Fig. 7.2. ES, preferably including CNV analysis and in trio, would be the first-tier test of choice, focusing on de novo and recessive variants (in case of non-affected parents) within a panel of CP genes. In the absence of a diagnosis, CMA/sWGS is the next step, especially if the CNV detection in the ES data is not performant. *Additional*, case-based testing can be considered, including mtDNA sequencing and repeat expansion testing (SCA2/3/6/7) in case of ataxic CP. In the absence of a diagnosis, a

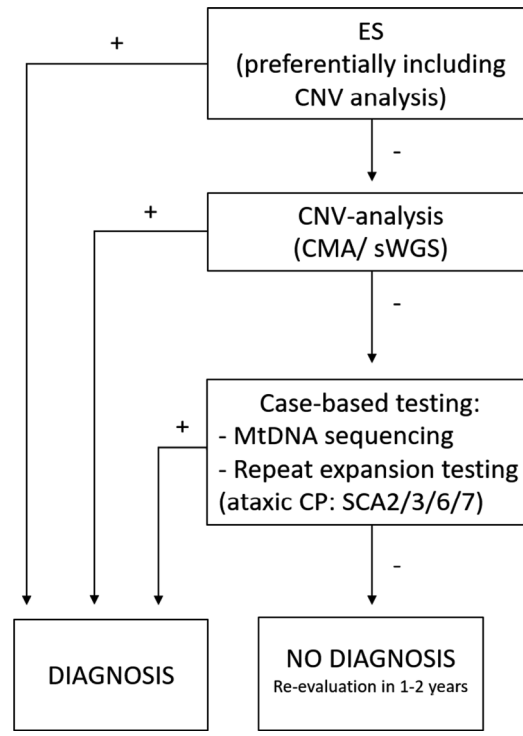


Fig. 7.2 Testing strategy in CP. +, *pathogenic* variant detected; – *no pathogenic* variant detected

re-evaluation of the genetic data is recommended after 2 years, but earlier re-evaluation can be considered in urgent situations, e.g. pregnancy of a mother with a previously affected child or sudden changes in clinical findings in the index case.

7.5 CP Is of Genetic Origin in Your Patient—Relevance of a Genetic Diagnosis

Although recent insights underscore an important genetic contribution to CP aetiology, in many healthcare systems genetic testing is still not part of the routine diagnostic work-up of CP. However, detection of a genetic *aetiology* of CP is not only paramount to the patient him/herself, but also to his/her family and even to the society.

First, a genetic *diagnosis* ends the diagnostic *odyssey* for the parents of a CP patient, avoiding any further unnecessary and invasive investigations that are time- and money-consuming and can put a high burden on a family. *Second*, more detailed understanding on the phenotype and the natural course of the condition enables optimisation of patient management and was shown to improve overall well-being of families [63]. Moreover, for a subset of individuals, specific treatment targeting pathophysiology might become available, especially for neurometabolic disorders associated with CP mimics [2]. These targeted therapeutic options and/or early intervention may improve long-term outcomes and disease severity, not only lowering the financial burden for the families, but also for the society as a whole [1]. Fourth, the detection of an underlying genetic cause of CP has important consequences regarding family planning. *Historically*, with oxygen deprivation due to environmental factors long thought to be a major contributor, the recurrence risk was estimated to be low, but the ever-growing importance of genetics slowly but surely changes this perception.

Indeed, apart from an important contribution of de novo variants, autosomal recessive, X-linked and even autosomal dominant inheritance are also seen in CP. For de novo variants, the recurrence risk is low (~1% due to potential germline mosaicism), but it goes up to 50% in case of autosomal dominant inheritance. To complete the picture, rare somatic variants (with no increased recurrence risk) and mitochondrial inheritance (with an even higher recurrence risk) have been reported [1].

Since most CP patients are isolated cases, the increased recurrence risk can only be appreciated after genetic analysis. Once the *genetic defect* has been established, appropriate genetic counselling in families of CP patients can be provided by a clinical geneticist or genetic counsellor. Invasive *prenatal testing* on a chorion villus biopsy or amniocentesis is the test of choice in case of a low recurrence risk. In case of a recurrence risk of at least 25%, some health care systems offer preimplantation genetic testing (PGT) as an alternative in, in which genetic testing is performed on 3–5 days old embryos obtained after in vitro fertilisation.

Of note, an international discussion was held on whether a genetic diagnosis should alter the diagnosis of CP. The current *consensus* states that when a genetic diagnosis of a chromosomal abnormality or syndrome is made, the CP diagnosis should remain if the child meets the clinical criteria for CP, with the syndrome or genetic abnormality recorded [1]. This is not only a semantic discussion, but is truly of relevance to the patients and their families. For example, in many countries a CP diagnosis leads to eligibility for governmental support and follow-up in multidisciplinary teams [64].

7.6 Future Perspectives

Although current data point to an important contribution of monogenic causes to CP with a diagnostic yield with state-of-the-art testing strategies of around 30%, the majority of CP individuals remain genetically undiagnosed. This may be explained by the absence of a genetic aetiology, the presence of a variant in a gene that at the time of testing is not yet correlated to a CP of *NDD phenotype*, the presence of a '*cryptic*' variant in a CP-related gene that cannot be interpreted properly or is missed due to technical limitations or a

multifactorial aetiology of CP in which both environmental and combinations of more common, low-impact genetic factors play a role.

Van Eyk et al. [1] performed pathway analysis of the 190 recurrent CP genes they identified in their review of literature. Several *functional gene* clusters were identified including components and regulators of the tubulin cytoskeleton, regulators of cellular metabolism, cell-cell signalling molecules, regulators of intracellular transport, chromatin modifiers and genes with a key role in nervous system development [1]. These findings underscore that CP-associated pathways are diverse and that a better understanding of the mechanistic pathways that are dysregulated in CP *pathophysiology* is instrumental for two reasons. First, it facilitates the prioritisation of CP candidate genes, thereby accelerating the discovery of new CP genes. Second, it can provide us with clues for the identification of potential therapeutic targets.

From a technical perspective, improvement of diagnostic yield can be expected from the implementation of GS, as it overcomes several of the limitations of ES: It is more sensitive for the detection of *CNVs*, can pick up repeat expansions and allows the detection of non-coding variants. At present, GS is too expensive to be applied in routine diagnostics, both in sequencing cost and analysis cost—about a hundredfold of data needs to be stored and sifted out. However, both the cost of sequencing and data storage are expected to drop and with the advances of bioinformatics and artificial intelligence, the prioritisation of variants will keep on improving.

Lastly, transcriptomics, the study of the expression levels of mRNA in a cell population, is being implemented in the diagnostic approaches for NDDs [65]. By comparing outliers in gene expression as well as aberrant transcripts, 'cryptic' variants that were unidentified or overlooked using ES or GS approaches can be uncovered.

7.7 Conclusion

While cerebral palsy is a clinically descriptive term, research of the past decade has unequivocally proven that in many cases, it is a disorder with a genetic aetiology. A *genetic diagnosis* is crucial for both patients and their families. At the patient level, it contributes to a better understanding of the disorder and associated *comorbidities* and may facilitate early intervention; at the family level, it supports family planning by appropriate assessment of the recurrence risk and the possibility to offer *prenatal* diagnostics or preimplantation genetic testing for parents and/or the extended family. Up-and-coming developments in genetic medicine are expected to further boost the diagnostic yield in CP patients in the near future.

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8 Magnesium Sulfate for the Prevention of Cerebral Palsy

Dwight J. Rouse

Abstract

Four 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 three of these 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. Since the publication of that meta-analysis, an additional trial also found a lower rate of cerebral palsy with $MgSO_4$. The use of magnesium sulfate to prevent 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. All fields are reviewed in this chapter.

Keywords

Cerebral palsy · Magnesium sulfate

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 and 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, four large, randomized placebo-controlled trials of antenatal $MgSO_4$ for fetal neuroprotection have been completed, and their results are available. Separately and together, they demonstrate that $MgSO_4$ diminishes the risk of cerebral palsy among the survivors of early preterm birth (see Chap. 27).

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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-g intravenous bolus and then a constant infusion of 1 g/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 from 24 through 31 weeks' gestation were enrolled [4]. In this study, $MgSO_4$ was administered as a 6-g loading dose and then a constant infusion of 2 g/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 g 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].

More recently, Wolf et al. reported the results of their multicenter Danish study in which 560 women at risk for preterm delivery before 32 weeks of gestation were randomly allocated to a 5 g loading dose of $MgSO_4$ followed by a constant infusion of 1 g/h or placebo [7]. Moderate or severe cerebral palsy occurred less often in the children of women allocated to $MgSO_4$, 2.0% vs. 3.3% (adjusted odds ratio 0.61, 95% CI 0.23–1.65).

Secondary analysis of the BEAM trial provides reassurance as to the neonatal safety of magnesium sulfate when used for fetal neuroprotection. Johnson et al. [8] 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 [9], the American College of Obstetricians and Gynaecologists (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 31 weeks and 6 days be the upper gestational age limit for the use of magnesium sulfate for neuroprotection [10].

Gibbins et al. [11] 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 [12].

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 g of intravenous calcium gluconate should be administered and the $MgSO_4$ discontinued [13].

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Neurological Examination of the Newborn

9

Christos P. Panteliadis

Abstract

The neurological examination (NE) of the newborn is a basic criterion of its extrauterine life. Simultaneously, a station that will mark the future course of his life, both in terms of organically and development. The *neurological assessment* includes a detailed medical and pregnancy history, and a full neurological examination, such as evaluating motor and sensory function. Assessing the status of the cranial nerves; testing from primitive reflexes and atypical responses or other neurodevelopmental pathologies. A reexamination after 3–4 days is essential. NE can *help* to identify newborns with central and peripheral nervous system involvement and accurate knowledge of the newborn's gestational age is important. This *chapter* described particularly the newborn neurological examination and his future.

Keywords

Newborn examination · Primitive reflexes · Milestones · Neurological examination · Neurodevelopmental

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9.1 Introduction

Primitive reflexes are *automatisms* that are usually triggered by an external stimulus. Most primitive reflexes begin to occur in utero through the early months of the child's postnatal life and is the notion of age-specific repertoire of neural functions. These *automatic* responses that are measured in terms of timing, strength, and symmetry and indicate how the signals are (a) sent from the brain to the spinal cord and (b) outward to individual muscles of the face, neck, torso, and extremities that are involved in postural control and movement. Some reflexes (e.g., *rooting, sucking*, and *grasp*) have survival value. Placing and stepping reflexes usually disappear by 2 months. Moro, grasp reflexes, and the ATNR usually disappear by 5 months [1] (see below).

Although in the last 40 years, various methods of evaluation have been suggested for the *neurological* and *neurodevelopmental* assessment of the newborn. The assistance of different neuroinvestigations, such as ultrasound, computed tomography, magnetic resonance imaging, and electroencephalography has greatly contributed to the correct assessment and prognosis.

The *neonatal examination* consisted of assessment of posture, extremity and axial tone, deep tendon reflexes, pathologic reflexes, primitive reflexes, symmetry, oromotor function, cranial nerve function, auditory and visual responses [1]; delay in the acquisition of psychomotor developmental mile-tones and behavior. Muscle tone is

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usually defined as the resistance to passive movement (see Chap. 21). Muscle tone is most easily shown as movement of an extremity but certainly including the trunk, neck, back and the shoulder, and pelvic girdles. *Premature* infants, whose neonatal neurodevelopmental examination results were abnormal, had significantly higher incidences of both cerebral palsy.

9.2 Historical Review

According to *historical* documents, Hippocrates (460–390 B.C), in his work of the eighth month fetus, already referred to associations between prematurity, congenital infections, and perinatal stress in ancient Greek times. He was the first to point out that pregnant women who have fever or lose too much weight, without any obvious cause, go through difficult and dangerous births [2, 3] (see Chap. 1).

In early Byzantine times, *Soranos* of Ephesus (98–138 A.D), active in Alexandria and Rome, published a four-volume work *On the Woman*, in which he also discussed the assessment of the newborn and used a kind of score that was very similar to the later one by Virginia Apgar [4–6]. In *addition* to the five parameters comparable to the Apgar score, Soranos also provided guidelines beyond the newborn age. Thus, Soranos and Apgar worked on a method to assess the postpartum condition of the newborn more than eighteen centuries apart [3, 4]. The Moro reflex was first described by Ernst Moro in 1918 and the Ortolani Test (*dysplasia of the hip*) was first described in 1936 by an Italian pediatrician Marino Ortolani [7, 8]. The Landau reflex or radiopronator superius reflex (*eponyms* from Arnold Landau reflex) described this reaction. In 1923, Arnold Landau, a Prof. of anthropology, anatomy, and neurology, described first this reflex [9]. The Landau reflex is an indication, e.g., main of cerebral palsy or muscle weak-ness ad about 3–4 months onwards, until 6 months of life [10]. After 1918, other reflexes were developed whose names are not known. But also from our own experience in the years after 1966 in developmental screening of newborns, we also applied our own experience in screening of newborns.

In 1953, the *anesthesiologist* Virginia Apgar developed a *simple score* that could quantitatively describe the vital parameters of the newborn after birth and which has remained current to this day [6]. At that time, it was believed that this score could provide a prognosis for cerebral health, which is now only partially true. However, the *Apgar Score* significantly increased attention to the condition of the newborn child. In 1958, Apgar published a second report [11]. This scoring system provided a standardized assessment for infants after delivery and comprises 5 components: (1) color, (2) heart rate, (3) reflexes, (4) muscle tone, and (5) respiration. *Historically*, at the beginning of the twentieth century, various scientists of this time discussed the importance of *primitive* reflexes for the life of newborns [12–14].

From the mid-1950s, Erich Saling in Berlin developed further methods for assessing the condition of the child during birth [15]. The *pH measurement* from the blood of the preceding part of the fetus opened up the possibility of early diagnosis of fetal acidosis and thus a threat to the child. The sum of these works from the 1950s and early 1960s was laid down by Saling in his book *The Child in the Field of Obstetrics* in 1966, which initiated a departure in the field of birth medicine and led to the establishment of the subject '*Perinatal Medicine*' [16]. In 1968, Victor Dubowitz reported the description of a floppy infant (*generalized hypotonia*) in newborn, based on clinical examination and thus is a clinical diagnosis. The causes are diverse, such CNS involvement, genetic, and metabolic ([17] see Dubowitz).

9.3 Definitions and General Aspects

The neurological examination (NE) of the newborn is a basic *criterion* of its extrauterine life. Simultaneously a station that will mark the future course of his life, both in terms of organically and development.

The neurological *assessment* includes a detailed medical and pregnancy history, a *full* neuro-logical examination, and an *evaluation* of motor and sen-

sory function. This neurological evaluation presents a high diagnostic predictive value that should guide the etiological investigation.

Assessing the status of the cranial nerves, testing from primitive reflexes, developmental milestones, and atypical responses to further any developmental pathologies. A *re-examination* after 3–4 days is essential. According to knowledge based on my long experience in neonatal and intensive care, the neurological *examination* of the newborn includes a detailed medical history, drug history, social and family history, a full neurological inquiry, and special investigations. The neurological findings (*clinical, laboratory*) depend on the maturity of the CNS and therefore an accurate knowledge of the newborn's gestational age is important. Observing neonates, especially those who are in the *intensive care* unit, gives invaluable information similar to that obtained from observing older children. The assistance of different neuro-investigations, such as ultrasound, CT, MRI, fMRI, EEG has greatly contributed to the correct assessment and prognosis (see Chaps. 13, 15, and 16).

A *newborn* will collaborate better after being fed when the room is quiet and adequately warm, and when sure *movements* in undressing and examining are very gentle. The way the neonate lies and moves gives us *indirect* information about his muscular tone and power. Muscle tone is usually defined as the resistance to passive movement. Muscle tone is most easily shown as movement of an extremity but certainly including the trunk, neck, back and the shoulder, and pelvic girdles (see Chap. 21). The head is observed for size and shape and the face for asymmetries and stigmata. *Spontaneous* movements of the face and extremities are observed for amplitude, symmetry, fluency, and coordination. The *examination* includes control of *cranial* nerves, eyes (*mydriasis*, *meiosis*), *muscle tone* (*postural tone*, *hypotonia*, *hypertonia*), *early* automated responses, *primitive* reflexes, and *sensory* examination.

During the past 40 years, research in developmental neurology has provided a number of *new methods* for the functional development of the human nervous system, clinical neurophysiology, genetics, and neuroimaging. An *early* decision can be made about early intervention and the optimal time for this operation. Most importantly, it enables reliable selection of those infants who need intervention. The *clinical* relevance of the qualitative assessment of *GMs* is beyond doubt. The nine tests have tremendous overlap (see below).

9.4 Clinical and Neurological Examination

The first examination of the newborn is carried out by a *neonatologist*, or a *trained* pediatrician or qualified obstetrician immediately after the birth, usually within the first half hour, either still in the delivery room or in the newborn ward. He *informs* himself about the course of pregnancy and delivery, examines the newborn (NE) taking into account skin color, motility, muscle tone, and recognizable malformations, checks heart, lungs, and breathing, and arranges for a NE screening [18, 19]. *In addition*, body length, weight, and head circumference are measured. In the case of complicated pregnancy, premature birth, cesarean section, or expected birth problems, the neonatologist is already present at the delivery.

The clinical-neurological examination by a neonatologist or neuropedia-trician experienced in this regard, *includes* a detailed medical history, a general neurological assessment, and specific tests for newborns. The *examination* should ideally be conducted between two meals in a quiet room at a neutral temperature and while the newborn is in a calm awake state. The traditional assessment includes spontaneous posture and movement, primitive reflexes, muscle tone examination, inspection of skin color, head circumference, vigilance and arousability, positional reactions, genitalia, and joint mobility (*concerning* the hip with the Ortolani test or better ultrasound) [8, 18, 19, 20]:

- Spontaneous posture and movement.
- Examination of muscle tone.
- Inspection of skin color.
- Head circumference.
- Vigilance and arousability.

- Positional reactions.
- Genitalia.
- Joint mobility (concerning the hip with the Ortolani test or better ultrasound).

Special importance is also given to the examination of the so-called *primitive* or *newborn reflexes*. The neuronal development and myelination of the spinal cord and the bridge are completed by birth [1] (see Chap. 4). This allows the newborn to respond to external stimuli with spinal reflexes and simple fixed motor programs. With *increasing* maturation of the *frontal lobe* and the *cortico-strial* system (supplementary motor cortex—putamen—thalamus) in the first year of life, these stereotypical stimulus responses are then increasingly modified or completely suppressed by voluntary motor skills (see Chaps. 4 and 10). However, as a result of pre- and postnatal damage to the frontal lobe and the corticostrial system, these primitive or newborn reflexes may persist or reappear.

Most of these newborn reflexes appear sequentially and can be triggered over individual time periods. They are *stereotypical*, involuntary, characteristic reactions of the newborn and infant, which can be triggered by exogenous stimuli. These *reactions* include, for example: the Moro, Stepping, Climbing, Hand and foot Grasp reflex, the rooting, Suck-swallow, Glabella, Galant reflex, the Asymmetrical Tonic Neck Reflex (ATNR), the Symmetrical Tonic Neck Reflex (STNR), and the tonic labyrinthine reflex (TLR) [1] (Figs. 9.1, 9.2, and 9.3). For *example*, if the Moro reflex can only be triggered on one side, this may indicate an upper arm plexus paralysis or clavicle fracture on the opposite side. *Other* examples are the Grasp reflexes. Palmar grasp reflex and plantar grasp reflex are primitive reflexes. Both reflexes have great diagnostic value as part of the newborn examination. In preterm newborns, these even appear between 25 and 30 of postconceptional age (Fig. 9.4). According to Futagi et al. (2012), the *absence* of palmar grasp reflex or persistence of the reflex beyond about

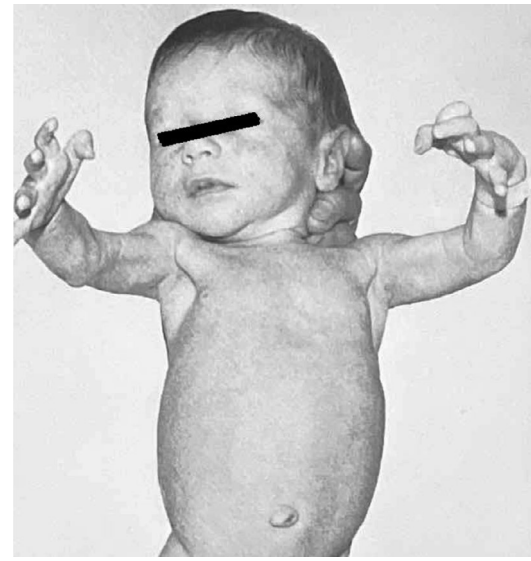


Fig. 9.1 Moro reflex



Fig 9.2 Step reflex



Fig. 9.3 Climbing reflex



Fig. 9.4 Palmar Grasp reflex

6 months is usually present in spastic cerebral. The plantar grasp reflex is also frequently a high sign of spasticity [1, 18]. Fenichel (1993), Blasco (1994), and Bax (1998) have extensively described the evaluation of primitive reflexes and their significance for predicting cerebral palsy [19–21].

As part of the neurological assessment, it is important to evaluate not only the absence of certain reflexes and reactions, but also their *persistence* or *reappearance* after the normal period; both are to be considered pathological. Thus, a persistence of the ATNR after the Sixth- to seventh-month of life indicates a possible organic brain damage. Indeed, these screening examinations are important and indispensable tools for the neuropediatrician to obtain early information about the maturation of higher cortical networks, brainstem, and spinal cord functions [1, 19–21]. The *Landau* reflex reaction in full-term and preterm infants usually appears after the third- to fourth-month of life to control of muscle tone. An absence of the response in infants over this age is an indication of a disturbance in muscle tone, CP, or other signs of motor neuron [10] (Figs. 9.5 and 9.6).

An assessment of visual ability in the first days of life is also significant: The newborn reacts in a calm awake state to an optical stimulus (e.g., *by a light source*) with a head turn towards the stimulus. Since 2009, every newborn has been entitled to a hearing screening in the first days of life. This can be done *clinically* by assessing the reaction to adequate noises or better and

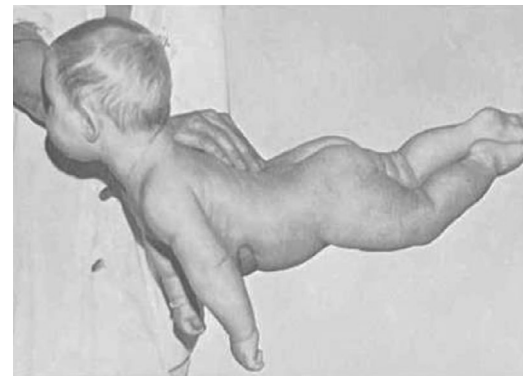


Fig. 9.5 Landau reaction, Reflex 1



Fig. 9.6 Landau Reaction, Reflex 2

more objectively by measuring the otoacoustic emissions (see Chap. 11).

Over the last 20 years, various other screening tests, developmental and neurological examination methods have been developed (see Chap. 11). In the years 2005/08, Bodensteiner et al. and Mercuri et al. [22–24] reported their experiences with a test consisting of standardizable parameters for the routine neurological examination of newborns, with an assessment of:

- Posture.
- Traction at arm and foot (as a test for extensor—or flexor tone).
- Head control.
- Ventral suspension.
- Moro-reaction.
- Tremor and startles.
- Spontaneous movements.
- Acoustic and optical orientation.
- Alertness.

With this *method*, both central and peripheral disorders of the nervous system can be detected early. In 2005, Dubowitz et al. [23] described again and emphasized the importance of the neurological examination of the newborn and the clinical signs with accuracy. NE is a guide to differentiate infants with peripheral neuromuscular disorders from those with central nervous system involvement. The diagnosis can be identified as hypotonic on routine neonatal examination immediately after delivery. A reexamination of the newborn by a pediatrician neurologist can confirm the fest diagnosis. Our many years of experience with more thousands of newborn examinations in the gynecological clinics in Hamburg can confirm this.

The National Institute of Health and Clinical Excellence (NICE) in England published revised guidelines in 2008 for the management of mothers and their newborns in the first 6–8 weeks of life. The NICE *guidelines* precisely describe what to pay attention to in the postnatal period from a developmental neurological perspective in order to detect functional disorders in time and to act accordingly [25].

Prechtl developed a new qualitative and sensitive examination method, the *General* movement assessment as a paradigm for the screening of young infants [26] (see Chap. 11). Already from the eighth gestational week (*postmenstrual age*), the human embryo moves. These first spontaneous movements are lateral neck movements and/or simple Startles (*Startle reactions*) as well as complex *General Movements* (GM) [26]. The GM remain largely unchanged until the end of the second month of life after the due date, until the small-amplitude, elegant, and variable so-called fidgety movements appear all over the body in the third to fifth-month of life. The GM are diagnostically significant because they are complex, occur frequently, and last long enough for objective observation (see Chap. 11).

The *assessment* of GM opens a window for early identification of later developmental neurological diseases [24, 25]. A recent literature review describes a possible connection between a motor abnormality of the GMs in the first 5 months of life and a later diagnosed autism spectrum disorder or Rett syndrome. These children showed a high percentage of "poor *repertoire GMs*" in the first 2 months of life. Their *fidgety* movements were often judged as abnormal or missing. Further studies are needed to confirm the significance of GMs as prognostic markers in early infancy [27–29]. Cioni et al. (1997) described in a publication that the GMs should be added to traditional neurologic assessment, neuroimaging, and other tests of preterm infants for diagnostic and prognostic purposes [30]. Later, Scharf RJ et al. (2016) described that special care

is required when examining premature newborns or newborns taken care for in an incubator. Preterm birth (*corrected age*) is a leading cause of neurodevelopmental disabilities in children, and the degree of newborn examination is inversely correlated with gestational age at birth. Extremely preterm infants had poorer neurodevelopmental examination than children born at term [31].

According to Örtqvist et al. (2022), extremely preterm (EPT) birth is a major *risk factor* for neurodevelopmental impairments [32] (see Chap. 12). The Prechtl GMs, including the Motor Optimality Score-Revised (MOS-R), at 3 months corrected age for adverse neurodevelopmental outcome at the age of 12 years [26]. The Prechtl GMs, *can improve* early identification of long-term adverse neurodevelopmental outcomes at mid-school age in children born extremely preterm. Salandy et al. [33] in a recent publication describe exactly the benefits of a more accurate neurological examination of all newborns. Mayston et al. [34] in a last publication describe with accuracy "The Bobath Clinical Reasoning Framework (BCRF)." These *guidelines* are important for intervention and management programmes in infants with neurodevelopmental disorders. In a recent and detailed publication, they describe the neurological consequences of premature birth infants in subsequent brain development [35]. All *Figures* (year 1975) are from our Children Hospital Borgfelde/General Hospital St.Georg/Hamburg/Germany.

9.5 Conclusion

The neurological examination (NE) of the *newborn* is an easy and intelligent method and the first reflex in 1918 was Moro. Physical postnatal examination remains the standard for assessing the normal or abnormal function of the nervous system. NE describing clinical signs and can *help* to identify newborns with central and peripheral nervous system involvement, and accurate knowledge of the newborn's gestational age is important. An experienced examiner can rapidly perform this assessment and then exercise the best judgement in selecting laboratory investigations. The *assistance* of different neuroinvestigations, such as US, CT, MRI, and EEG have greatly contributed to the correct assessment and prognosis. The good *prenatal* follow-up and organization of neonatal intensive care units and obstetric clinics for early treatment is the main way to reduce the rates of cerebral palsy.

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Antenatal Factors and Ultrasound in Pregnancy and Cerebral Palsy

10

Michael E. Tsimis and Marcos Cordoba

Abstract

The chapter focuses on the antenatal factors which contribute to CP. There is accumulating evidence that various antenatal factors carry a predisposition for CP. As such, pregnancy is an ideal opportunity to assess foetal factors that elicit newborn outcomes. The *majority* of these factors are largely derived from sonographic assessment which we introduce where applicable. We begin by discussing the *history* of brain injury and CP. We then proceed to outline the various antenatal aetiologic factors of the term neonate focusing on hypoxic-ischaemic encephalopathy and its distinction from neonatal encephalopathy after which we will discuss ongoing investigations for prevention of these entities.

We will then shift gears and focus on entities that disproportionately affect preterm neonates such as respiratory distress syndrome, intraventricular haemorrhage and ischaemia. We then explore other aetiopathologies including perinatal infection, foetal growth restriction, multifoetal pregnancy, preeclampsia, congenital malformation, the role of the placenta and end with a discussion of placental metabolomics. A specific focus will be the inextricable link between antenatal sonographic assessment and obstetric clinical diagnosis of the aforementioned risk factors.

Keywords

Antenatal factors · Ultrasaund · Preclinical models

10.1 History

10.1.1 The Crossroads of Obstetrics and CP

The term *asphyxia neonatorum* was later utilized to be a proximal cause of cerebral palsy that was also linked to traumatic delivery. This engendered a false belief that intrapartum events caused the majority of neurologic anomalies. As a *corollary*, neonatal encephalopathy intrapartum period was characterized by an increase in the rates of caesarean section beginning in the 1970s, attempting to lower the incidence of CP. This assumption is fallacious as the CP rate has not changed in the last four decades [1].

The studies of Nelson and Ellenberg heralded investigations to determine the aetiopathogenesis of CP [2]. The *investigators* were first credited with definitive evidence that few neurologic disorders, including those that may cause CP, were

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caused by peripartum events. Their provocative conclusion was pivotal and shifted the conceptualization of CP as a complex process involving genetic, environmental, physiological and obstetric contributions.

10.2 Antenatal Aetiologic Factors

10.2.1 Hypoxic-Ischaemic Encephalopathy and Neonatal Encephalopathy

The work of Nelson and Ellenberg spurred international attention to delineate the extent of peripartum events causing neurologic injury and CP [3]. The American College of Obstetrics and Gynecology (ACOG), in conjunction with the American Academy of Pediatrics (AAP), convened a task force which published guidelines in 2003. In 2014 [4], a second task force updated the findings and defined the requisite causes of peripartum hypoxic-ischaemic encephalopathy (HIE) to distinguish them from aetiologies of neonatal encephalopathy (NE) (see Chaps. 9 and 15).

Firstly, they defined NE as a clinically derived syndrome of disturbed neurologic function in the earliest days of life for infants born at or beyond 35 weeks gestation, manifested by a suboptimal level of consciousness or seizures with associated difficulty initiating or maintaining respiration and depressed tone and reflexes. The 2014 Task Force also made clear that both proximal (occurring intrapartum) and distal (occurring at conception or antenatally) risk factors can contribute to NE, which can evolve to CP [4].

The *Task Force* did maintain focus on HIE and its direct contribution to NE using a multidimensional assessment. They subcategorized NE into mild, moderate and severe forms and concluded that of the various forms of CP, only the spastic quadriplegic form can originate from acute peripartum ischaemia [4]. *According* to the ACOG Task Force, findings consistent with acute *peripartum* or *intrapartum* event leading to HIE are summarized in Table 10.1 [4].

The role of *prevention* for NE in the term newborn has revolved around postnatally induced hypothermia therapy. Therapeutic hypothermia is applied in the first 6 h of life for neonates who meet specific clinical criteria including moderate to severe NE [5, 6]. The treatment strategy has been shown to prevent death and attenuate moderate to severe neurologic disability in term neonates and randomized controlled trials have shown improved outcomes in newborns born >36 weeks of gestation [5, 6]. Moreover, MRI imaging has shown a relative reduction in mean diffusivity abnormalities and fewer infarctions with therapeutic hypothermia [7].

Since the establishment of *hypothermia* therapy for a subset of term and near-term neonates, there has been interest in establishing adjunctive neuroprotectants to magnify the therapeutic benefit. Neonatal erythropoietin (EPO) has been investigated as a novel treatment to reduce the burden of brain injury in this cohort but the results appear mixed. While initially Fauchère et al. [8, 9] showed no difference in short-term outcomes in very preterm infants, Malla et al. [9, 10] showed that EPO monotherapy reduces the risk of death or disability in term neonates with moderate to severe encephalopathy. More *recently*, the preclinical data from the High Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) trial has shown that a high dose EPO

Table 10.1 Neonatal findings, type and timing of risk factors

Neonatal findings
Apgar score: <5 and 5 and 10 min
Umbilical arterial acidaemia: pH < 7 and/or base deficit ≥12
Neuroimaging evidence of acute brain injury (MRI between 24–96 h of life)
Multisystem involvement consistent with HIE (i.e. renal, GI, hepatic or cardiac injury)
Type and timing of risk factors
Sentinel hypoxic or ischaemic event occurring before or during delivery (e.g. uterine rupture, placental abruption, cord prolapse)
Foetal heart rate monitor patterns consistent with acute peripartum event

regimen in conjunction with therapeutic hypothermia provides additional reduction in neurodevelopmental disability in neonates with moderate to severe HIE [9, 10].

A *multicentre* trial investigating the beneficial effects of maternal allopurinol treatment during acute periods of foetal hypoxia are at best, mixed. The results showed no difference in the umbilical cord levels of a tissue-specific biomarker for brain damage in the treatment cohort. Post hoc *analysis* within the treatment group revealed that only neonatal girls had lower levels of neuroketal levels, which is associated with reduced white matter damage [11].

10.2.2 The Limits of Foetal Viability: Extreme Prematurity

The sustained advances of neonatal *intensive care* in the last half century have dramatically altered the threshold of foetal viability, or survival outside the womb, in developed countries. As a corollary, a neonate born at 22–23 weeks is the timepoint at which neonatal resuscitation can be offered. The *success* of such resuscitation is contingent not only upon gestational age but also foetal sex, foetal weight and the use of antenatal corticosteroid treatment preceding delivery. For example, a female neonate born at 23 weeks, weighing 500 g has a 43% chance of survival according to the NICHD Neonatal Research Network calculator.

The deeper understanding of foetal and neonatal *pathophysiology* has improved both the survival and the neurodevelopmental outcomes of very preterm neonates. However, the pace of improvement in CNS morbidity has lagged behind the strides in survival [12]. That same female infant born at 23 weeks has a 37–52% of moderate to severe neurodevelopmental impairment and a 9–15% of moderate to severe CP; the rate of moderate to severe CP in a male neonate with the same characteristics can be as high as 22%. The study of *neurodevelopmental* outcomes in preterm infants is a complex interplay of anatomic abnormalities and functional aberrations which are hard to align. The extent of neurodevelopmental delay can persist well into school age and long-term neurologic outcomes can be influenced by a variety of environmental factors. In *addition* to CP, preterm neonates are a higher risk of respiratory distress syndrome, intraventricular haemorrhage, periventricular leukomalacia, sepsis, necrotizing enterocolitis and retinopathy of prematurity (see Chap. 9).

10.2.3 Respiratory Distress Syndrome (RDS)

The most common complication that a preterm neonate can encounter is RDS. The developing bronchial tree cannot readily meet the oxygenation needs of the neonate, which predisposes to prolonged periods of hypoxia. This sustained period of hypoxia can result in CP (see Chap. 5).

10.2.4 Intraventricular Haemorrhage (IVH) and Periventricular Leukomalacia (PVL)

IVH is a process arising from the fragility of the capillary network supporting the perfusion of the germinal matrix, the ventricles and surrounding brain parenchyma. It is a pathologic process that is almost exclusively seen in preterm neonates, especially at less than 32 weeks. The *subependymal* germinal matrix provides a relatively poor support for developing blood vessels rendering them more susceptible to stasis, congestion and eventually, rupture. The latter is more likely in preterm neonates owing to the inability of primitive blood vessels to autoregulate, that is to constrict and dilate in response to pressure changes to maintain constant blood flow (see Chap. 4).

The *aetiopathogenesis* of IVH is multifactorial and can be influenced by factors such as: hypoxic-ischaemic events, carbon dioxide elevations, anatomical aberrations, blood pressure fluctuations, coagulopathy and genetics. The mechanism of preterm birth often involves infection, which upregulates endothelial activation, platelet adherence and thrombi [13] (see Chap. 7). The *sequela* of these insults causes damage to the germinal matrix and if severe enough, haemorrhage into the lateral ventricular (LV) space and ultimately, the brain parenchyma. The four

Grades (I–IV) of IVH first described by Papile and coworkers [14] is the most commonly utilized system to gauge the level of IVH severity and estimate prognosis.

- Grade I—haemorrhage limited to germinal matrix
- Grade II—intraventricular haemorrhage occupying <50% of LV volume
- Grade III—haemorrhage occupying >50% of LV usually causing LV dilation
- Grade IV—parenchymal extension of haemorrhage

Nearly half of IVH lesions show some level of neurologic aberrations and not surprisingly, severe IVH portends major neurodevelopmental impairment and higher odds for CP [15]. Moreover, Bassan and colleagues developed a scoring methodology for periventricular haemorrhagic infarction (*PVHI*), using transcranial sonographic characteristics [15, 16]. They consider PVHI on a spectrum of severity for anatomic brain abnormalities whose most severe form can lead to hydrocephalus and cystic damage of the surrounding brain parenchyma, termed periventricular leukomalacia (*PVL*) (see Chaps. 4 and 15). Secondary to the preterm neonate having minimal gliosis, the damaged areas of the developing brain as cystic areas affecting brain white matter. Survivors of PVHI show a 50–85% incidence of CP [17, 18]. In more recent studies, infants born ≤28 weeks, the rate of CP was twofold greater in infants with grade I and II haemorrhage and fivefold greater in the cohort with grade III and IV haemorrhage versus infants with no IVH [19] (see Chap. 4).

10.2.5 Ischaemia

The preterm newborn is more susceptible to brain ischaemia which can lead to PVL secondary to developing brain neuroanatomy, notably prior to 32 weeks gestation. The vascular supply for foetal brain perfusion relies on the development of two concurrent, yet distinct, systems. The *ventriculopedal* system enters the cerebral cortex, while the ventriculofugal reaches down to the ventricles before curving to flow outward (see Chaps. 4 and 9). The two systems are not connected and the resultant watershed region, through which the pyramidal tracts pass through, is more vulnerable to ischaemia. Any potential vascular insult to the developing fetus prior to 32 weeks would affect the watershed region first with subsequent damage to the pyramidal tracts, engendering *spastic diplegia*. After 32 weeks, blood flow is redirected towards the cortex so that a similar perturbation causing hypoxia at this gestational age will damage the cerebral cortex (see Chap. 5).

10.2.6 Perinatal Infection and Inflammation

Intrauterine infection and inflammation are known risk factors for subsequent brain damage. Maternal immune activation can lead to the foetal inflammatory response system mediated by pro-inflammatory cytokines. The downstream effects of this cascade predispose to preterm birth and brain anomalies including PVL and CP development [20] (see Chaps. 5 and 9).

10.3 Foetal Growth Restriction (FGR)

Foetal growth restriction occurring in utero can result from a plethora of factors including maternal, foetal and placental conditions. Its prevalence sits at 10% and has been implicated as a leading cause of foetal demise but also *postnatal* morbidity and mortality. The *most* recent statement from the Society for Maternal-Fetal Medicine defines FGR as an estimated foetal weight or abdominal circumference <10th percentile for gestational age using population-based fetal growth reference biometry via ultrasonographic measurements. The *initial management* upon identification has moved away from reflex serologic testing for congenital infections and leans more heavily on diagnostic genetic testing, most commonly, through amniocentesis to assess chromosomal number, microarray analysis and PCR assessment for CMV in otherwise unexplained FGR [20].

Subsequent management revolves around serial surveillance of foetal status with umbilical artery (UA) *Doppler* waveform. The waveform is derived from the foetal *cardiac cycle* which generates a systolic (S) and diastolic (D) wave for which a systolic to diastolic ratio (S/D) is calculated.

Most cases of severe FGR go through a predictable deterioration in which the S/D is elevated secondary to a decreased D wave which can then evolve to absent or reversed end-diastolic flow indicative of severe uteroplacental insufficiency. The *recommendation* to undertake delivery for any abnormal UA waveform is well-defined, 33–34 weeks for absent end-diastolic flow and 30–32 weeks for reversed end-diastolic flow (Fig. 10.1a–c). These are the timepoints whereby the benefit of delivery outweighs risk of continued in utero surveillance [20]. FGR is the third most common indication for preterm delivery behind preeclampsia and multifoetal pregnancy.

While data surrounding the surveillance and management of FGR evolves, there is a known

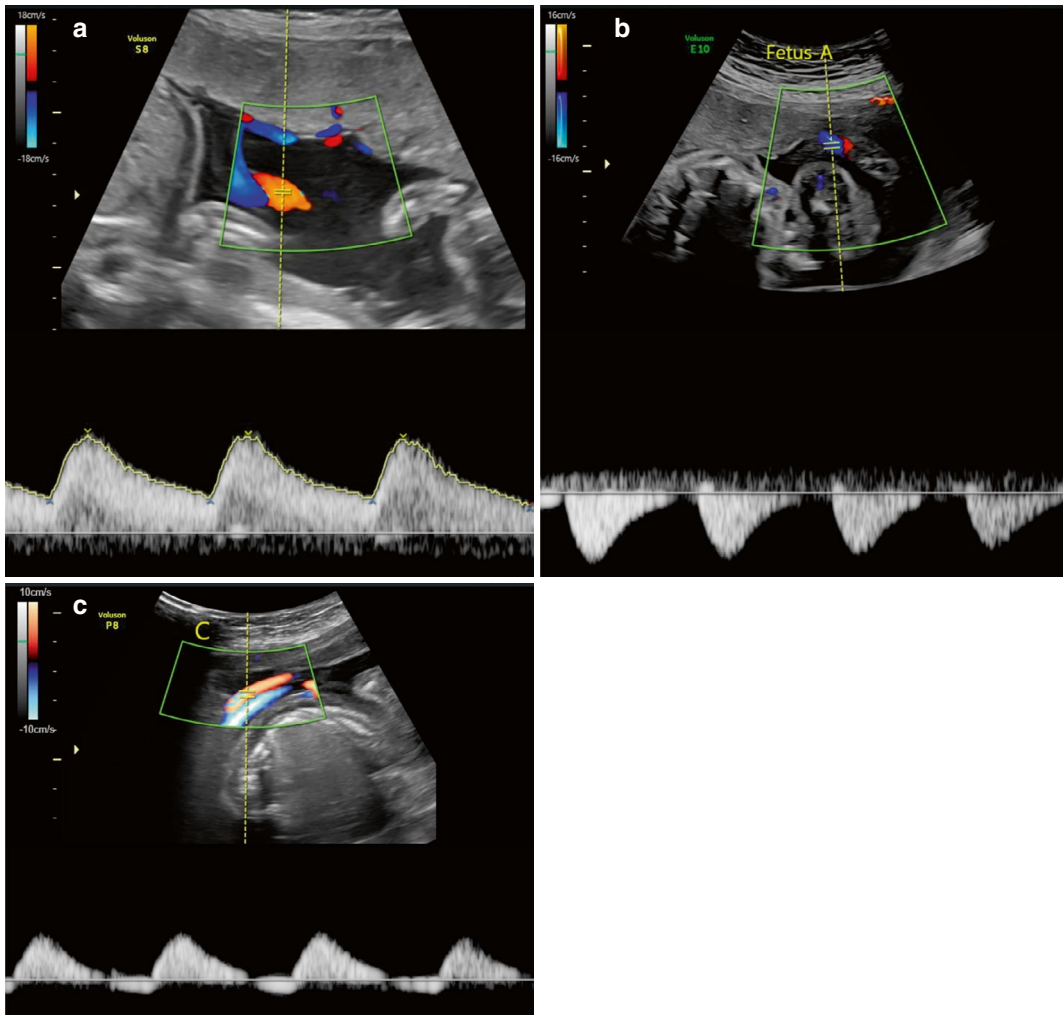


Fig. 10.1 (**a**) Normal forward flow of the umbilical artery. (**b**) Absent end diastolic flow of the umbilical artery in a set of monochorionic diamniotic twin gestation at 23 weeks with selective growth restriction of twin A. (**c**) Pregnancy at 23 5/7 weeks with reversed end diastolic flow of the umbilical artery in a monochorionic triamniotic triplet gestation and selective growth restriction of triplet C

association between FGR and CP development. DeJesus, et al. [21] set out to extrapolate if a cohort of small for gestational age (SGA) infants defined as birthweight <10th percentile, born <27 weeks were subject to increased risk for mortality, morbidity and poor neurodevelopment at 18–22 months corrected age. Poor neurodevelopment was defined as one of the following: moderate or severe CP, <70 on the *Bayley Scales* of Infant Development III, hearing loss or blindness. The 385 infants in the SGA cohort had higher mortality, postnatal growth failure and increased risk of neurodevelopmental impairment with an odds ratio (OR) of 3.91 after controlling for confounders. The *development* of moderate or severe CP had a 2.6-fold increased risk compared to non-SGA neonates [21]. Moreover, Blair and Nelson followed late preterm infants diagnosed with severe FGR and revealed that there was near fivefold increased risk of CP development [22]. Furthermore, in growth restricted singletons, a major birth defect was noted in just over half the cohort and this increased the odds of CP a staggering 30-fold.

10.4 Multifoetal Pregnancies

Multiple gestations have increased in prevalence since 1980 due to advances in obstetric care, in vitro fertilization, and increasing maternal age at pregnancy [24–26]. As many as 12 in 1000 twin births will be affected by CP, a risk at least four times greater than in singletons, and increases to an even greater extent in higher order gestations [23–26]. These significant associations are partly due to the substantially greater risk for multifoetal births to occur before 37 weeks and for neonates to weigh less than 2500 grams. US data reports that the percentage of singleton preterm births was 8.42% in 2020 versus 59.94% in twin gestations and 98.72% in triplet gestations [27] (see Chap. 5).

Multiple *gestations* are often accompanied by unique risk factors that are not typically present in singleton births. These include intrauterine or infant death of one co-twin, twin to twin transfusion syndrome and birthweight discordance [27]. Multifoetal pregnancies also experience a high incidence for neurodevelopmental disorders like CP [28, 29] (Fig. 10.2).

Though twins are disproportionately affected by *LBW* and *PTB*, several studies have confirmed that the greatest difference in CP rates for twins versus singletons exists among those of normal birthweight, suggesting that other risk factors aside from preterm birth and low birthweight are also at play [29]. Twins have a higher frequency of malformations and CP than singletons [30]. Indeed, among twin gestations, an affected twin with CP increases the risk by a factor of 15 that the other twin will have this syndrome as well [31]. The *prevalence* of CP in an Australian study [31] was 1.6, 7.3 and 28 per 1000 births in singletons, twins, and triplets, respectively. The authors also reported that in the case of co-twin death, the risk for CP increases by a factor of 8, from 12/1000 to 96/1000. The *explanation* for this observation was that the dissolving twin releases thromboplastin and emboli that may lead to brain injury of the surviving twin and subsequent development of CP.

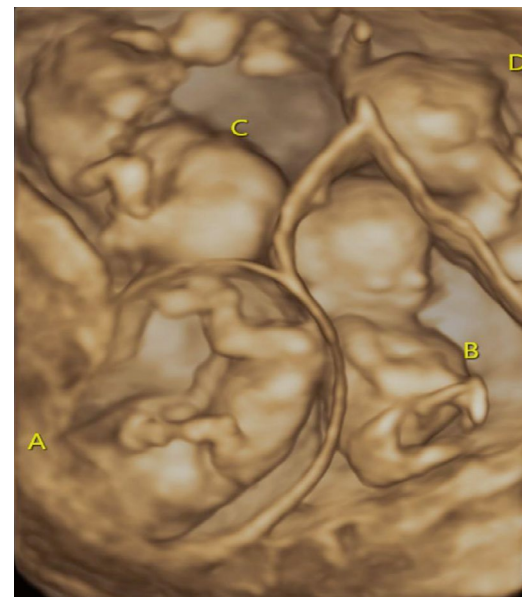


Fig. 10.2 3D rendering of a G4P1021 at 12 2/7 weeks with a quadrichorionic quadriamniotic gestation (**a**) foetus 1, (**b**) foetus 2, (**c**) foetus 3, (**d**) feotus 4

10.5 Preeclampsia

The association between preeclampsia and subsequent development of CP has been under constant debate. Recent studies suggested that *preeclampsia* may be an additional risk factor for the subsequent development of CP [32–34]. A Norwegian study reported that children born to mother with preeclampsia were more likely to experience CP than those delivered of normotensive women [33]. In another study, women with preeclampsia had a double rate of CP than did normotensive patients. Early onset preeclampsia and SGA neonates were independent risk factors for the subsequent development of CP, even after adjustment for gestational age at delivery. Infectious morbidity, prematurity complications and birth asphyxia were all independent risk factors for CP among neonates of women with preeclampsia that further implicated the role of a multi-hit model in the pathogenesis of CP [35]. These associations were not the case regarding preeclampsia at term [34, 35]. Women with early onset preeclampsia are at especially high risk for the development of this dire late sequela of the offspring. Moreover, the association of early-onset preeclampsia with cerebral palsy is independent of other risk factors, such as SGA and early gestational age at delivery. Counselling these patients must take this association into account.

10.6 Congenital Malformations

The association between congenital malformations and subsequent cerebral palsy (CP) is well documented. Major birth *defects* were the most frequently occurring risk factor in children with CP and when combined with foetal growth restriction, they were associated with the highest relative risk [36].

Congenital *microcephaly* is the most common birth defect in CP [31]. Other non-cerebral malformations were also frequently coexisting with CP, especially cardiac, urinary and musculoskeletal [37] (Fig. 10.3).

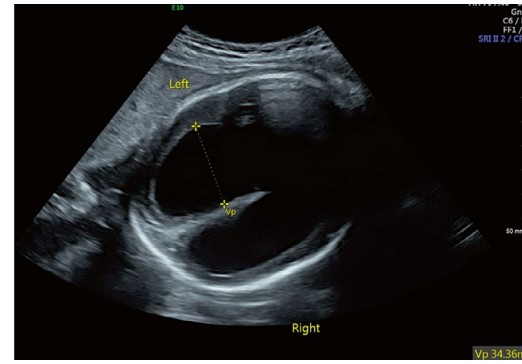


Fig. 10.3 Foetus at 27 4/7 weeks gestation with severe ventriculomegaly. Lateral ventricles measure approximately 34 mm. Foetus was diagnosed with aqueductal stenosis

Despite the multifactorial nature of CP, genetic causes have also been studied alongside congenital malformations and have implicated individual genes as causes of CP. Whole exome sequencing (*WES*) has opened new avenues for novel gene identification. Applying WES in large sets of families who have multiple members with various levels of intellectual disability, the ZC4H2 zinc-finger gene was uncovered as a cause of CP-related spasticity. *Further* animal model studies have shown that loss of function mutations of ZC4H2 gene produced reduced dendritic spine density and impaired central and peripheral synaptic plasticity which, phenotypically, presents as CP [38]. McMichael and colleagues showed that 14% of 200 cases of CP had a plausible disease-causing gene variant, half of which were novel genes [39]. These early investigations utilizing WES are emerging evidence that genetic aetiologies for CP are inevitably going to increase.

10.7 The Placenta

The placenta is a complex organ that links foetal and *maternal circulation*. Following the implantation of the ovum, the placental development follows and is largely influenced by the hormonal milieu of the uteroplacental interface. This unique interaction between foetal trophoblasts and mater-

nal endometrium creates the decidua. The steps involved in placental development include endometrial invasion, spiral artery modification and villus branching. The ability of the mother and fetus to coexist and be in constant communication is the result of immunologic modification, termed the '*immune-privileged state*'. The foetus is dependent on the placenta for pulmonary, hepatic and renal function. During gestation, the placenta modulates immune and endocrine responses and actively supports gas and nutrient exchange for the foetus utilizing the foetal capillary blood system [39]. Recognized histologic patterns of placental dysfunction continue to evolve. Based upon consensus diagnostic criteria, two main classes of histological placental lesions arise: the vascular processes and the placental inflammatory processes [40, 41]. Disorders in each class may occur in either acute or chronic phases.

Given the role of placental functioning in *neurodevelopment*, it is unsurprising that acute antenatal disruption can lead to clear sequelae on placental pathology and can subsequently be associated with subsequent neurological impairment [42]. Panteliadis and Troll [42] described the standard distribution of fatty acids in the total lipids of serum with *gaschromatographically* in the respective umbilical cord blood of 24 mothers, their newborn, and well as in 20 placentas. The *same* examinations were made with 30 newborn on the day of birth, 14 newborns, 22 young infants between 3 and 10 weeks old and 16 older infants between 4 and 12 months old. The *results* were compared and existing differences were discussed. It was further established that an advance towards the adult's fatty acid pattern already takes place at an age between 4 and 12 months.

Multiple large studies dating back to Nelson and Ellenberg's seminal study have been identified associations with CP for placental abruption [2, 3]. Tronnes and colleagues suggested 3.5 to 7.7-fold increased risk following placental abruption [41]. However, most children born following placental abruption do not develop CP and additional risk factors for CP have been identified within this high-risk cohort. Amongst children born following placental abruption, a large case-control study has suggested additional superimposed risk factors, *such* polyhydramnios, maternal hypertension, maternal use of ethanol, tobacco, or midodrine, and multiparity, while intravenous oxytocin and magnesium sulphate administration were found to be associated with a lower incidence of CP [45].

Multiple converging lines of evidence suggest that chronic placental insufficiency contributes to risk of CP. In the study by Simonazzi et al. [43], their cohort study suggested that severe placental insufficiency at 20–23 weeks gestation, defined by the abnormal UA Doppler and low foetal weight was associated with very preterm birth, low birth weight and neonatal death and other complications, including one child who developed CP.

10.8 Placental Metabolomics and Cerebral Palsy

Biological systems such as cells, tissue and whole organisms require a blueprint to direct information flow and to engender function. This flow goes from the genome with epigenome, to the transcriptome, to the proteome and finally to the metabolome. The 'omic' sciences study each step of this flow and thus, we have genomics, epigenomics, transcriptomics, proteomics and metabolomics [43]. This last branch studies metabolites, which inform the biological phenotype. The methodology uses analytical chemistry to study metabolites in a biological system. The two predominant platforms in metabolomics include nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) (see Chap. 14).

The placenta serves as the interface between the mother and foetus and recent research has focused on metabolomic profiling within this complex organ. In its infancy, the predominant characterization has occurred with placental ischaemic disease, the underlying pathophysiologic process in preeclampsia.

Additionally, placental metabolomic studies have shown links between amino acid metabolism and small for gestational age (SGA) and low birth weight (LBW) foetuses [44]. Troisi and colleagues [45] showed that placentas from SGA and LBW gestations were characterized by lower levels of

taurine, ethanolamine, beta hydroxybutyrate, glycine and higher levels of multiple amino acids, deoxyribose, erythritol, glycerophosphocholine and lactic acid. The findings carry high biological plausibility as these metabolites function at the foetoplacental interface and have been involved in the pathophysiology of foetal growth restriction and preeclampsia. In much the same way that metabolomics is utilized to study preeclampsia, it can look at the metabolites of the placenta to gain an understanding of CP. Disruption of vital placental functions can significantly impact foetal development, including the brain [46–48].

The *temporal* specificity of early pregnancy has been identified as a vulnerable period for neurodevelopmental disorders, and understanding the metabolic changes in the placenta during this period may provide insights into conditions such as CP [37]. Metabolomic profiling of CP brain tissue has revealed novel central biomarkers and biochemical pathways associated with the disease. Savasan et al. [49] were the first to report on the metabolomic profiling of post-mortem brain tissue from patients who died from CP. The *study aimed* to identify specific biomarkers and pathways that could provide insights into the underlying mechanisms of CP. The study found significant alterations in the metabolic profiles of CP brain tissue compared to control tissue. They discovered that the significantly perturbed pathways in CP samples were folate, propionate and androgen/oestrogen metabolism. These findings suggest dysregulation in quintessential metabolic pathways in the brains of individuals with CP. The *dysregulation* of these pathways may contribute to the pathogenesis of CP and provide potential targets for therapeutic interventions.

10.9 Conclusion

Placental metabolomics offers the *potential* to predict cerebral palsy by identifying metabolic shifts tied to foetal development issues and placental abnormalities. By examining the *placenta's* metabolic profile, scientists can more comprehensively understand the risk factors and root causes of cerebral palsy, paving the way for early diagnostic tools.

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Early Markers for Cerebral Palsy

11

Christa Einspieler, Peter B. Marschik, and Arend F. Bos

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 of *typical movements*, and 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, and 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. In *all* these fields, the early markers for CP are reviewed.

Keywords

Fidgety movements · General movements · Infant · Pattern recognition · Preterm age · Video analysis

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11.1 General

One of the most challenging tasks for paediatric healthcare professionals is to predict in *early* infancy what sort of development may 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 6–12 months old. During the last decade, evidence is accumulating that *early* interventions for children at risk for developing CP improve their functional abilities and skills later on [1]. The best results are

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achieved if *appropriate* interventions start early, that is before the age of 6–12 months [1, 2]. This makes it crucial to have tools that assess the risk of developing CP reliably within the first year [3]. Systematically reviewing the many existing tools in the literature has revealed that the General Movement Assessment (GMA), according to *Prechtl's* method, is the best tool for risk assessment of CP during the first year of life [3].

GMA has a history that lasts for more than 30 years. 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 [4]. 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 [5, 6]. They are the predominant motor pattern in awake infants aged 3–5 months [5, 7]. Infants develop typically if 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 [8].

11.2 The Absence of Fidgety Movements at the Age of 3–5 Months Marks CP

Various working 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, for example [3, 7, 9–13]. 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 [7]. Such high values can be achieved after a mere 3–4 days of extensive training [14]. Kappa values from 0.90 to 0.96 *demonstrate* the high interindividual consistency [15].

Already more than 15 years ago, a *Trondheim* work group has developed a software called General Movement Toolbox that provides assistance in identifying absent fidgety GMs in infants [16]. 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 [17]. More *recently*, developments in this area have broadened, introducing mobile solutions for GMA [18] and by developing more advanced tools based on machine learning and artificial intelligence [19–21]. It is expected that developments of additional tools, for example, pressure distribution analysis, may further improve the accuracy of computer-assisted GMA [22].

The mere *absence* of a particular motor pattern cannot predict the subtype or the severity of CP. Recently, it has been shown that a more *detailed* analysis of the whole motor repertoire of 3- to 5-month-old infants can provide deeper insight, particularly when using the motor optimality score revised version (MOS-R) [23]. Based on this *large* study and earlier smaller studies, several markers are associated with a lowered level of self-mobility at school age (assessed using the Gross Motor Function Classification System [GMFCS]):

- Cramped-synchronised movement character [24–27]
- Lower motor optimality score [23, 28]
- Repetitive opening and closing of the mouth [27]
- Abnormal finger postures [27]
- Monotonous kicking [24]
- Absence of fidgety movements [23–25, 27]

Mostly fidgety movements are absent or only sporadically present [27, 28] in all eventual subtypes of CP (Table 11.1), which indicates that it takes intact *cortico-spinal* fibres and normal outputs from the basal ganglia to generate normal

Table 11.1 Developmental trajectories with a high predictive power for typical 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 [29]. Fidgety movements are also absent in infants with genetic disorders, for example, **Rett** syndrome, whereby the infants with the most severe phenotypes show no fidgety movements when aged 3–5 months, while otherwise their development is found to be more or less normal [30].

Interestingly enough, some infants *diagnosed* later with CP have had normal fidgety movements around 3 months after term. In a large, worldwide sample of 468 children, all of whom were diagnosed with CP after 2 years, approximately 8% showed normal fidgety movements [23]. Among these children with normal fidgety movements, the CP was not severe (*mostly* GMFCS 1 or 2), and a majority of them had unilateral spastic CP. *Strikingly*, in the later unilateral CP children, a clear asymmetry of finger postures and segmental movements of the wrists was observed [23], underscoring the significance of assessing asymmetries of the wrists and fingers, also in infants with normal fidgety movements, particularly in cases of unilateral lesions on neuroimaging.

After *discovering* fidgety movements as an age-specific, distinct form of GMs, Prechtl [31] 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 motor, proprioceptive, and visual systems. This hypothesis is supported by the fact that fidgety movements emerge during the transformation of neural functions at 3 months of age [32] and *therefore* precede visual hand regard, the onset of intentional reaching and visually controlled manipulation of objects [31]. 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 [33]. Infants with a total loss of sight due to *retinopathy* of prematurity but without brain lesions 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 [34].

11.3 Consistently Present Cramped-Synchronised General Movements: A Predictor of Spastic CP at Preterm Age

In the late 1980s, *Prechtl* and his group demonstrated that foetuses and preterm infants moved differently if their nervous systems were impaired [35, 36]. 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 [7]. 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 [37]. 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 [38]. No *matter* how variable the movements, they always appear graceful and fluent in character.

While referring to *foetal* or 'preterm GMs' before term [39], we call them '*writhing movements'* from term until about 6–9 weeks post-term age [6]. The latter are characterised by a slower pace and a moderate amplitude [7]. When 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 [35]. 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 [25].

11.4 How Can We Identify a High Risk for Unilateral CP by Means of Observation?

Infants with a *future* unilateral spastic CP show abnormal (usually cramped-synchronised) GMs during term age; moreover, they mostly lack fidgety movements at 3–5 months post-term age [40]. 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 wrist, finger, ankle, and toe movements) are reduced or even absent [40, 41]. At this age, *neurological* examination, for example, 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 [42] (see Chaps. 1 and 9). 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 the absence of fidgety GMs. This *finding* is especially remarkable since nine of the infants had a persistent flare on the brain ultrasound without any 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 [42]. 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 and finger movements is at a high risk of developing unilateral CP [23, 43] (see Chap. 9).

In infants with *normal* fidgety movements and *asymmetrical* segmental and finger movements, the risk of developing unilateral CP is also increased, but the extent of this risk is as yet not known. In any case, it is *recommended* to follow-up these latter infants carefully, for example, checking whether asymmetries emerge or increase at 5 months and later, using the HINE [1, 3].

11.5 A Lack of Fidgety Movements Coinciding with Abnormal Arm Movements Is a Marker for Dyskinetic CP

Until the *second* month post-term, infants who later become *dyskinetic* display a so-called poor repertoire of GMs [44]: 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

[35]. Apart from the poor repertoire GMs, the infant moves his/her arms 'in circles', with spreading of the fingers [44]. *Characteristically*, these abnormal circular arm movements are present at least until 5 months. They are *uni-* or *bilateral*, monotonous, slow forward rotations originating in the shoulder. 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, such as particularly foot-to-foot contact, are another marker for *future* dyskinetic CP [23, 44] (see Chap. 12).

11.6 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 the HINE as an age-specific neurological assessment is even more effective in predicting the neurological outcome than the GMs assessment alone [45] (see Chaps. 1 and 9). As yet, assistive *technologies* and artificial intelligence to facilitate automated GMA do not play a prominent role in the clinical context to date. They may, *however*, prove essential for bringing the field scientifically forward and enhancing detection of high risk CP in infants now considered to be at low risk.

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 has a positive effect on the child's *functional* abilities in the future. *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 of Cerebral Palsy

12

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Abstract

Cerebral palsy (CP) is the most frequent motor disability in childhood, beginning early in development. The prevalence is declining and estimated to occur in about 1.6 per 1000 live births in high-income countries and higher in low- and middle-income countries. The motor *impairment* may be accompanied by disturbance of other functions, such as cognition, communication, sensation, perception, behaviour, and epilepsy. Multiple *aetiologies* result in brain injury that affects movement, posture, and balance. The evaluation of the child includes *differentiating* CP from progressive causes of neuromotor disability and spinal lesions; defining the musculoskeletal impairment and decide on ways of treatment; and identifying, evaluating, and addressing 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. More than half of the patients also have additional clinical problems, affecting activity and participation. The *present* chapter has been in all fields revised.

Keywords

Cerebral palsy · Classification · Child · Clinical evaluation · Spastic · Dyskinetic · Ataxic · Management

12.1 Introduction

The word *palsy* undoubtedly has its roots in ancient Greek. It is most likely derived from paresis (*πάρεση* in Greek), denoting weakness [1]. Cerebral palsy (CP) is the most frequent motor disability in childhood. The prevalence is declining in high-income countries and is now estimated at 1.6 per 1000 live births, while in low and middle-income countries the prevalence is probably 3–4 per 1000 live births [2]. The motor disorders of CP are often *accompanied* by disturbance of sensation, cognition, communication, perception, behaviour, and/or by a seizure disorder [3] and may be highly complex; they tend to become even more complicated in severely

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affected patients. The occurrence of associated impairments increases with gross motor severity in most CP types, while some impairments are specific for the type of lesion and clinical CP type. Archana et al. [4] found a prevalence of 26% for epilepsy in the studied population of children with CP. The *highest* incidence of seizures (30.4%) was found in children with spastic hemiplegia, and the extent of cortical injury correlated with the risk to develop epilepsy; 38% had focal epilepsies, 57% had generalised epilepsies, 6.3% had dyskinetic CP, and 3% had combined focal and generalised epilepsy.

The primary deficits *include* muscle tone abnormalities, influenced by position, posture, and movement; impairment of balance and coordination; decreased strength; and loss of selective motor control. Primitive reflexes, sustained to adult age, may interfere with motor function. With age, also fatigue may interfere with function [5]. *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. *Several* instruments have been developed to classify the gross motor function, manual ability, and commu nication skills of children and adolescents with CP.

12.2 Clinical Evaluation

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

- Certify the diagnosis and rule out other causes for the motor impairment such as progressive disorders 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. A 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, 11, and 17).

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 (see Chaps. 9 and 11) [6]. A standardised 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 [7, 8]. A recommended age for MRI is 2 years or more (see Chap. 13). A neuroimaging classification for the newborn child at risk for CP is also available at the European Academy of Childhood Disability's website (http://scpe.edu.eacd.org/scpe/reference-and-training-manual/rtm.php).

A careful *definition* of the accompanying impairments is of great importance. For children with an established diagnosis of CP, a 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 [9]. 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, primitive reflexes, balance, and equilibrium responses in standing position

12.2.1 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 (see Chap. 21). Hypertonia is an abnormally increased resistance to an externally imposed movement about a joint. Hypertonia may be caused by spasticity, dystonia, rigidity, or a 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 [10]. 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 [11]. It has been validated for detection of the changes in spasticity resulting from botulinum toxin. A treatment in a double-blind, randomised, controlled trial [12] (see Chap. 25).

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 by 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 et al. as a movement disorder in which involuntary sustained or intermittent muscle contraction causes twisting and repetitive movements, abnormal postures, or both [13], while the *Surveillance* of Cerebral Palsy in Europe (SCPE) describes dystonia as dominated by abnormal postures, fluctuating tone, involuntary movements, distorted voluntary movements, discriminating dystonia from choreoathetosis, which is described as hyperkinesia with rapid, involuntary jerky and often fragmented movements (*chorea*), and/or slow, constantly changing, writhing, or contorting movements (*athetosis*). 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. [13] have more specifically defined rigidity as hypertonia characterised 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. 21).

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 for isometric strength measurement [10]. This is a valid and reliable tool; validity depends on appropriate positioning, stabilisation of the child, and experience of the examiner. Normal values for young children exist as well as data for CP.

12.2.2 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 [14]. It is important to include a selective motor control measurement in the evaluation of the child with CP. *Recently* developed assessment tools are the Selective Control Assessment of the Lower Extremity (SCALE), which can be used for spastic CP [15], and the

Selective Control of the Upper Extremity Scale (SCUES), which can be used in unilateral CP [16]. Assessment of selective control is usually carried out together with strength measurement and typically has three levels:

0: No ability to isolate movement (unable)
1: Partial ability to isolate movement (impaired)
2: Complete ability to isolate movement (normal)

12.2.3 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 *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 [17, 18] (see Chap. 21).

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 gastrocsoleus complex and the *Achilles* tendon. If there is a 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 the 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 [17]. The *Duncan-Ely* test had a sensitivity of 73%, a specificity of 29%, a positive predictive value of 60%, and a negative predictive value of 42%.

Thomas test: this test assesses shortening an d 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.

12.2.4 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 out-

come measurement is important: the observational gait scale [19] and the Edinburgh visual gait score [20]. 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. Computerised gait analyses with or without force plates and EMG give a more objective description of t he gait, useful for evaluation of interventions [12]. *However*, this is not available in all centers. Recent development of markerless three-dimensional motion capture may in the future facilitate such analyses, as it can be done outside a laboratory [21].

12.2.5 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 researchers (see Chaps. 9, 11, and 17). 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 decided, after harmonisation of the data, to include cases of CP who were 5 years of age at diagnosis [12]. For the clinician, early signs of CP should elicit assessment, management, and follow-up of impairments (*motor and other*) already in the small child (Table 12.1).

The child who is eventually diagnosed with CP shows slow and/or asymmetric neuromotor development in infancy, and in many of these infants, the clinical picture is more or less established early. It is usually characterised 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 (Table 12.1) (see Chaps. 9 and 11). These advanced postural reactions form the basis for the control of movements and balance as the infant grows up and are expected to progress from the *primitive* and reflexive movement patterns of the neonate to the voluntary and controlled movements of the older child. Another typical finding is *asymmetry* in using arms and hands, or tiptoeing. 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. The national *quality* register and follow-up program CPUP in Sweden includes not only children with an established CP diagnosis but also those with symptoms suggestive of CP in order to provide early follow-up and management. At an age of 4 years, it is decided by the child neurologist whether the child fulfils the criteria of CP, and those who are not excluded [22].

Early and accurate diagnosis is important as it allows prompt access to early intervention during the critical periods of brain development. A combination of medical history taking, standard clinical examination, neuroimaging, and genetic testing should be started at the time of referral (see Chap. 9). The *diagnosis* can often be made as early as in the first days of life.

Today, with the progress of *diagnostic* methods, the *diagnosis* can often be made as early as in the first days of life, but at the latest in the first 4 months after birth (Table 12.1) (see Chap. 9). The initial assessments should be carried out

Table 12.1 Early signs of cerebral palsy (see Chap. 9)

Muscle tone alterations	Examination of muscle tone, Hypotonia, floppiness, scissoring, fisting, stiffness, opisthotonic posturing, passive resistance to stress, dystonia
Persistence of primitive reflexes	Moro, asymmetric tonic neck reflex, crossed extensor reflex, persisting support reflex (lags), placement reflex, palmar reflex
Asymmetric neurological signs	Tone, parachute reflex, asymmetric placing reaction, asymmetry of upper-lower limbs
Deep tendon reflexes	Sustained clonus, persistent crossed abductor reflex

by an experienced intensivist or a paediatric neurologist and should be repeated after 3–5 days in case of any suspicion of brain damage. Thus, a reliable diagnosis of CP can be established within the first 4 months of life, and the measures of rehabilitation can start in time. *Over* the last 20 years, the *prevalence* of CP has shown a downward trend due to advances in gynaecology, prenatal diagnosis, and improved intensive care units. The gynaecologists are well prepared for complicated births, such as underweight premature babies, multiple births, or placental problems (see Chaps. 6, 9, and 17). A *recent* review [23] by a multidisciplinary, international group of CP experts focused on the following tools with the best predictive validity for detection of CP before 5 months of age: neonatal MRI (86%–89% sensitivity), the Prechtl's Qualitative Assessment of General Movements (98% sensitivity), and the Hammersmith Infant Neurologic Examination (90% sensitivity) (see Chap. 11).

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 brain lesion that is responsible for the motor impairment
- The exclusion of a progressive disorder or spinal lesion

12.2.6 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 [24]. GMFCS as a clinical and research tool 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 classification is based on everyday functional performance while sitting and during transfers and mobility. The expanded and revised GMFCS provides a useful level of detail for clinical service provision and planning. The gross motor function at different ages (*age bands*) is described for the five levels up to 18 years of age. Developmental curves based on the motor test Gross Motor Function Measure (GMFM) have been produced for each of the GMFCS levels [12], which are helpful when informing parents about the prognosis of motor function (see Chaps. 24 and 25). GMFCS levels are considered quite stable already at an early age and rarely change after 2 years of age, even after intervention. This five-level classification has inspired the development of classifications of other impairments in CP, such as the Manual Ability Classification System (MACS), Communication Function Classification System (CFCS) [25]. The psychometric measurement properties of the GMFCS, MACS, and CFCS when administered to children and adolescents with CP have been assessed [26] (see Chap. 1). CFCS describes the development and validation of a communication classification system for children with CP, including content validity and reliability, and is analogue of GMFCS and MACS.

12.3 Types of Cerebral Palsy

CP is clinically categorised into spastic, dyskinetic, and ataxic types based on the predominant motor disorder. *Terminology* varies between classifications throughout the world, which historically has hampered collaborative research. The description of CP type by limb distribution does not indicate severity level and very often does not offer prognostic utility [12]. 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 [27] with description of the distribution into bilateral and unilateral with further characterisation of type by dominant neurological sign and severity by GMFCS level is favoured (see Chaps. 24 and

25). The need for *harmonisation* was most needed in bilateral spastic CP (BSCP), where different terms coexist and cut-off limits between similar terms differ between countries. The SCPE classification is adopted by many countries, facilitating worldwide collaborations. However, the old classification has been kept in parallel in many countries.

12.3.1 Spastic CP

Spastic CP is characterised by muscle *hypertonia* of the pyramidal type, increased deep tendon reflexes, clonus, Babinski sign, co-contraction of agonists and antagonists, a tendency for permanent deformities, for example, femoral anteversion resulting in scissoring, pes equinus, wrist flexion deformity, etc. Spasticity is the commonest type of CP, comprising 85–90% of the total group. Depending on the topographical distribution, bilateral and unilateral spastic CP are described. In an overview on all aspects of movement disorders in CP, Vitrikas et al. [28] distinguished the following categories: spasticity, dyskinesia, ataxia, and mixed/other. *Spasticity* is observed most frequently, occurring in 80% of children with CP. Movement disorders in CP may also result from secondary problems, including hip pain or dislocation, imbalance, hand dysfunction, equinus deformity, and comorbidities (see Chaps. 31 and 38).

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 [12, 29]. 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 [12, 30].

12.3.2 Bilateral Spastic CP

Overall, bilateral spastic CP (BSCP) constitutes about 50% of all CP, and the prevalence is decreasing [31]. Periventricular white matter lesion is the most common finding, especially in the preterm (see Chaps. 4 and 13). These lesions are detected early with the use of ultrasound and MRI (see Chap. 10). Neuroimaging findings may be different in the full-term and the preterm with BSCP [32].

In ambulating children with BSCP, the upper limb is less involved. The involvement is bilateral but may be asymmetrical. Rodda et al. [33] described five gait patterns recognised 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 spasticity and excessive ankle dorsiflexion.

Jump gait is a very common gait pattern observed in the young child in the sagittal plane, characterised 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 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 characterised 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. 12.1). 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 [34]. 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 [34]. The child is at *great risk* of not being able to sit without support. Contractures are common later in life.

The most frequent secondary musculoskeletal deformities in the non-ambulatory bilateral spastic patient that requires orthopaedic intervention are dislocation of the hip and spinal deformity (*scoliosis*) (see Chap. 23).

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 (see Chap. 24). 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 utilisation of the upper limbs (see Chap. 24); this, in combination with 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, the occurrence of accompanying impairments is lower than in severe cases. Intellectual impairment, learning and memory [34], epilepsy, visual impairment, and pseudobulbar palsy (*paresis* of facial, lingual, and pharyngeal muscles) resulting in drooling, feeding, and speech difficulties are common in severe BSCP [29, 30]. Recurrent infections of the respiratory tract are also common. Neuropsychiatric disorders (autism and/or ADHD) occur in 12% of all BSCP cases [35]. 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 [36], while intellectual impairment in 39–74% and epilepsy in 14–53% were reported from Australia [37]. In severe BSCP (*tetraplegia*), epilepsy was found in all cases in a population-based follow-up study [38]. Visual impairment may include visual field impairment, oculomotor dysfunction, and reduced visual attention (see Chap. 33).

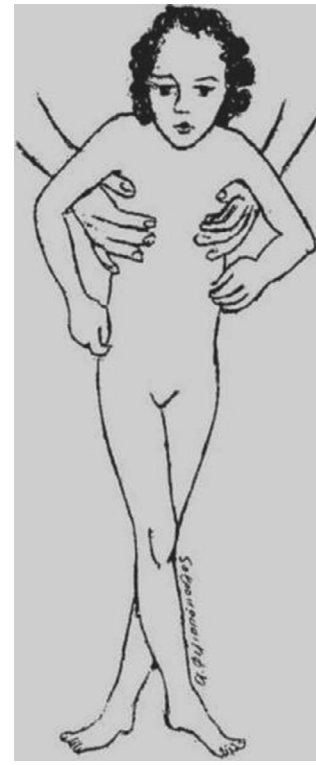


Fig. 12.1 Bilateral spastic cerebral palsy (*tetraplegia*) with scissoring

12.3.3 Unilateral Spastic CP

Unilateral spastic CP (USCP) constitutes about 35% of all CP and is *increasing* in prevalence [29, 30]. The aetiology is heterogeneous, mostly pre- and perinatal (70–90%), while in 30%, the cause is unknown. In *premature* infants, the commonest causes are periventricular haemorrhage and infarctions. In full-*term* infants, the most frequent aetiologies are cerebral malformations, cerebral infarction, or haemorrhage [29, 30]. Most cases of unilateral hemiplegia are due to perinatal stroke.

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, or middle cortical lesions [8, 28, 29, 39].

The *diagnosis* of USCP is rarely possible immediately after birth, even though some evidence may be found after a detailed examination of 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 (see Chap. 9). Later, there is *asymmetry* in the parachute reflex, while even later, differences in the movement patterns and in the use of the involved limbs become 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 an inability to perform fine movements. The *elbow* is in a flexed posture, and 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 [12, 29]. 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. 12.2). Spontaneous movement of the upper extremity is reduced and abnormal. Fine movements are clumsy or impossible to perform. 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.

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 [33] a comprehensive classifi-



Fig. 12.2 Unilateral spastic cerebral palsy (*hemiplegia*) on the right side

cation system with four hemiplegic gait patterns that is very relevant to the clinician when treatment decisions are made. Graham et al. [12, 40] describe in detail all fields of CP, such as classification, epidemiology, aetiology, diagnosis, pathophysiology, the muscles, screening and prevention, physiotherapy, rehabilitation, management of CP, comorbidities, and quality of life of young people and adults; further, therapies management strategies, management of pain, hip surveillance, sleep and feeding, swallowing and nutrition, prognose and futures studies, the role of stem cell therapy, and the topographical [12] description in unilateral and bilateral CP:

- In monoplegia: is one limb affected, and it is more often the lower limb
- In hemiplegia: is one side of the body affected
- In diplegia: the lower limbs are much more affected than the upper limbs
- In triplegia: the usual pattern is unilateral upper limb involvement and bilateral (asymmetrical) lower limb involvement
- In quadriplegia or tetraplegia: all four limbs are involved according to SCPE terminology

Comorbidities and functional limitations are common and disabling, including chronic pain (75%), epilepsy (35%), intellectual disability (49%), and musculoskeletal problems, for example, hip displacement (28%), behavioural disorders (26%), sleep disorders (23%), functional blindness (11%), and hearing impairment (4%) [41] (see Chaps. 31 and 33). Epilepsy is a common accompanying clinical problem of USCP occurring in 25–40% (see Chaps. 15 and 16). Impaired growth of the affected upper and lower limb may be noted as well. Most children with USCP have no intellectual or speech impairment [37]. Neuropsychiatric disorders (autism and/or ADHD) have been shown in 13% of children in a population-based study [35]. An ipsilateral visual field impairment may be present, as well as strabismus [42]. Wu et al. [32] 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 (see Chaps. 13 and 14).

12.3.4 Dyskinetic CP

Dyskinetic CP is *characterised* 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. 12.3) mainly of the distal muscles that result in the inability of the child to maintain a position [43]. Dystonia, chorea, and

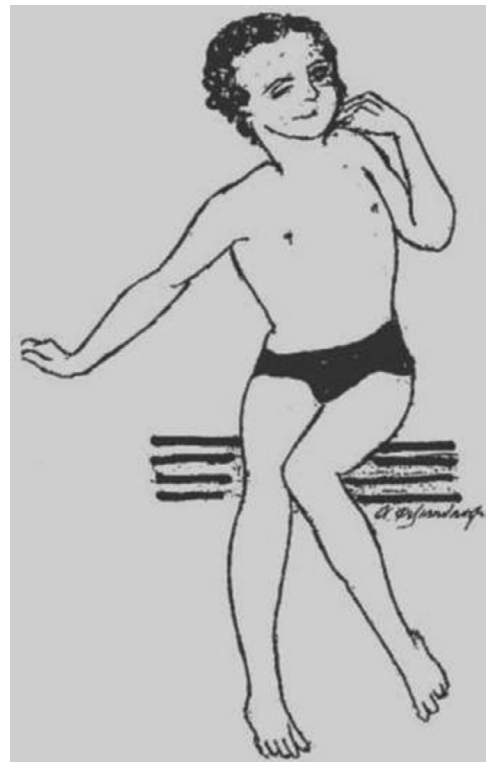


Fig. 12.3 Athetotic type of dyskinetic cerebral palsy, typical position

athetosis frequently co-occur in the child with dyskinetic CP [44].

Dyskinetic CP is classified into dystonic and choreoathetotic 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 [12, 45]. 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 presentation and a different evolution; it results to a lesser extent in contractions. It would respond well to therapies modifying motor nerve or muscle activity, such as botulinum toxin (see Chaps. 25 and 26).

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, characterised by prolonged or increasingly frequent generalised dystonia, requiring early detection and urgent management. A high correlation was found between dystonia and the level of gross motor function and manual ability [44].

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 hyperbilirubinemia 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 [46].

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 [46]. This CP type had the highest occurrence of epilepsy in a Swedish population-based follow-up study [43]. About 45% have ADHD and/or autism [35]. In a Belgian study, 47% of individuals with dyskinetic CP were able to communicate (sending and receiving messages, regardless of method) with unfamiliar partners [44]. Augmentative and alternative communication is often needed.

12.3.5 Ataxic CP

Ataxic CP is characterised by a disturbance of balance, coordination, and control of fine movements (Fig. 12.4). The *motor pattern* is characterised 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 [47], and comprised 2.4% of the total number of children with CP in an American study [48]. A last article of the European collaborative study of the surveillance of CP provides data for children with disabilities [49].

A neuroanatomical correlate, such that is found in other CP types, is rarely found in children with ataxic CP. Children are usually hypotonic (Fig. 12.5) in infancy, 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 dysequilibrium syndrome (DES). Recognising ataxic diplegia and disequilibrium syndrome as special subtypes within the ataxia group is helpful in the

clinical setting [50]. DES mostly affects cases with dialysis in neurological patients, in the very-low- density lipoprotein receptor gene, non-progressive cerebellar ataxia, dysarthria, and short stature. It is important to rule out a neurodegenerative disorder, such as neuromotor disorders and intellectual inabilities. Minor congenital anomalies were more frequent in those with ataxic CP than in control subjects [51]. 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 [52]. In a last *publication*, the authors attempt to ataxia and hypotonic types of CP. They conclude that the rate of prevalence is less than 5% of all CP cases. They also try to explain if it is a genetic disease or another prenatal aetiology [53]. Only a few children have congenital hypoplasia of the cerebellum.



Fig. 12.4 Ataxic cerebral palsy with wide gait and tendency to fall

A Canadian study [41] 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. The *ataxic forms* are correlated with GMFCS level IV or V. Epilepsy is common, and the risk increases with decreasing gestational age at birth. An *assessment* is difficult because most publications only provide local data, and percentage is not possible because many factors play a role, such as information from the most developed countries or from less developed countries. In our experience, there are 10% more convulsions than with other forms of CP. *Autism* and/

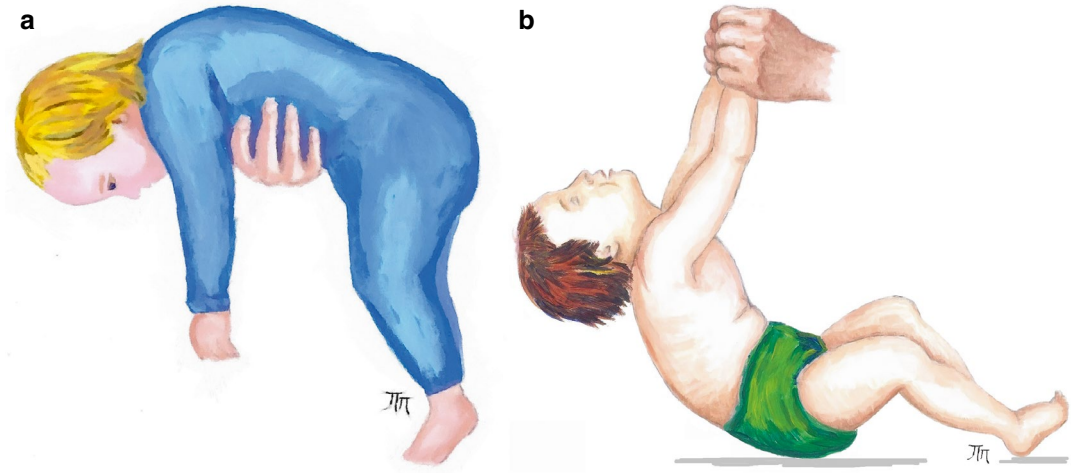


Fig 12.5 (**a** and **b**) A hypotonic infant

or ADHD are found in 43%, according to a Swedish population-based study [35]. The high occurrence of associated impairments despite a less pronounced motor impairment is confirmed in a recent European study [54]. In this group, a genetic background is believed to be more frequent than in other CP types.

12.4 Additional Comments

12.4.1 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 clinical symptom and an assessment of muscle tone (*hypertonia* or *hypotonia*) or both (Fig. 12.6). 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 [http://scpe.edu.eacd.org/-scpe/reference-and-training-manual/rtm.php] (Fig. 12.6). Pure hypotonia is not considered part of the CP classification according to the SCPE, while some other classifications do. One may ask why this is important. Spastic CP is the largest subgroup, and management is often designed with this in mind. *However*, children with dyskinetic CP often display spastic signs and may be mistaken as mainly spastic, while their greatest problems in everyday life are created by the dystonia. In another publication, the distribution by predominant motor type was 85% spastic, 14% dyskinetic, and 1% ataxic [55]. This may mislead the management and treatments of the child, leading to unforeseen consequences from, for example, surgery.

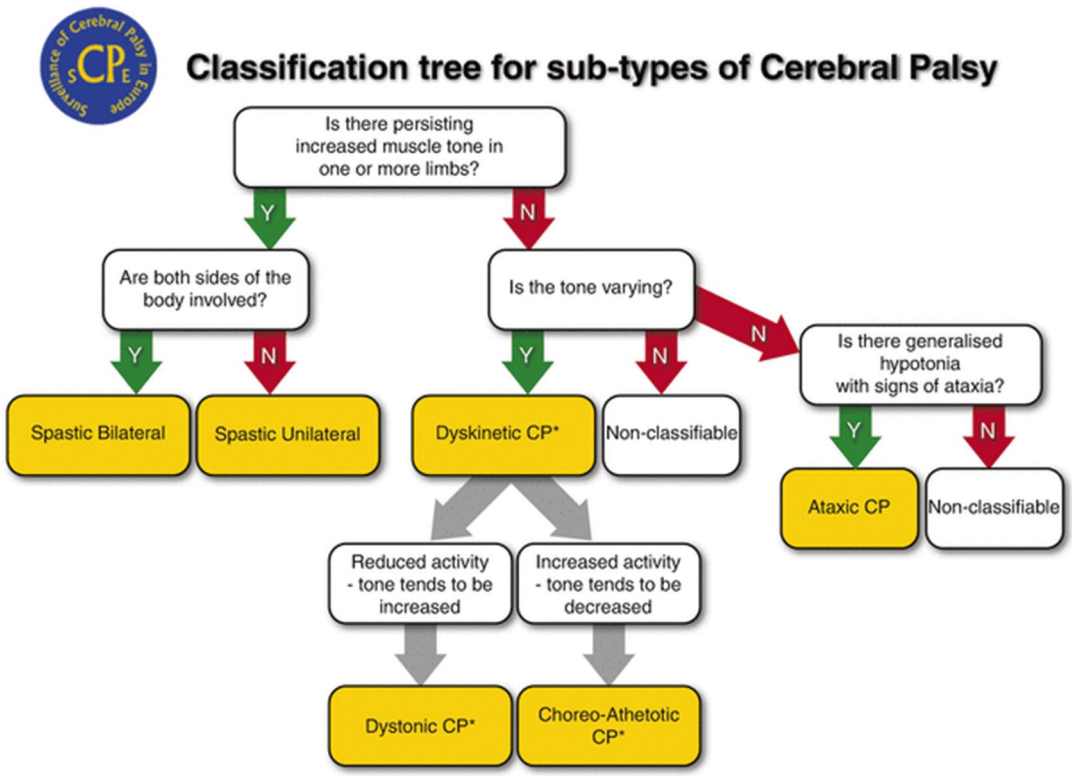


Fig. 12.6 Classification tree for cerebral palsy subtypes. (Cans C. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Dev Med Child Neurol. 2000; 42: 816–824)

Children may also miss out on appropriate treatment options.

12.4.2 Associated 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. Bilateral lesions are associated with a more severe impairment profile [48]. Some impairments are specific for the type of lesion and clinical CP type [41]. The associated impairments may sometimes be affecting 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 Chaps. 33, 36, and 38).

The early recognition, intervention, and management of signs of CP are important in the 4 months of life (see Chaps. 9 and 11) [56]. The aim should be to reduce the CP numbers all over the world. This can be done by organising through pregnancy and newborn intensive care units.

Follow-up programs, such as the CPUP (CP-follow-up-programmes), include children with signs of CP and early recognition [12] (see Chap. 20). This way, *secondary* complications due to increased muscle tone can be avoided, and early intervention, such as constrained-induced therapy (Baby-CIMT) for babies displaying asymmetric hand (unimanual ability in children with unilateral CP), can be applied already in the first year of life [25] (see Chap. 20). The regular neurological examination in newborns can identify in the first days of life a hypotonic. A second examination a few days later can confirm the suspected diagnosis of floppy infant [57]. Our many years of experience with newborns demonstrated this 25 years ago.

12.5 Conclusion

Cerebral palsy (CP) is the most frequent motor disability in childhood, beginning early in development. *Classification* into spastic, dyskinetic, or ataxic CP. Spastic CP is the most common type classified as uni- or bilateral spastic CP, and dyskinetic CP is classified as choreoathetotic, dystonic or ataxic-hypotonic, mixed-types CP. The *early* recognition, intervention, and management of signs of CP are important in the first 4 months of life. The clinical characteristics of all types of CP as well as rare clinical manifestations were described in detail. The *additional* clinical problems, comorbidities, and functional limitations are common and are described in detail. The *most* serious accompanying problems are epilepsy and disabilities. It is encouraging that the prevalence of CP has decreased in recent years.

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Brain Imaging: Magnetic Resonance Imaging

13

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.

Keywords

Cerebral palsy · Magnetic resonance imaging · Hypoxic-ischaemic injury · Perinatal stroke · Neonatal white matter injury · Neonatal brain haemorrhage

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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 a 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 subtype of CP may also be possible on detection of characteristic neuroimaging findings. These can help in providing adjunct data in planning early

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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 an increasing number of cases and advancements in various neuroimaging modalities has further facilitated the diagnostic imaging studies in CP. These comprise primarily 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 the 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], we 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 was detected [14]. PVL and post-haemorrhagic porencephaly have been

categorised as preterm-type brain injuries because they are often based on the immaturity of the 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 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 anomalies 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 affect 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 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

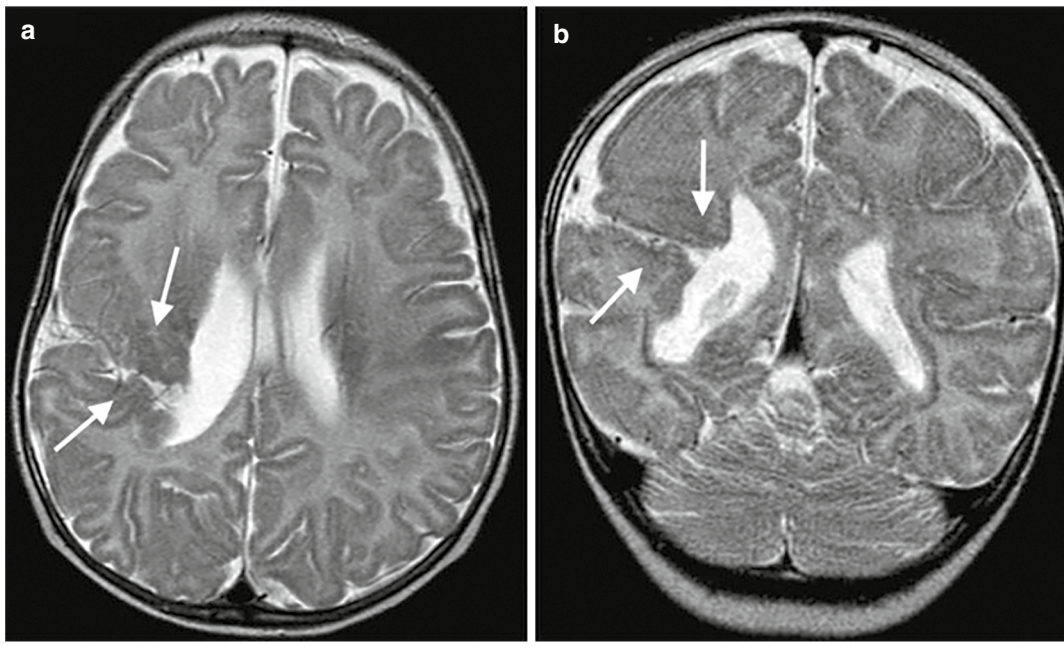


Fig. 13.1 Right-sided schizencephaly shown on axial (**a**) and coronal (**b**) imaging. The margins of the schizencephalic cleft are lined by grey matter (*arrows*)

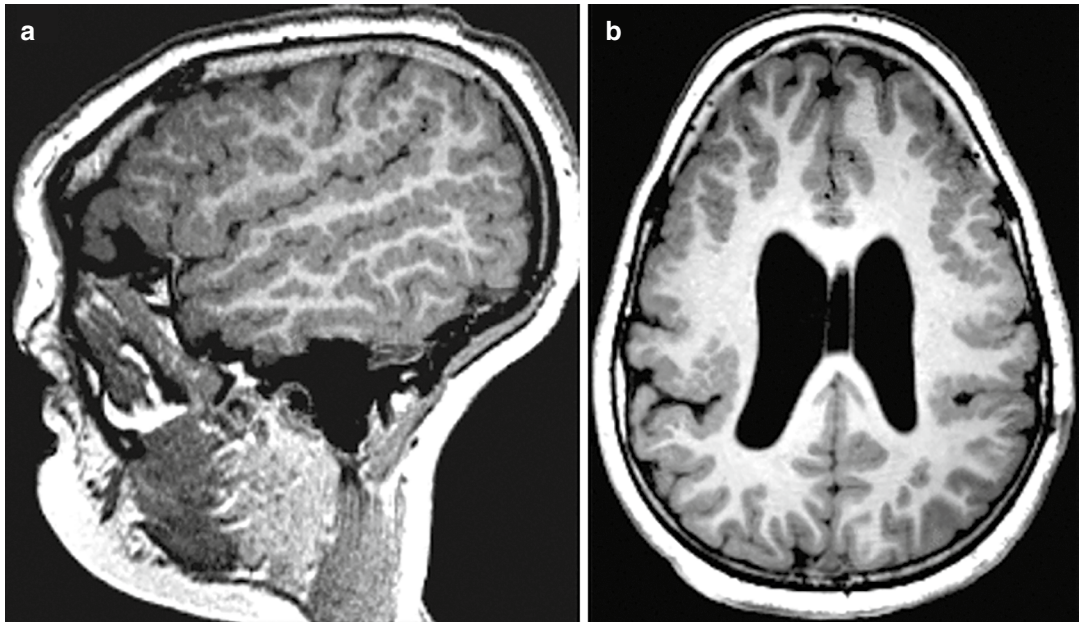


Fig. 13.2 Extensive bilateral perisylvian, frontal, and temporal polymicrogyria as demonstrated on high-resolution sagittal (**a**) and axial (**b**) T1-weighted imaging at 3 T. Note the small serrated appearance of the grey-white matter junction due to polymicrogyria compared to a smoother junction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

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 the 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 haemorrhage 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:

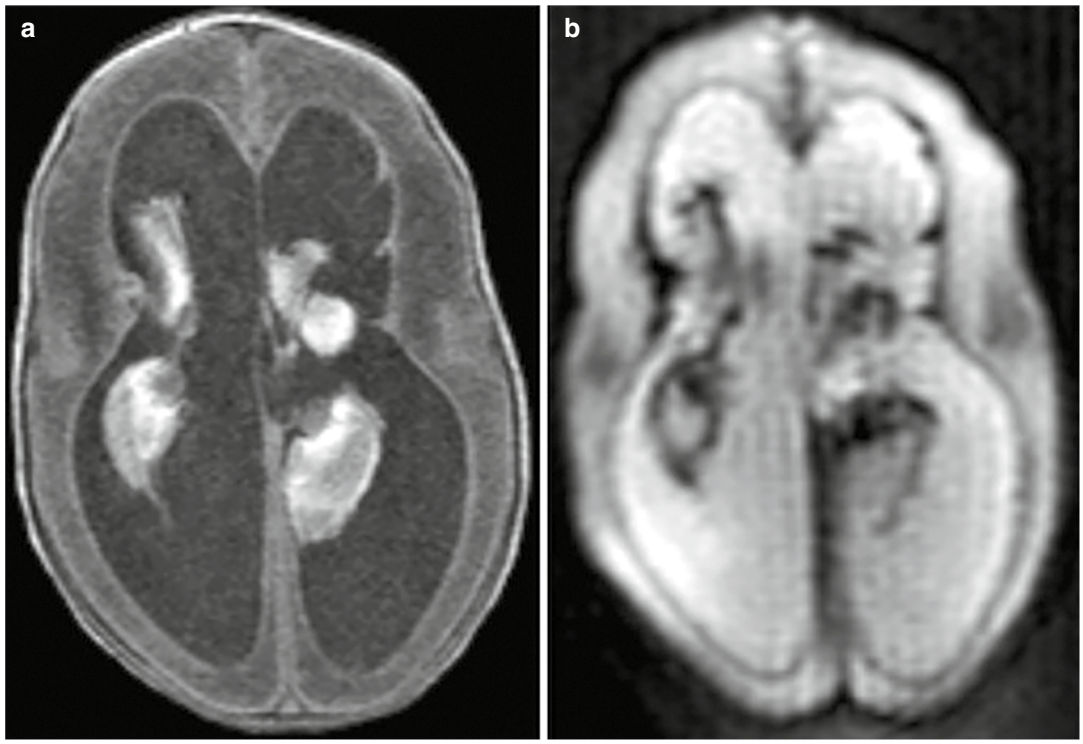


Fig. 13.3 Intraventricular haemorrhage in a 1-week-old neonate as depicted on MRI. (**a**) A T1-weighted image demonstrates a hyperintense signal of blood within the ventricles. (**b**) Gradient echo T2* image demonstrates foci of low signal due to haemorrhage. Also note the hypointense staining along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

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 an 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-thirds 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). A mass effect with a 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 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 non-

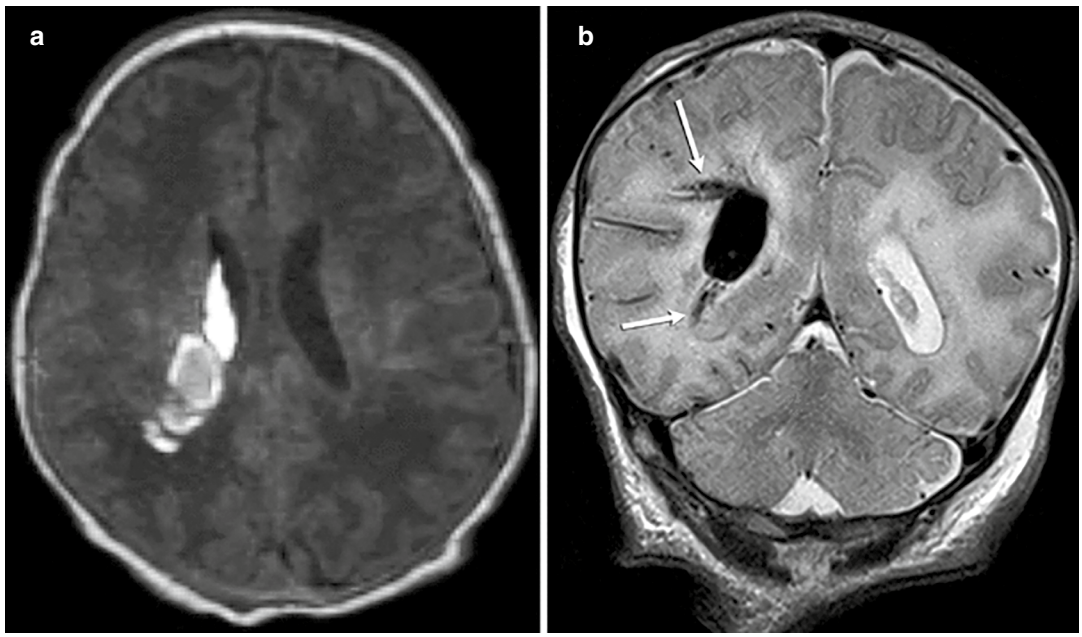


Fig. 13.4 In this patient with intraventricular haemorrhage (**a**), there is adjacent prominence and thrombosis of the medullary veins in the white matter (*arrows* in **b**), leading to periventricular haemorrhagic infarction

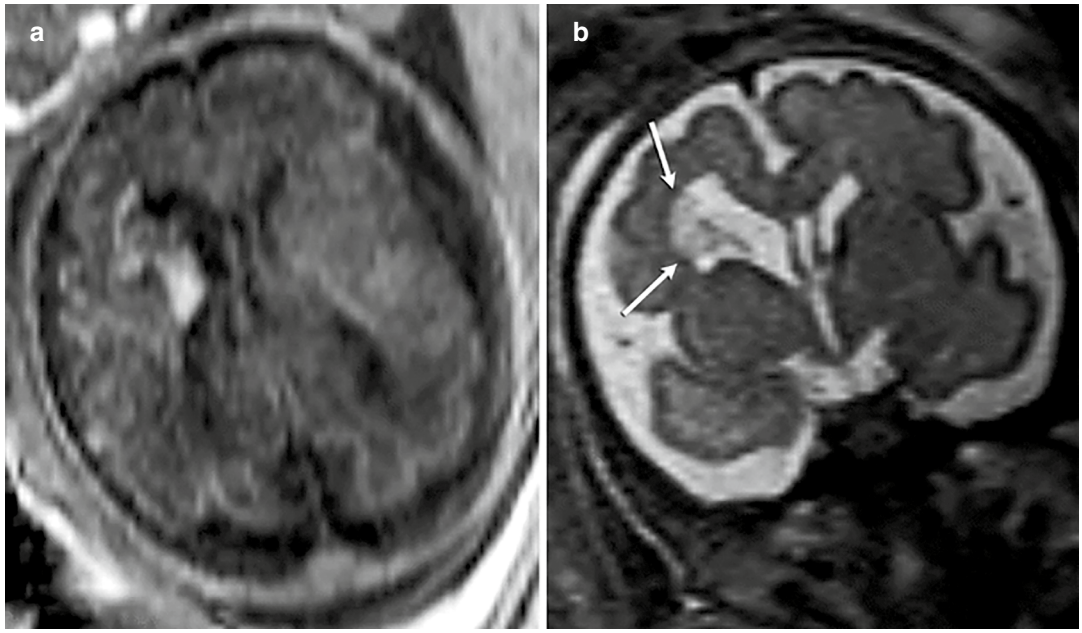


Fig. 13.5 In-utero grade 4 intraventricular haemorrhage on foetal MRI at 28 weeks gestation. (**a**) Axial T1-weighted image shows hyperintense blood within the right lateral ventricle extending into the adjacent parenchyma. (**b**) Coronal single-shot fast spin-echo T2-weighted image shows extension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

communicating 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 effects 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 neonates. 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 an MRI. Over time, as the haematoma undergoes lysis and clot retraction, the haematoma 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

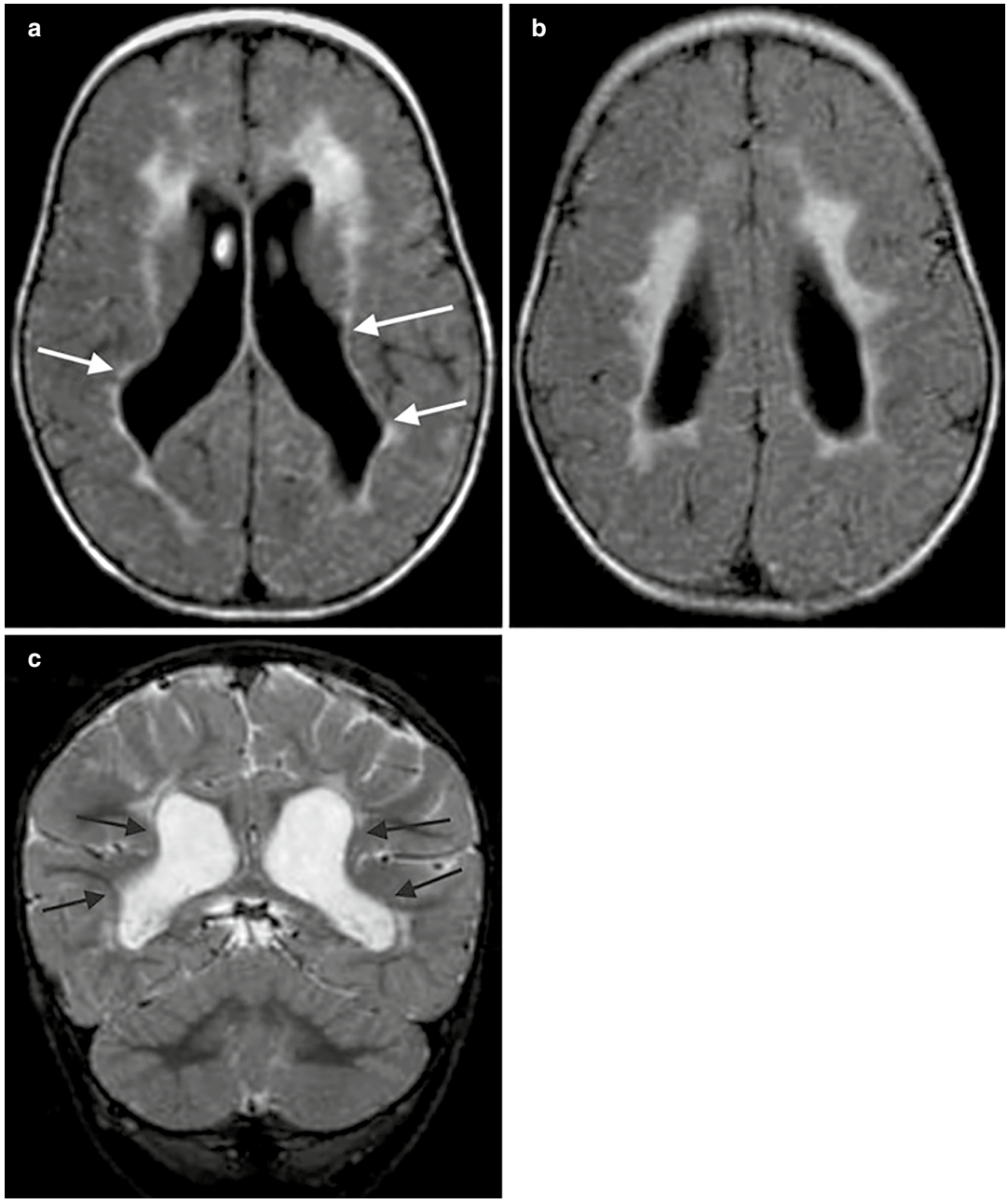


Fig. 13.6 Typical findings of periventricular leukomalacia. (**a**) The posterior lateral ventricles are distended within the undulated margin (*arrows*), there is decreased white matter volume, and there is a periventricular abnormal white matter signal on FLAIR imaging (**a** and **b**). (**c**) Coronal 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

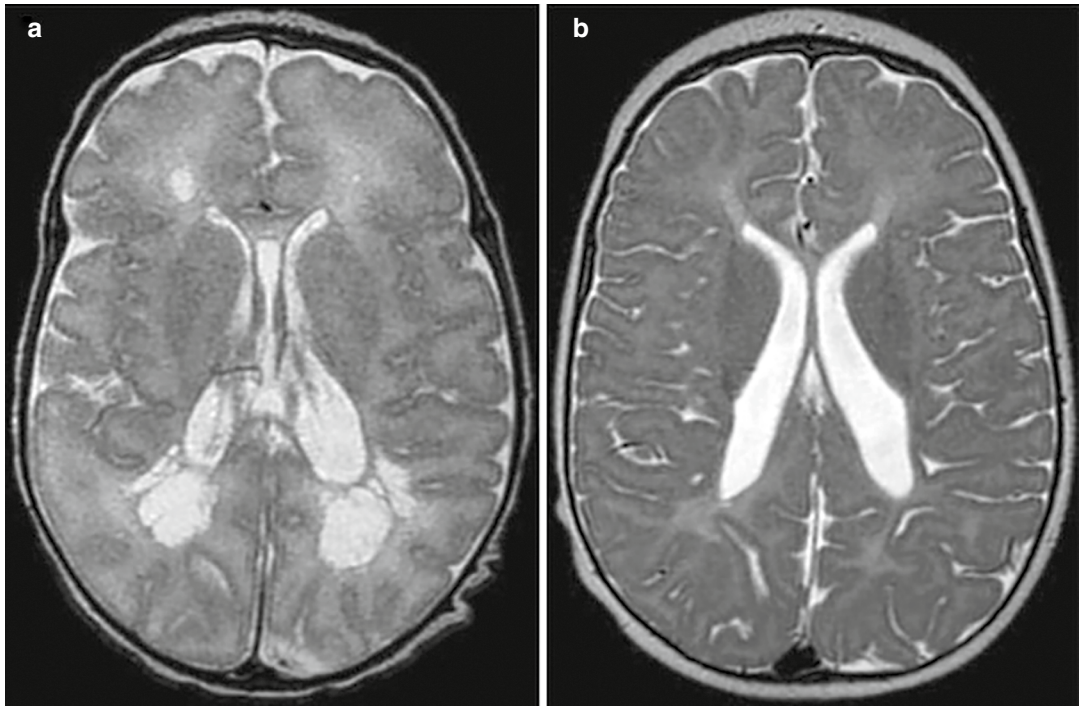


Fig. 13.7 (**a**) Axial T2-weighted image shows multiple foci of cystic periventricular leukomalacia in a 6-week-old infant. (**b**) Six months later, the cystic areas are no longer seen, but now depicted are undulated margins of distended posterior lateral ventricles and associated white matter volume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

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 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 interm 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

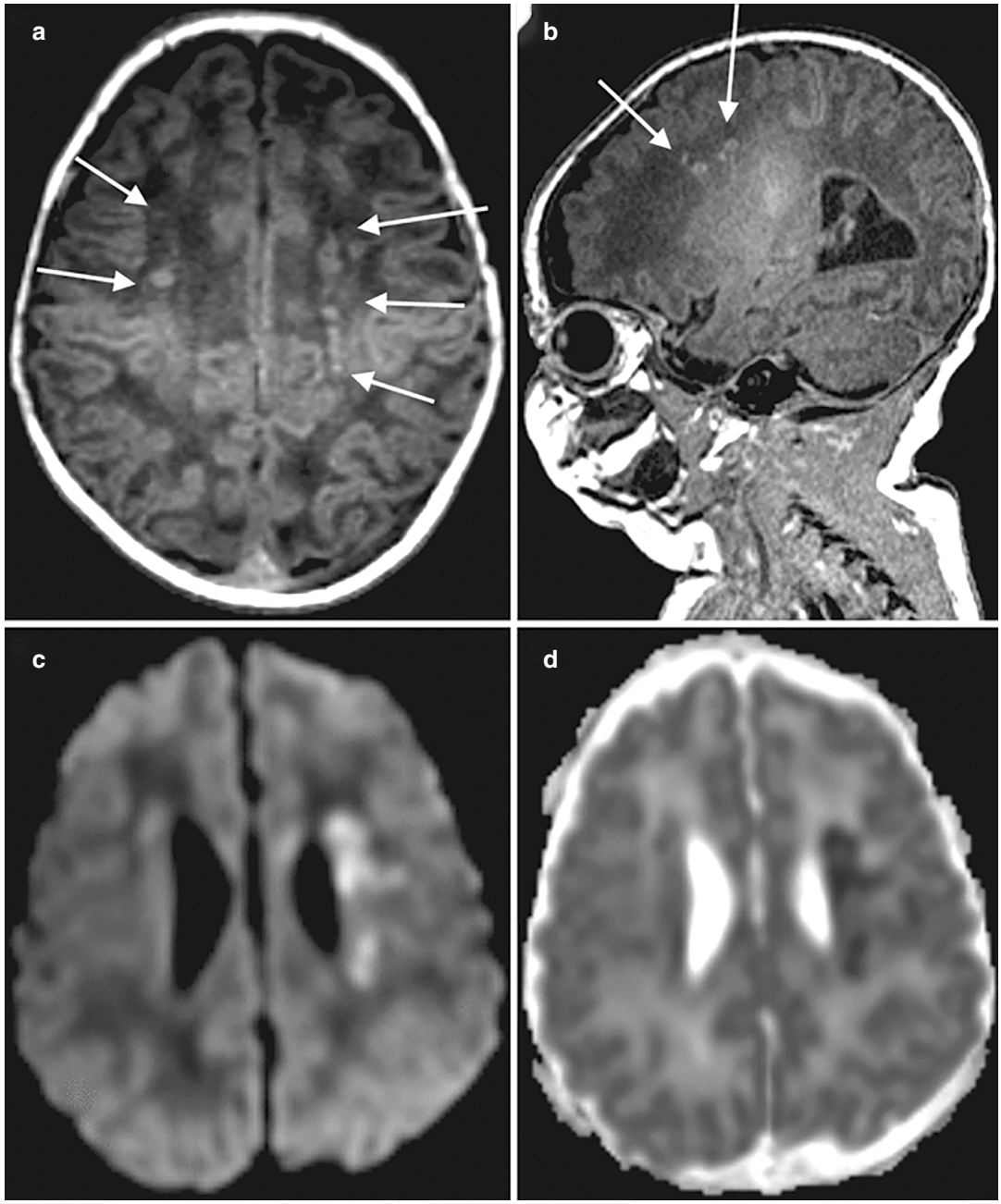


Fig. 13.8 Punctate foci of white matter injury in a term neonate with transposition of the great arteries. Axial (**a**) and sagittal (**b**) images demonstrate multiple small foci of abnormally high T1 signal intensity in the deep white matter. DWI (**c**) and ADC (**d**) images showed that a few of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

highly subjective [33], and there is no neurodevelopmental 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.

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. The presence of very wide subarachnoid spaces and interhemispheric fissures, 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 the 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].

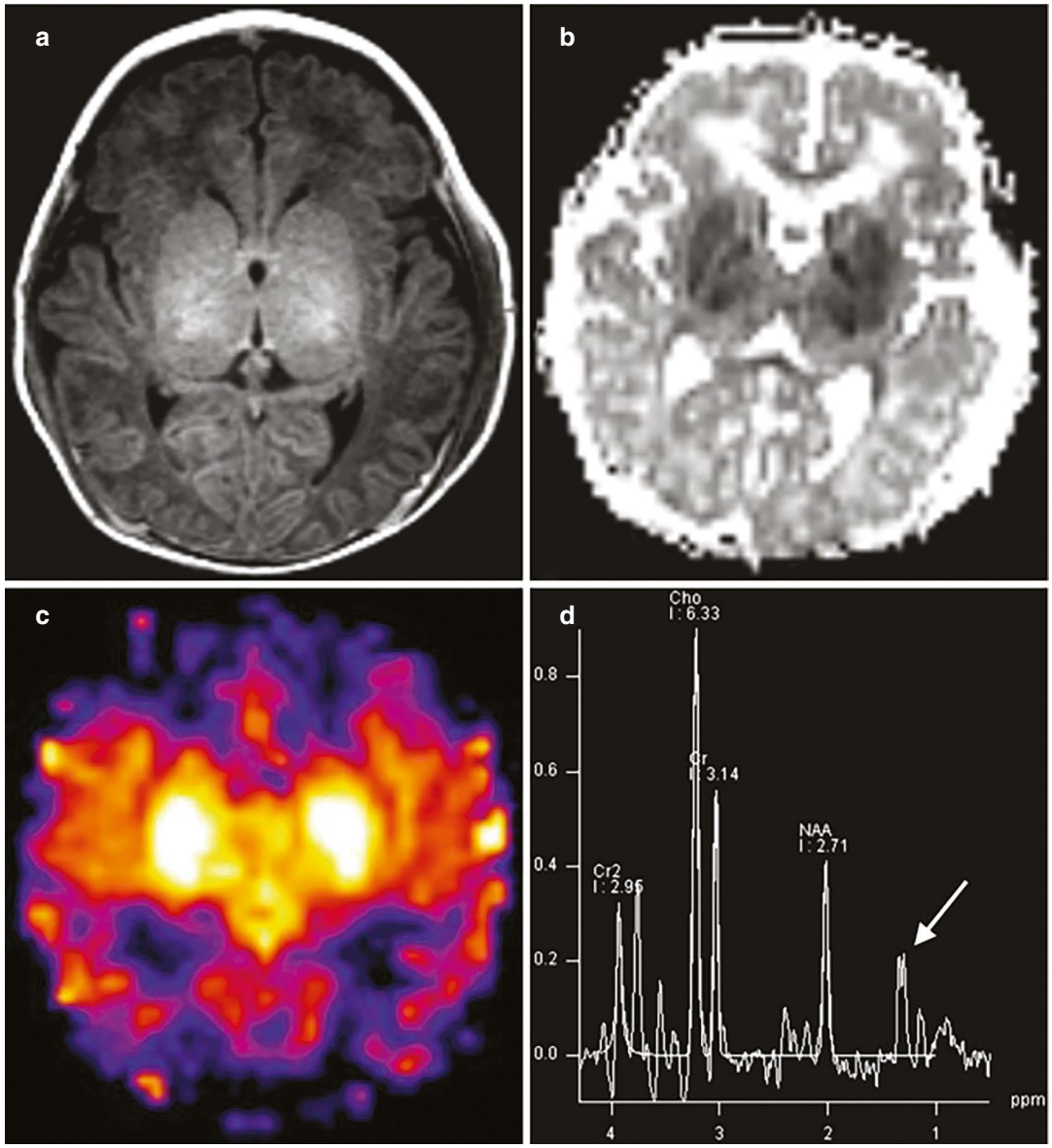


Fig. 13.9 Neonate with seizures after emergency caesarean section delivery due to close on full abruption, showing a deep, profound pattern of hypoxic injury. (**a**) T1-weighted image demonstrates a subtle increased signal in the basal ganglia and parts of the thalamus. Differentiating an abnormal signal from normal myelination in the lateral thalamus and posterior limb of the 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*)

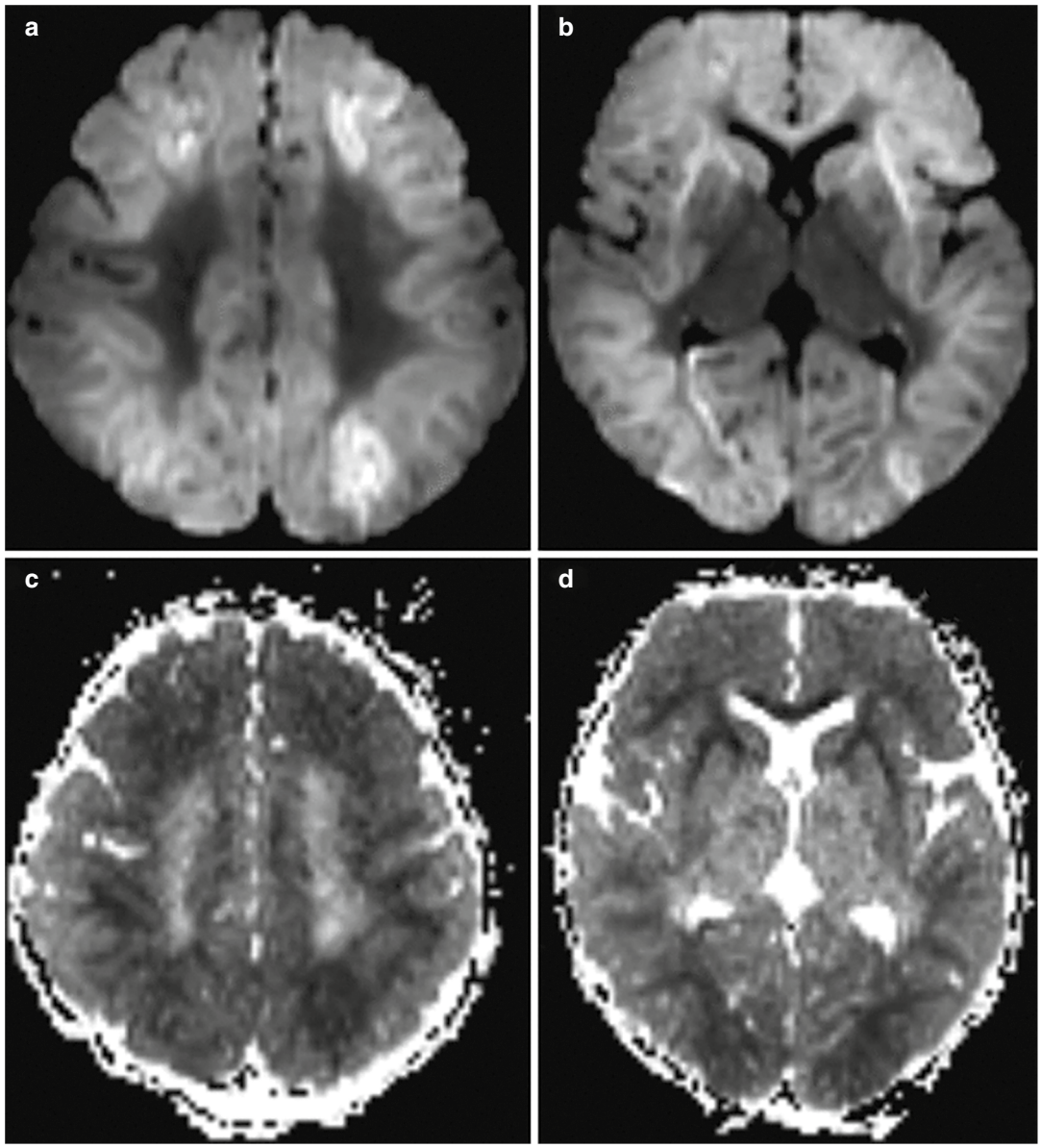


Fig. 13.10 DWI (**a** and **b**) and ADC (**c** and **d**) maps demonstrating a watershed-type injury to the brain, also involving white matter and parts of the cortex with relative sparing of the basal ganglia, thalami, and other parts of the cortex

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

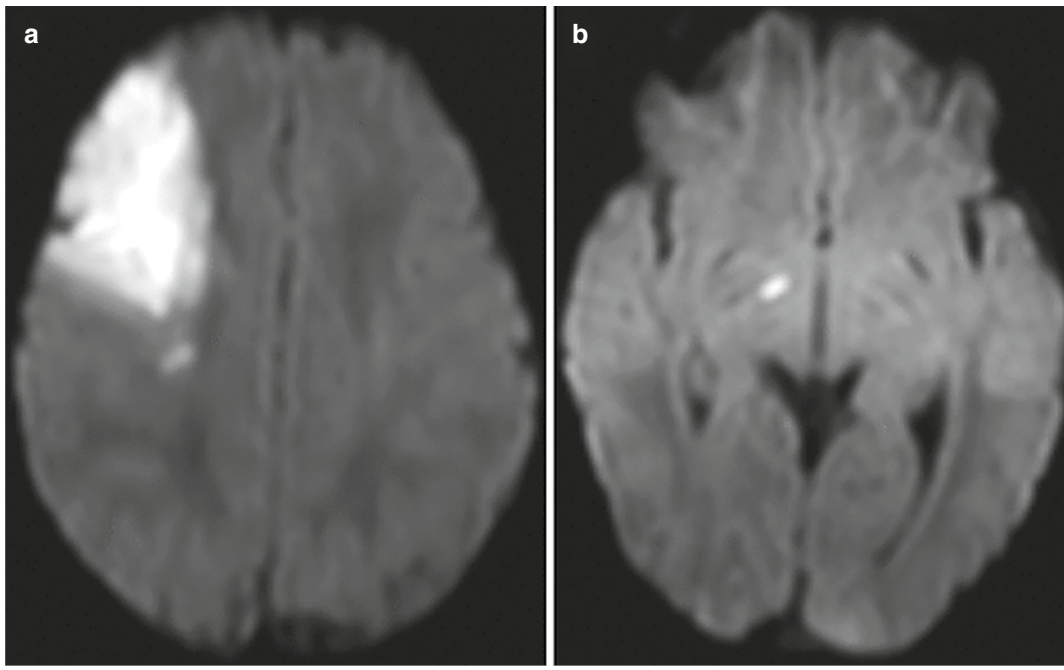


Fig. 13.11 Neonatal arterial ischaemic stroke (AIS) in a term infant. Diffusion imaging shows a large area of restricted diffusion in the right cerebral hemisphere in keeping with an infarct in the right middle cerebral artery territory (**a**). On a lower slice distant from the infarct zone (**b**), 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

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, and posthaemorrhagic hydrocephalus requiring shunting and death. Outcome will be highly dependent on the location and extent of venous structures involved and whether there are associated venous infarcts. Diagnosis can be made by detecting 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 the imaging appearance of a chronic arterial territory infarct (Fig. 13.12).

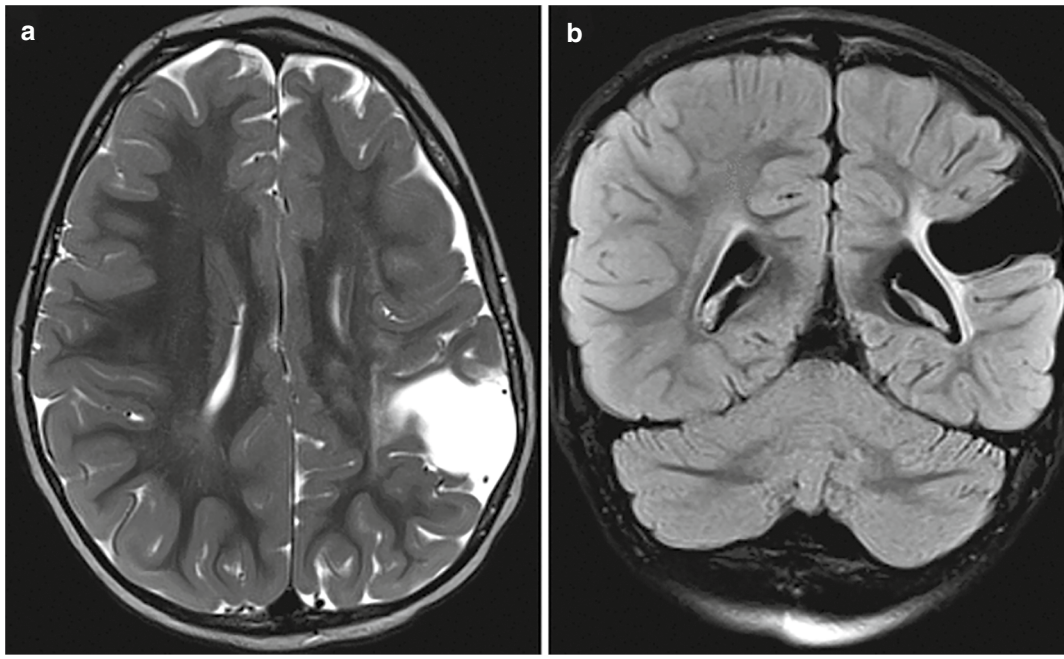


Fig. 13.12 Presumed perinatal arterial ischaemic stroke (PPAIS). A 15-month-old patient without a significant past medical history is brought to a neurology clinic with preferred use of the left hand and shows some gait abnormality, with increased tone and reflexes in the right extremities. MRI shows 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

13.8 Advanced MRI Techniques

Newer MRI imaging methods have been utilised in the 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 system processes that underlie development and outcome in children with cerebral palsy [45].

Widespread use of high-field magnetic resonance systems and advances in MRI pulse sequence design has enabled the 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 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 the 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. 13.9d) 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 with regard to the 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 a 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 that although the fractional anisotropy DTI measure within most of the major white matter tracts was significantly lower than that of age-matched healthy controls, fractional anisotropy mainly within the bilateral corticospinal tracts and posterior body and isthmus of the

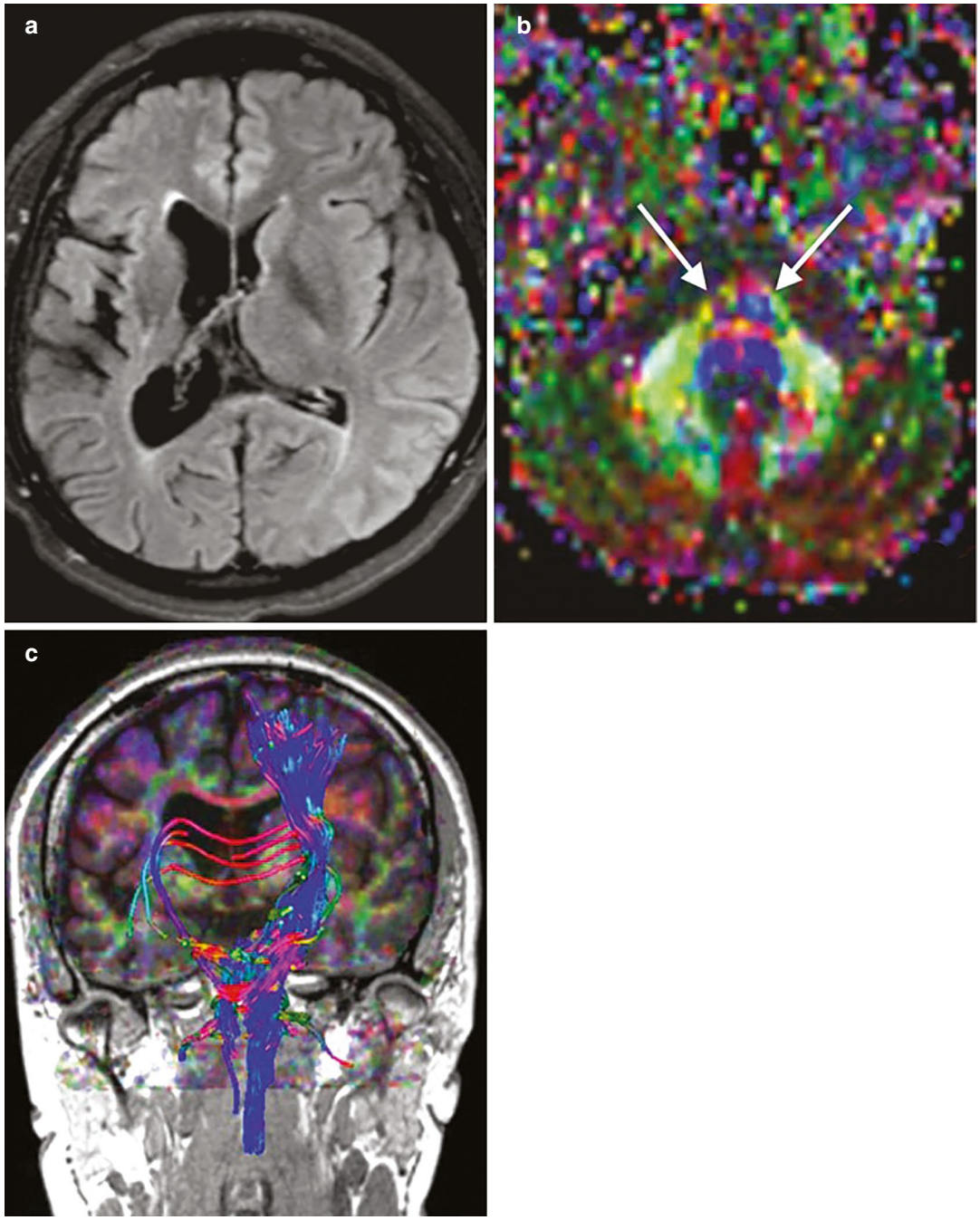


Fig. 13.13 Diffusion tensor imaging (DTI) in a patient with left hemiplegic cerebral palsy. Child with previous right-sided haemorrhage, with resultant volume loss and dilatation of the right lateral ventricle (**a**). (**b**) Colour-coded fractional anisotropy maps through the brainstem demonstrate 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

corpus callosum showed a 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 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 outcomes and means to evaluate the efficacy of neuroprotective strategies and interventions.

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14 Nuclear and Molecular Imaging in Cerebral Palsy

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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 and infection) and are administered in absolutely safe and harmless small quantities. N/MI provides a non-invasive evaluation of patients with or at risk of developing cerebral palsy and predicts the 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. Other positron emission tomography (*PET*) tracers are used in some neurological centers, including ^{18}F-fluoroflumazenil for the evaluation of gamma-aminobutyric acid (*GABA*) receptor and ^{11}C-alpha-methyl-L-tryptophan to assess serotonin function. Finally, PET imaging may have a role to assess the effectiveness of stem cell transplants in patients with cerebral palsy.

Keywords

Nuclear medicine · Molecular imaging · Positron emission tomography · Cerebral palsy · Epilepsy

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 and infection) and are administered in absolutely safe and harmless small quantities. As such, they provide information about function at the molecular, cellular, or organ level and 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 (cam-

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eras): single-photon emission computed tomography (*SPECT*), based on detecting single photons emerging from the body, and positron emission tomography (*PET*), based on the detection of two photons generated by the collision and annihilation of an electron with a positron. In this chapter, we will review the clinical applications of these two imaging techniques as these 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 (see Chap. 15). Thornberg et al. (1995) reported that the clinical severity of HIE correlates with the outcome of the term infants [1]. Mild HIE usually results in a normal outcome, and severe HIE usually results in either death or CP [2]. Since moderate HIE may result in a normal outcome or CP [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 cortical glucose metabolism (*rCGM*) by FDG-PET or the regional cortical 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 semi-quantitatively the local absence/decrease in rCGM or 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 (Table 14.1).

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

SPECT (single-photon computed tomography)		
Agent	Function	Clinical utilization
(a) HMPAO (Ceretec) (^{99m}Tc-Hexa-methyl-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-lsopropyl-*p*-lodo-amphetamine)	Tumor imaging	Tumors
(e) Receptor-specific studies	Receptor studies	Receptors, ischemia, tumors
PET (positrons emission tomography)		
Agent	**Function**	**Clinical utilization**
(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 CP
(c) ^{18}F or ^{11}C-flumazenil	GABA (A) receptor binding	Asphyxia, CP and seizures
(d) ^{11}C –AMT) (^{11}C-alpha-methyl-L-tryptophan)	Amino acid analog	Seizures
(e) ^{11}C-PBR28	Translocator protein	Neuroinflammation

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 (Fig. 14.1).

When evaluating 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 (see Chap. 4). Chugani et al. (1987) using FDG-PET described the evolution of the regional glucose metabolism of the brain in infants during different stages of development [6]. 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. (1996) also reported quantitatively similar observations during the first 6 months of life [8]. They demonstrated that absolute values of regional cerebral glucose utilization also vary with age. Grey matter regions have low glucose utilization at birth (13–25 g). These rapidly rise to reach adult values (19–33 μmol/min/100 g) 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 g 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;

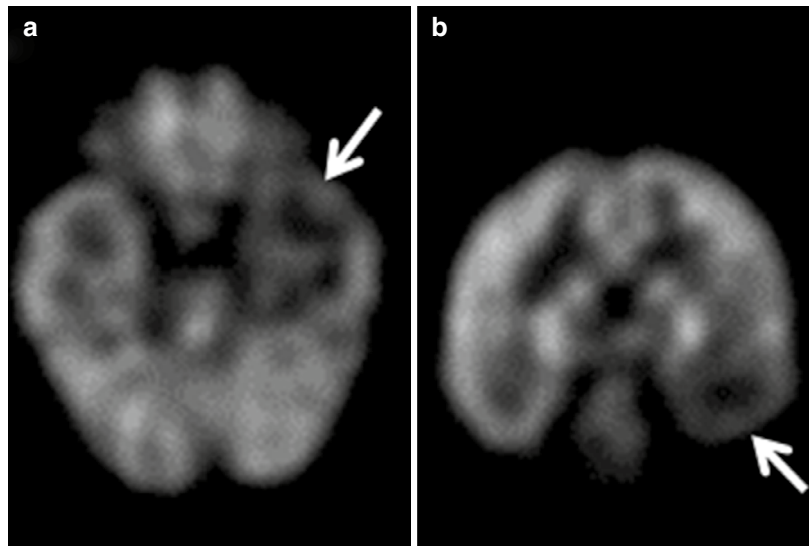


Fig. 14.1 This 22 year old with history of medically refractory recurrent episodes of seizures had undergone FDG-PET scan of the brain. Transaxial (**a**) and coronal (**b**) images demonstrate hypometabolism in the left temporal lobe (arrow). The patient subsequently had undergone anterior left temporal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

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. (1998) reported that nuclear medicine is complementary to magnetic resonance imaging (*MRI*) for the diagnosis of cerebral palsy [10]. 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. (2001) 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 [11]. 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. (2001) studied the correlation of the regional cerebral glucose metabolism (rCGM) on FDG-PET with the clinical severity of HIE and the clinical outcome. In that study, there was a clear correlation between the rCGM and the clinical outcome [2]. They reported a sensitivity, specificity, and accuracy of 70%, 100%, and 96.5%, respectively, for an adverse outcome with abnormal anteroposterior regional cortical perfusion [2].

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 CP 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. (1991) correlated the finding of FDG-PET imaging in 23 children with four clinical subtypes of CP: (a) spastic quadriparesis, (b) spastic diplegia, (c) infantile hemiplegia, and (d) choreoathetosis [12]. FDG-PET images were correlated with MRI or CT. 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 (Fig. 14.1) [10]. Other interesting observations in some of the specific subtypes of CP 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 (see Chaps. 4 and 12). In most patients with choreoathetoid cerebral palsy, a relatively normal pattern of cortical metabolism associated with marked hypo-

metabolism in the thalamus and lenticular nuclei was observed. In patients with infantile hemiplegia, FDG-PET disclosed symmetric cerebellar glucose metabolism with absence of crossed cerebellar hypometabolism (*diaschisis*), which is often seen in adult patients with stroke [12].

Denays et al. (1990) 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 [13]. *Additionally*, they reported normal findings in patients with mild diplegia; bilateral hypoperfusion in the superior motor cortex in patients with moderate di- or tetraplegia; and bilateral reduction of perfusion in the superior motor, inferior motor, pre-frontal, and parietal cortices in patients with severe di- or tetraplegia (see Chap. 12). In 36 children with bilateral spastic CP, Yin et al. (2000) reported a 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].

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. (2002) reported in children with congenital hemiplegia of subcortical origin a normalization or relative increase in rCGM in the ipsilateral sensorimotor cortex [15]. 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 calloso-marginal sulcus, and the cingulate gyrus (see Chap. 4). 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/MRI. In HIE within the first 24 h after birth, there is evidence of global increased cerebral blood flow, which decreases after 7 days [16] (see Chap. 5). This initial, transient cortical hyperperfusion is abnormal for infants <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 to 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 towards minimally supportive management from the clinical perspective.

In accordance with this finding, a 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 [17] (see Chap. 5). 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 [18]. 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 prognostic information regarding the severity of cerebral palsy. In a study of 34 preterm infants, Valkama et al. (2001) assessed rCBF with SPECT and ultrasound and compared the results with clinical follow-up. Perfusion defects measured by ^{99m}Tc-ECD SPECT predicted CP with 82% sensitivity and 70% specificity, compared with 73% and 83% for ultrasound, respectively [19]. 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 [19] (see Chap. 10). 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 and granulocyte colony stimulating factors is a potential novel treatment strategy complementary to rehabilitation for CP [20]. PET has also demonstrated its potential value for the assessment of treatment in CP [21, 22]. The changes seen on imaging may be present before any objective clinical improvement becomes evident [23]. Future studies are planned with PET imaging as a monitoring tool for those patients [20] (see Chap. 13).

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 6–18 times less than that reported with computed tomography (*CT*) scans [24]. By comparison, the average annual background effective dose amounts to 3.6 mSv in the USA [25].

On hybrid imaging with PET/CT and SPECT/CT, the CT component is of low dose, having approximately 5 mSv, which is much less radiation than a diagnostic CT. Thus, the typical dose of PET/CT is approximately 10 mSv. The CT component adds very little information due to the lack of soft tissue contrast in the brain [26]. One potential modality to overcome the lack of soft tissue contrast as well as the presence of ionizing radiation with the CT component is PET/MRI. One study reported a superior diagnostic accuracy of PET/MRI to PET/CT [26].

14.8 Cerebral Palsy and Epilepsy

Approximately two-fifths of children with CP suffer from epilepsy [27], as compared to approximately 0.5–0.7% in the general population [28, 29] (see Chaps. 15 and 16). 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 [30]. 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) [31]. Seizures and epilepsies are considered to have either a partial (*focal*), generalized, or unknown onset. Partial seizures account for approximately one half of all epilepsy and initially affect only one hemisphere. Partial seizures can involve the temporal, frontal, parietal, and occipital lobes (Table 14.2). Generalized seizures are associated with bilateral initial hemispheric involvement. Seizures that cannot be classified as partial or generalized with a high level of confidence can be categorized as of unknown onset.

Anti-seizure medications are the first-line treatments for epilepsy [28]. However, nearly one-third of patients become refractory to medical treatment. Epilepsy surgery may be effective for the treatment of medically refractory epilepsy

Table 14.2 ILAE 2017 classification of seizure types basic version

Focal onset	Generalized onset	Unknown onset
Aware or impaired awareness	Motor • Tonic-clonic • Other motor Nonmotor (absence)	Motor • Tonic-clonic • Other motor Nonmotor
Motor onset or nonmotor onset		Unclassified
Focal to bilateral tonic-clonic		

if the focus of the 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*), SPECT, PET, and 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 perfusion agents: ^{99m}Tc-hexamethylene propylene amino oxime (HMPAO) or ^{99m}Tc-ethyl cysteinate dimer (ECD). ^{18}F-Flurodeoxyglucose (FDG) is most commonly used for PET imaging of CP (see Chap. 1).

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 at the target site. With interictal *FDG-PET*, the seizure focus is identified as a hypometabolic site. FDG-PET is a valuable noninvasive modality for the presurgical evaluation of patients with refractory epilepsy [32]. 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 [33]. Co-registration of FDG-PET with high-resolution MRI may improve the surgical localization of an epileptogenic focus in patients with refractory extratemporal-lobe-epilepsy and no seizure focus detected on conventional MRI [34]. FDG-PET rarely demonstrates focal hypermetabolism at the site of the epileptogenic focus. However, if this finding is present, it is associated with a favorable outcome after surgical resection [35].

Multifocal seizure foci pose a significant challenge for the presurgical evaluation of 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 the 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 [36]. 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 [37]. 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 is estimated at up to 90% in temporal lobe epilepsy and approximately 66% in extratemporal lobe epilepsy [33].

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 <50% [33]. 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-dimensional standardized coordinate system of the brain. This technique may improve the accuracy of identifying the focus of a 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 gamma-aminobutyric acid (*GABA*) receptors and those acting in the serotoninergic pathway. Cerebral gamma-aminobutyric acid 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 effects on the development of motor plasticity [38, 39]. Activated microglial cells express peripheral benzodiazepine receptors and may be helpful as a screening biomarker for detecting patients at risk of developing CP due to a perinatal insult [40].

Other *investigators* reported ^{18}F-fluoroflumazenil and GABA expression and binding might also be 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 [41]. ^{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 [42].

^{11}C-alpha-methyl-L-tryptophan (^{11}C-*AMT*)-PET has also been shown to be helpful for the identification of the focus of seizures in children [43]. 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 ^{11}C-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.

Stem cell therapy was reported to be potentially beneficial in patients with CP. Improvement of FDG activity post-stem cell therapy at the site of the brain was shown to correlate well with a favorable clinical outcome [44]. Therefore, FDG-PET has the potential to evaluate the effectiveness of stem cell therapy in patients with CP.

14.10 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 effectiveness of stem cell therapy. It has also been *shown* to be valuable for the evaluation of the seizure focus in patients suffering from epilepsy, which is more prevalent in patients with CP as compared to the general population. There are other tracers that are used in some centers for the evaluation of these patients.

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Epilepsy in Children with Cerebral Palsy

15

Athanasios Covanis and Christos P. Panteliadis

Abstract

Seizures are commonly encountered in children with cerebral palsy (CP) and are one of the most common chronic conditions treated by paediatric neurologists. The estimated prevalence of seizure burden ranges from 20% to 45% in children with CP. More than 50% of infants with CP are born at or near term, with the vast majority having *pre-peri-postnatal* problems. Hypoxic-ischaemic encephalopathy, ischaemic stroke or perinatal strokes, and intracranial haemorrhage are the most common causes in neonates. The most prominent seizures are focal aware or focal impaired awareness seizures (*motor*, *nonmotor*) and focal to bilateral tonic-clonic. A combination of perinatal and clinical history, physical examination, prenatal and antenatal sonography, and neuroimaging, they help significantly for early diagnosis and early intervention to optimise outcomes. This *chapter* describes the aetiology, clinical characteristics, diagnosis, management, and prognosis of epilepsy in children with CP.

Keywords

Seizure in newborns · Epilepsy in children · Risk factors · Management · Prognosis

15.1 Introduction

Cerebral palsy (CP) is a term that has been applied over the years to a group of children with motor disabilities and related service requirements. The *first* conceptions of CP and our knowledge about aetiology and pathogenesis allow us to assume that CP existed in the Ancient World [1] (see Chap. 1). Based on *international* consensus, CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are non-progressive disturbances that occurred in the developing foetal or infant brain. These are often *accompanied* by disturbances of sensation, perception, cognition, communication, and behaviour disturbances, as well as epilepsy and secondary musculoskeletal problems [2, 3] (see Chaps. 12 and 21). Risk factors for development of CP are mostly detected in the prenatal (~20%), perinatal (~30%), or postnatal (~20%) period. In about one third of the cases the risk remains unidentified.

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The neurological *examination* of the newborn is a basic criterion of its extrauterine life, such as detailed medical prenatal, perinatal and pregnancy histories, a full neurological examination, and an evaluation of motor and sensory function (see below). Simultaneously a station that will mark the future course of his life, both in terms of organically and development (see Chap. 9). During the past 40 years, research in *developmental* neurology has provided a number of new methods for the functional development of the human nervous system, clinical neurophysiology, genetics, and neuroimaging. An *early* decision can be made about early intervention and the optimal time for this operation. Most importantly, it enables reliable selection of those infants who need intervention and to be saved (see Chap. 9).

Epilepsy and CP are two of the *most common* neurological disorders in childhood and epilepsy is common in children with CP. In general and in different studies, approximately 26–45% of people with CP have epilepsy, and the highest incidence was in the spastic hemiplegia subtype with 30.4%.

The prevalence rates differ based on the study type, during clinic-based studies showing a prevalence of 46.4% and population-based studies showing a prevalence of 31.6%. *Certain* subtle tonic or atonic seizures manifestations can easily be missed relevant to underlying *cognitive* dysfunction, requiring a video-EEG recording findings of seizures associated with CP and white matter injury [4, 5]. The *majority* of seizures are focal, though in some cases they could be obscured or unknown. In *motor* onset symptoms, the first prominent sign or symptom may be automatisms, tonic, clonic, atonic, myoclonic, hyperkinetic, and epileptic spasms, while in *nonmotor* onset symptoms, the symptoms are autonomic, cognitive, emotional, sensory, or behavioural arrest. Furthermore, a focal sign or symptom may evolve to focal bilateral tonic-clonic seizure. *According* to the ILAE Commission for Classification and Terminology, the clinical manifestations of a seizure in CP are determined by their anatomic location and the affected neural networks [6]. *Focal* aware seizures, focal onset seizures with impaired awareness, and focal motor or nonmotor onset with evolution to focal or bilateral tonic-clonic convulsions, tonic, clonic, epileptic spasms, myoclonic, hyperkinetic, sensory, emotional, cognitive are all possible and common seizure types in CP [7–9].

15.2 Prevalence of Epilepsy in Cerebral Palsy

The *incidence* of seizures in the neonatal period is reported to be approximately 1–3.5/1000 live births. This may be an underestimate, as the majority of studies rely on observation of clinical seizures rather than seizures also identified with continuous video-EEG monitoring for at-risk neonates (Fig. 15.1, 15.2). The *incidence* in preterm infants is very high (57–132/1000). In a study, the most common seizure aetiologies were hypoxic-ischaemic encephalopathy (38%), ischaemic stroke (18%), the middle cerebral artery is most commonly involved, and intracranial haemorrhage (11%) [7]. Seizure burden was high, with 59% having ≥7 electrographic seizures and 16% having status epilepticus.

Neonatal status *epilepticus* is relatively common and is associated with poor outcome but no widely accepted definition exists. *Almost*, two thirds of seizures occur the first 2 days after birth.

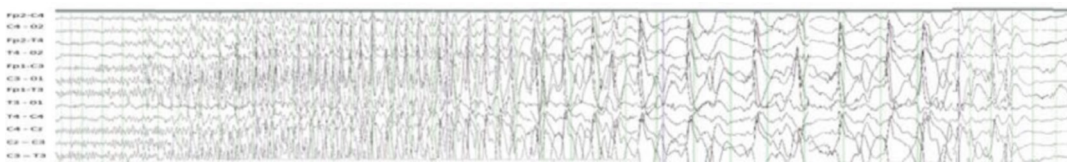


Fig. 15.1 A 5-month-old female. Seizure started neonatal period. Frequent focal tonic seizures, usually in clusters. MRI indicated a large cortical dysplasia left hemisphere. A video-electrographical seizure with clinical correlate at the age of 5 months was recorded (Fig. 15.2). Seizure video-EEG: The left side fast activity in the EEG was correlated with tonic spasms of the right upper limp that gradually extended to the right lower limp, the whole body, and then the left upper limp, ending with rhythmic clonic movements more marked right upper limb. The whole episode lasted about 58 s

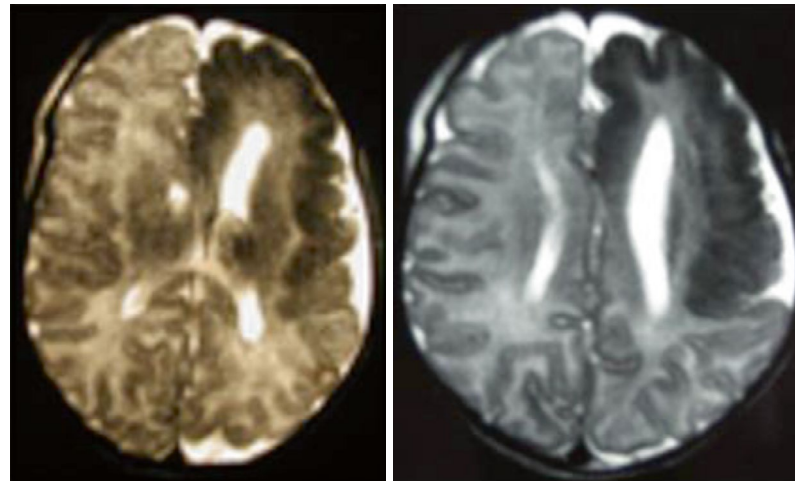


Fig. 15.2 Left cortical dysplasia

Other *disabilities* are learning, behaviour, language and mental problems [6].

In children with CP, epilepsy is a common disorder that occurs frequently in children who are more severely impacted by cerebral palsy and in children with CP and concomitant mental retardation. In general, the prevalence of epilepsy in children with CP varies between 30% and 45% [7, 10, 11] compared with the prevalence of epilepsy and cerebral palsy of 0.84% and 0.21%, respectively, in the general population [12, 13]. In *general*, one-third of young people with CP experience epilepsy, with an overall prevalence of 38.0%. The clinical *manifestations* of a seizure in CP are determined: (a) from their anatomic location and (b) of the affected neural networks. Prevalence rates differ based on the study type, with clinic-based studies showing a prevalence of 46.4% and population-based studies showing a prevalence of 31.6% [14]. A similar variability of epilepsy prevalence between 15% and 55% of children and adults with CP was reported in 2001 [14]. Variations in *prevalence* may be due to differences among selected patients. Archana et al. [8] found a prevalence of 26% for epilepsy in the studied population of children with CP. The highest incidence of seizures (30.4%) was found in children with spastic hemiplegia, and the extent of cortical injury correlated with the risk to develop epilepsy. The European *collaborative* study of the surveillance of cerebral palsy-based registries can provide useful data for generating health indicators [15]. Sharing PHIs (public health indicators) for CP helps to improve public health policies for people with disabilities in Europe and to increase public awareness of this complex condition (https://ec.europa.eu/health/indicators_data/).

According to Gong et al. [16], approximately one-third of children and adolescents with CP have epilepsy. Prenatal, perinatal and antenatal diagnostic, family history, EEG findings, MRI abnormalities, intellectual disturbances, and quadriplegia may be contributing factors to epilepsy in CP. *Many* prenatal, perinatal, and postneonatal injuries, *such* as hypoxic-ischaemic encephalopathy, infection, and congenital brain *malformations*, can cause CP and epilepsy. This study aids in identifying the clinical characteristics of young people with CP at risk of developing epilepsy, which may assist clinicians in the early prevention and diagnosis of epilepsy within this population.

15.3 Aetiology of Seizures in Cerebral Palsy

Infants born *preterm* are at increased risk of CP, with the risk increasing with decreasing gestational age. In a publication, the seizure incidence, time of onset, and aetiology of neonatal seizures were related to gestational age [17]. Those born under 30 weeks and over 36 weeks gestation age manifest seizures earlier, compared with neonates 30–36 weeks. The *prevalence* of CP was in

an increasing trend in studies done before 1990 as there was better survival of preterm infants due to advances in medical technology; however, the prevalence decreased subsequently as there was an improvement in prenatal care too after that.

The *aetiology* of CP and, as a consequence, the most common associated focal seizures is multifactorial. The multiple aetiologies result in brain injury that affects movement, posture, and balance and are also the cause of the majority of seizures in CP [18]. However, the causal pathways to CP are complex and not completely understood. The *timing* of brain injury or maldevelopment is generally classified as pre/perinatal, which accounts for 85–90% of CP or postneonatal (see Chaps. 4 and 5). The most common causes of neonatal seizures are prematurity and/or low birth weight, haemorrhage, intrauterine infection, hypoxic-ischaemic events, periventricular leukomalacia, brain malformations, stroke, metabolic disorders, and consanguinity. The other review paper [16] summarises aetiology, epidemiology, the risk factors associated with CP, and the advances in its treatment.

Many studies have shown that CP and *epilepsy* share common aetiologies and risk factors in seizure development in childhood and adolescence. The most common risk factors for developing epilepsy in childhood include low birth weight, low APGAR scores (see Chap. 9), seizures in the neonatal period and first year of life, positive MRI findings, intellectual disability, spasticity, and severity of cerebral palsy (Table 15.1). Children with CP with a *history* of neonatal seizures were 3.3 times more likely to have a poor prognosis for epilepsy than those without a history of neonatal seizures. In addition, the prevalence of epilepsy in children with CP and with a *family* history of epilepsy was 5.5 times higher than that in children without a family history of epilepsy [17]. This indicates that *genetic factors* play an important role in the pathogenesis of epilepsy development in children with cerebral palsy. Genetic information may help for more precise early treatment and a better outcome (see Chap. 7). However, although cerebral palsy is a *neurodevelopmental* disorder diagnosed clinically, not aetiologically, the genetic diagnostic yield in CP and the concomitant seizures is similar to that of other neurodevelopmental disorders for which exome sequencing is recommended as standard of care [18]. In a study of 102 children with CP, 72 had epilepsy and 22 had intractable epilepsy. The following factors were associated with epilepsy: prenatal CP aetiology, spasticity, scoliosis, intellectual disabilities, poor motor skills, communication, and feeding problems were associated with epilepsy [19].

Table 15.1 The most common reported risk factors for epilepsy in children with CP

Family history of epilepsy
Low birth weight
Low Apgar score
Seizures in neonatal period
Structural brain abnormality
Mental retardation
Severity of cerebral palsy (*quadriplegia, hemiplegia*)

15.4 Clinical Characteristics

15.4.1 Newborn and Infant Seizures

Seizures in neonates are an acute symptom in the developing brain (see Chaps. 4, 5, and 9). Most seizures are symptomatic and are caused by an acute or earlier insult to the developing brain. Birth *asphyxia* in newborns is a significant problem in the perinatal period and is *associated* with high rates of mortality and neurological and mental disturbances. The *prevalence* of asphyxia is estimated between 2 and 4/1000 term newborn infants. Approximately 15–20% of such asphyxiated newborns develop hypoxic ischaemic encephalopathy (*HIE*) during the neonatal period, and of the survivors, 25% will exhibit permanent neurodevelopmental deficits (see Chap. 14). Thornberg et al., in 1995, reported that the clinical severity of hypoxic-ischaemic encephalopathy (HIE) correlates with the outcome of the term infants [20]. Neonates with a history of seizures have been found to have higher rates of developing epilepsy and a higher rate of poor epilepsy prognosis [7, 12].

The seizures in neonates that may also evolve in infancy are generally all focal onset classified as electroclinical (*with clinical sign*) and electrographic-only (*no evident clinical signs*) [21]. The *polygraphic* video-EEG recording is the gold standard for diagnosis and seizure type classification.

Pisani et al. [22] in an epidemiological study considering only EEG-confirmed neonatal seizures, a 5.0/1000 incidence was reported for neonates of 31–36 weeks of gestation (WG), 54.9/1000 for those of 28–30 WG, and 85.6/1000 for neonates of <28 WG. Frank *periventricular* necrosis due to severe perinatal anoxia necessitating resuscitation, diffuse white-matter-gliosis resulting from complications during intensive care phases, or between 25th–33th weeks of the pregnancy are the neuropathological substrates [22] (see Chap. 4).

It is known that *approximately* 70–75% of infants who subsequently display signs of encephalopathy are born prematurely, particularly with birth weights under 1500 g. This is a postnatal course typically complicated sign by severe *intraventricular haemorrhage* (*IVH*) and/or *periventricular leukomalacia* (*PVL*). The remaining 25–30% of cases are infants born at or near term, usually suffering from hypoxic-ischaemic encephalopathy (HIE) of antenatal and/or perinatal origin. The premature infants or birth weight under 1500 g are categorised as very low birth weight (VLBW), and those of birth weight under 1000 g are subcategorised as extremely low birth weight (*ELBW*). The term *micropremie* has been used to describe infants of birth weight below 600 g, many of which actually weigh less than 500 g.

15.4.2 Children and Puberty Seizures

Karatropak et al. [23] in a retrospective study of 234 children aged between 3 and 18 years, divided into 126 CP patients with epilepsy and 108 cases with CP without epilepsy. An *increased* risk of epilepsy was detected in term infants and appropriate for gestational age (2500–4000 g) infants. On the *other hand*, presence of parental consanguinity, being born from a primiparous mother, age of mother at birth, mode of delivery, presence of multiple gestation and labour problems, history of follow-up in neonatal intensive care unit and intubation, and cMRI findings were not significant risk factors for the development of epilepsy in CP [9].

Diverse review studies found that a prevalence of epilepsy in a tertiary centre is 26%. The highest *incidence* of seizures was in the spastic *hemiplegia* subtype (30.4%). The severity of cortical damage is positively correlated with the risk of having epilepsy, and isolated white matter or deep grey matter insults had a less likely predisposition to epilepsy [5, 8, 9]. Cerebral palsy is the most common disability of childhood that affects motor function and is a result of injury to the developing brain.

The children with CP and epilepsy, as a rule, do have other *comorbidities*, such as intellectual disability, neuropsychiatric disorders including behaviour, attention deficit/hyperactivity disorder, as well as hearing and visual impairment, which needed early assessment and a multidisciplinary approach. Such comorbidities in addition to epilepsy significantly have a negative effect on the quality of life of the child and whole family (see Chaps. 31, 37, and 38). Some will require continuous long-term treatment in order to avoid repeated fits compounding the original cerebral anomaly [24, 25], and some others may be drug resistant.

15.5 Diagnosis and Classification of Epilepsy

The diagnosis of cerebral palsy is primarily clinical, and the MRI can be helpful and shows the grade of brain injury. The diagnosis begins in the prenatal period with *medical history* of mother, *sonography* (3D), biochemical screening, and according to result follow; a fetal MRI, fetoscopie, amniocenthesis, and eventually chromosomal examination (see Chap. 10). 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 ischaemic encephalopathy (*HIE*) actually die during the neonatal period, and of the survivors, 25% will exhibit permanent neuropsychological deficits (see Chaps. 5 and 16).

It is the clinician's first task to determine that a paroxysmal event has the characteristics of an epileptic seizure and not one of the many imitators of seizures. It might be sometimes difficult to distinguish epileptic events from other involuntary movements, particularly in *dystonic/dyskinetic* or ataxic CP. Interesting diagnostic steps are a detailed, skilled history followed by a complete clinical and neurological examination. Family and prenatal history are important. In almost 80% of cases, the diagnosis of an epileptic or nonepileptic event is made by the correct history. Reviewing *videos* of EEG (VEEG) diagnosis and direct observation can help predict the utility of completing VEEG studies in individual patients [8, 9, 26, 27].

Supportive evidence will be provided from video recording of events, an awake-sleep-awake video (*polygraphy*) EEG recording and neuroimaging. In neonatal period some epileptic events may be electrical only diagnosed by a routine *video*-EEG [27]. Furthermore, because the seizures in the neonatal period have been shown to have a focal onset, a division into focal and generalised is unnecessary. Neonatal seizures may also be the first presentation of well-known *metabolic* or *genetic* variants of neonatal epilepsy syndromes and their aetiology will provide prognostic information and guide to establish targeted treatment. In CP children both generalised epilepsy *syndromes* and *focal* epilepsy have been described, but focal epilepsy is more prevalent [5, 9]. The focal seizures are *focal* aware, focal impaired awareness, such, *motor* automatisms, clonic, epileptic spasms, myoclonic, and tonic *or* non-motor onset (autonomic, behaviour arrest), focal to bilateral tonic-clonic seizures or have a sequential presentation (sequence of signs, symptoms, and EEG changes at different times) or even remain unclassified [7, 8, 21].

The *EEG* is an important tool for the management of newborns with HIE and children with CP and epilepsy. *Seizures* occur usually in the first days of life in neonates with HIE, and they are mostly electroclinical or electrical-only (50–80%). EEG *monitoring* is crucial to determine if unexplained clinical events are seizures or not. EEG is useful not only to diagnose and classify seizures, epilepsies, and syndromes but also to clearly identify the region of the epileptogenic foci. It is also important to *recognise* subclinical EEG discharges and their contribution to cognitive impairment or deterioration requiring particular aggressive treatment; *such* discharges may deteriorate cognitive function in those children acting normally or contribute to already impaired function. Cerebral magnetic resonance imaging (*MRI*) is a valuable diagnostic tool in the assessment of children with cerebral palsy and epilepsy. It is *recommended* as the first diagnostic test, particularly when aetiology of CP is not established, in order to discover possible underlying structural damage. In patients with neonatal seizures, cerebral dysgenesis and intraventricular haemorrhage proved to be predictors for poor outcome [9, 25] (see Chaps. 4 and 5). Periventricular white matter injury (*leukomalacia*) is a major aetiology in preterm-born and term infants and is the common cause of spastic CP. The lesions macroskopically impress as pale, yellowish or chalky, sharply demarcated areas with perifocal oedema. In the course of absorption, the lesions become cystic cavities, and finally a ventricular enlargement is seen (see Chap. 4). According to Jauhari et al. [28], the term-spastic diplegia is clinico-pathologically different from preterm-spastic diplegia. Another publication [29] described that fractional *anisotropy* in the corticospinal tract at the internal capsule level could aid in the early diagnosis of spastic CP with high diagnostic accuracy. EEG is useful to clearly identify the region of the *epileptogenic* foci, and MRI can identify most of the *structural brain* abnormalities (see Chaps. 13 and 14).

15.6 Epilepsy Management

Epilepsy and CP are two of the *most common* neurological disorders in childhood and are common comorbidities occurring approximately in 40–45% of people with CP [4, 6, 7, 30]. Moreover, epilepsy is an index of CP severity and associated disability, and mental retardation is much more common in CP. Epilepsy in children with CP significantly contributes to the poorer quality of life of the child and the family. Early correct diagnosis and appropriate management of children with CP and epilepsy will improve outcome. Therapeutic *hypothermia* initiated within 6 h of birth and lasting 72 hours decreases the risks of CP in term and late preterm infants with moderate CP [7]. In two last publications [31, 32], the authors found *differences* in CP profiles between children prior to therapeutic *hypothermia* and children in the post-therapeutic hypothermia time, and they conclude that these results can guide clinicians on how to better weigh these neonatal factors when predicting and counselling parents on later infant outcomes. Bonifacio and Hutson [31] in their publication describe that therapeutic hypothermia, in the 6 h after birth, is the standard of care and the only currently available therapy to reduce the risk of death or disability in newborns with moderate to severe HIE and the best act for neuroprotection.

Early *diagnosis* and *treatment* electroclinical seizures and/or electrical only activity may reduce the risk of developing epilepsy and/or improve outcome [3, 29, 30]. In children with CP and epilepsy, *seizures* lead to difficulties of management and education at school and add to parental anxiety; of all disabilities, seizures, particularly frequent, lead to isolation, emotional disorders, and decreased cognitive achievement. Existing evidence indicates that children diagnosed with focal seizures fail to achieve reasonably sustained remission with optimal anti-seizure medication [21, 30, 33]. Therapy with *antiepileptic* medication reduces the recurrence risk but does not alter the epilepsy course and outcome, and about 89% of children had drug-responsive epilepsy [6] (see below).

In the case of *drug-resistant* epilepsy (10.1%), one should consider alternative nonpharmacological methods of treatment, which include *ketogenic diets*, responsive *neurostimulation* (Vagus nerve Stimulators) and *neurosurgical* evaluation (resection of the focus) for possible selected surgical intervention, and implantable brain neurostimulators [27, 34–36].

Parents are usually concerned about injuries or even unexpected death, particularly with generalised tonic-clonic seizures. It is important to educate the parents and the child, if appropriate, about the risks, *early recognition*, especially nocturnal events, emergency treatment, and appropriate follow-up and contact information. Also, provide pre-hospital options of early (<10 min) emergency treatment, which may be rectal/intranasal diazepam, intranasal/buccal midazolam, or intranasal/buccal lorazepam. This data demonstrated more infants with severe CP rather than mild CP in your cohort of children treated with therapeutic *hypothermia* for intrapartum asphyxia. Five- and 10-min *Apgar scores* were significantly different between mild and severe CP phenotypes, and cord pH and first blood gas pH were not significantly different between these two groups [7, 31, 32].

15.7 Neonatal Seizures

Phenobarbital is still the drug of first choice for the management of acute symptomatic neonatal seizures, mainly due to its known safety profile. If there is no response to a loading dose 20 mg/kg of phenobarbital, the dose should be repeated before *second-line* drugs are used (benzodiazepines, levetiracetam, or even phenytoin). Phenobarbital (PB) and *levetiracetam* (LEV) are most frequently used in neonatal seizures [37]. In neonates with prolonged anti-seizure medication treatment is unnecessary after resolution of acute symptomatic neonatal seizures prior to hospital discharge [7, 25, 33].

In a randomised control trial, phenobarbital was more effective than levetiracetam for the treatment of neonatal seizures, and in another

levetiracetam [7, 25, 33, 37]. According the findings of a new publication PB was associated with more adverse effects than LEV, levetiracetam is a safe and effective alternative to PB, and a first-line therapy in these neonates [36, 37].

Nonresponders with HIE tend to have more severely abnormal EEG backgrounds, higher seizure burdens, and a more severe pattern of injury on MRI, e.g., *including* injury to the white matter, parenchymal cortex, and more severe watershed injury (see Chap. 4). A model has been described for predicting drug-resistant epilepsy in children with CP [32], using four independent predictors: low Apgar score at 5 min, neonatal seizures, focal epilepsy clinically, and routine electroencephalogram. *Their aim* was to improve the clinical picture of newborns and to apply alternative forms of seizure treatment control [31].

15.8 Children Seizures

The treatment of epilepsy in children with CP is largely dependent on the type and severity of CP. The *prophylactic* anti-seizure medication, as a rule in children, is not initiated after managing the first seizure but depends on relapses. In children with *spastic tetraplegia*, seizure relapses are common, and the drug resistance can be predicted by seizures in neonates, intense neuropathological changes in cerebrum, and mental retardation [8, 30, 37]. The use of appropriate ASM at an optimum daily dose is to abolish or minimise seizure and drug-related side effects. There are many available ASMs (Fig. 15.3), and the initial selection of an appropriate medication should be based upon the seizure type, EEG findings, *epilepsy syndrome*, if applicable, and side effect profile [38, 39]. *Side effects* should be closely monitored, as children with CP, particularly with co-morbid intellectual disability, may not be able to adequately express the effects of their medications. The *majority* of seizures in CP epilepsy are focal onset. In this respect, the initial choice is sodium channel blockers, narrow-spectrum, and anti-seizure drugs relevant to child's age, such as oxcarbazepine, carbamazepine, eslicarbazepine, and lacosamide. Richard et al. [40] in a last publication present rare coding variants and loss-of-function alleles in *SPATA5L1* that lead to hearing problems and diverse neurodevelopmental features, such as microcephaly, intellectual disability, spastic-dystonic CP, and focal or generalised epilepsy.

Epilepsy seizures in cases with cerebral lesions are more difficult to treat, and poor control of seizures is associated with an increased risk of mortality, sudden unexpected death in epilepsy, and increased psychosocial burden. Latzer et al. [33] described a model for drug-resistant epilepsy in children with CP: (a) a low Apgar score at 5 min, (b) neonatal seizures, (c) focal-onset epilepsy, and (d) focal slowing on electroencephalogram. Timely treatment of drug-resistant epilepsy has better results for control in children with CP [5, 27, 33]. However, if two or more appropriate anti-seizures are used and fail to control seizures, alternative non-pharmacological methods of treatment should be considered, such as a *ketogenic* diet and *neurosurgical* intervention. The *ketogenic diet* is a high-fat, low-carbohydrate diet that has shown success in aiding in the management of refractory epilepsy [27, 33]. A *ketogenic* diet (KD) should be used in children with drug-resistant seizures [27, 34]. At the beginning of the twentieth century, fasting was used to treat childhood epilepsies older than 2 years and adults with *drug-resistant* epilepsies. Since 1996, the *KD* has become known, and in cases where the seizures do not stop when 2 or more medications are administered [34, 35]. The **KDs** are: the classic KD, the modified *Atkins* diet, the medium-chain triglyceride, and the low-chain triglyceride. Epilepsy surgery is the most effective way to control seizures in patients with *drug-resistant* focal epilepsy. The main methods are hemispherectomy, corpus callosotomy, temporal lobectomy, selective resection of hippocampus, and others [41]. Neuromodulation techniques include principally *vagus* nerve stimulation (VNS), the *most common* technique [36, 42, 43]. In general, the results vary from

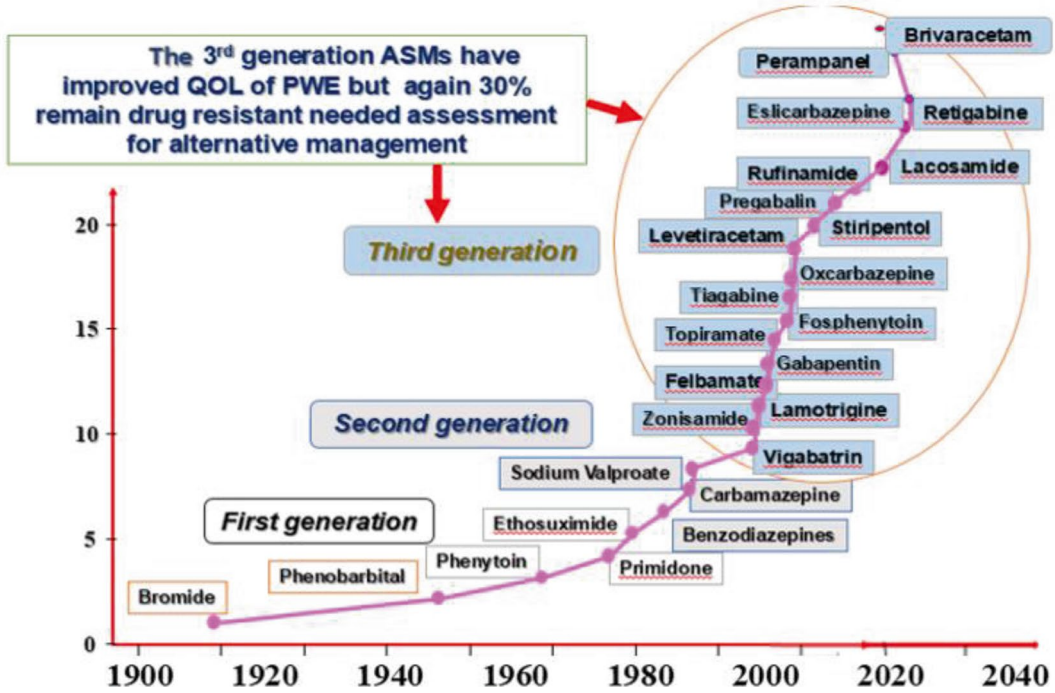


Fig. 15.3 Available anti-seizure medications (ASMs). *QOL* quality of life, *PWE* people with epilepsy

good to no effect. It is a safe method, and before using it, we must think about the positive and negative aspects of the method. Moreover, above all is the mental health of the patient [40]. Alternative treatments include surgical resection of the seizure focus, ketogenic diets, vagus nerve stimulators, and implantable brain neurostimulators.

15.9 Prognosis of Seizures in Cerebral Palsy

Early identification, correct diagnosis of seizure, epilepsy or syndrome, and appropriate anti-seizure management are likely important for the long-term outcome of seizures and relevant comorbidities [24, 25] (see Chap. 31). A sleep-awake *video-EEG* recording is the gold standard for seizure and EEG activity monitoring (Fig. 15.1) [27]. The goal of treatment is *complete* remission or to minimise seizures and side effects and also identify favourable or unfavourable relapse risk factors for early decision-making. Epilepsies in CP can remit with AED medication in approximately half of all cases of CP and in up to 20% in cases of spastic *quadriplegia* or *hemiplegia*, even with a history of status epilepticus or periods of daily seizures, up to 10 years from epilepsy onset. Anti-seizures could be discontinued without relapse in 14%. Older age, perinatal aetiology, and improvement on EEG were favourable factors [36, 42]. In a study of 107 children, polytherapy was used in 87.5% of patients over the 8 year period [35, 36]. Regarding *outcome*, 45.7% of patients had been seizure-free and 54.1% were still having seizures. A total of 45% of patients with CP and epilepsy achieved remission (*with and without antiepileptics*), but after a relatively long treatment duration (Fig. 15.3). Remission was affected by patient- and epilepsy-related factors [35, 36]. The *developmental* milestones and the clinical neurology follow-up examination are recommended for all neonates with seizures [44]. Chin [45], in a criti-

cal presentation of Szpindel et al. publication [12], writes that this work attempts to identify deficiencies in the medical care (healthcare utilisation) of children with epilepsy and cerebral palsy by comparing this with the medical care provided to children who suffer exclusively from epilepsy (https://www.hdruk.ac.uk/news/hdruk-launches-transformational-new-search-functionality-cohort-discovery/).

15.10 Conclusion

Epilepsy in children with CP is found in about *one-third* of cases and higher incidence in cases with spastic tetraplegia and hemiplegia. All seizure types can be found, such as focal or focal impaired awareness and focal to bilateral tonic-clonic seizures. In normal CP children, idiopathic generalised or self-limited epilepsy seizures may also be diagnosed. *Most* types of seizures in CP patients are *focal*, and the preferred anti-seizure medication is *sodium channel* blockers and/or broader spectrum drugs. Children with drug-resistant seizures should be assessed for *alternative* treatments, such as *ketogenic* diets, *vagus* nerve stimulations, and surgical resection of the seizure focus. In *general*, the management of children with CP and epilepsy require multi-disciplinary team assessment and subsequent follow-up and appropriate care.

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Epilepsy in Adults with Cerebral Palsy

16

Cliff Wayne Hampton

Abstract

Epilepsy is a common comorbid condition occurring in patients with cerebral palsy. Clinical features of seizures experienced will depend on the location, extent, and aetiology of the structural lesion causing the cerebral palsy. Physiologic and psychological non-epileptic episodes should also be considered as potential causes of paroxysmal events. Once a diagnosis of epilepsy is established, the goal of *pharmacologic* and *non-pharmacologic* treatments is to prevent seizures without producing toxicities or intolerable adverse effects. If *medical* treatments are unable to secure seizure freedom for a patient, there are several surgical and even some non-surgical options available to assist in reducing the seizure burden.

Keywords

Epilepsy · Adults · Management

16.1 Introduction

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures. This is clinically applied as an individual having at least two unprovoked seizures occurring >24 h apart, one *unprovoked* seizure, and a probability of further seizures similar to the general recurrence risk after two unprovoked seizures, or diagnosis of an epilepsy syndrome [1]. The lifetime prevalence of epilepsy in the general population worldwide is approximately 7.6 per 1000 people [2]. The *prevalence* of epilepsy in cerebral palsy, however, is substantially higher. Published studies show a prevalence of epilepsy in cerebral palsy varies widely, but most between 35% and 62%, with an average of 43% [3]. One systematic review of 72 epidemiology studies involving 53,969 individuals demonstrated approximately one-third of children and adolescents with cerebral palsy as developing epilepsy [4].

Seizures are the key clinical feature in *epilepsy* and are defined as transient occurrences of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The clinical *manifestations* of a seizure in cerebral palsy are determined by their anatomic location and the affected neural networks. Focal-aware seizures, focal-onset seizures with impaired awareness, and focal motor or non-motor onset with evolution to focal or bilateral tonic-clonic convulsions are all possible and common seizure types in cerebral palsy [5, 6].

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16.2 Aetiology

Epilepsy is the most common non-motor *neurological disorder* comorbidity in patients with cerebral palsy [5, 6]. The majority of electroclinical syndromes associated with cerebral palsy are considered as epilepsies attributed to and organised by structural-metabolic causes. Examples *include* but are not limited to malformations of cortical development, neurocutaneous syndromes, tumour, infections, trauma, vascular malformations, perinatal insults, metabolic conditions, hypoxic-ischaemic encephalopathy or perinatal stroke, and intracranial haemorrhage [7, 8]. Factors that have been shown to be associated with the development of epilepsy in people with *comorbid* cerebral palsy include positive family history of epilepsy, positive seizure history within 72 h of birth, quadriplegic cerebral palsy type, individuals with more severely affected gross and fine motor functions, and moderate to severe intellectual disability [9] (see Chaps. 2, 5, and 12).

The manner in which epilepsy develops is a complex, poorly understood process. However, it seems clear that involvement of the *cerebral cortex* is a common thread in the development of epilepsy, and emerging evidence suggests that epigenetic processes produce a kind of molecular memory that underlies epileptogenesis [10]. Since lesions from the aetiologies listed above often involve either malformation or damage to cortical tissue in cases of cerebral palsy, it is understandable that individuals with these lesions will be at *risk* for developing epilepsy (see Chaps. 12 and 15).

16.3 Clinical Characteristics

Epilepsy is a phenotypic *definition*, but in the current International League Against Epilepsy (ILAE) classification structure, epilepsy classification is strongly influenced by aetiology. An individual with CP and epilepsy is, by definition, assigned to a localisation-related epilepsy category and would, in most cases, be excluded from a self-limited *focal epilepsy classification* because the diagnosis of CP will frequently include an identifiable structural brain lesion. However, it is critical to consider alternative possibilities as well. For *example*, an individual with cerebral palsy could have epilepsy related to another underlying genetic factor, or an individual may have self-limited seizures that develop or remit due to a dynamic maturational factor even as the brain lesion for which the cerebral palsy was diagnosed remains a static condition [11]. These scenarios would have implications for prognosis and treatment. It is also important to understand that some underlying conditions, one example being *Lennox-Gastaut* syndrome, could lead to both a diagnosis of cerebral palsy and also a generalised-onset epilepsy syndrome, also with potential impact on medication selection and other treatment options.

16.4 Diagnosis and Differential Diagnosis

In addition to epileptic seizures, there are several psychological and physiologic non-epileptic causes of paroxysmal episodes. In *general*, the differential diagnosis of a paroxysmal neurologic episode would *include* psychogenic non-epileptic events and panic attacks, transient cerebral hypoperfusion (i.e. *syncope*), hypoglycaemia, acute dystonic reactions, hemifacial spasm, non-epileptic myoclonus, parasomnias, cataplexy, hypnic jerks, transient ischaemic attacks, migraines, and transient global amnesia. In *children*, non-epileptic staring spells, tic disorders, shuddering attacks, breath-holding spells, gastroesophageal reflux (*Sandifer syndrome*), benign myoclonus of infancy, mannerisms, and spasmus nutans are also considerations [12]. Differentiation between these diagnoses can usually be made with a thorough history, including a *detailed* semiological description of the episodes as well as a physical examination. Ancillary testing is often sought with an electroencephalogram (EEG), which has a low sensitivity but when abnormal can be fairly specific. Long-term video EEG with capture and characterisation of spells is the *gold standard* for diagnosis of epileptic seizure vs. non-epileptic aetiologies [13, 14].

16.5 Management

Due to the high prevalence of epilepsy in CP, the clinician should have a low threshold for initiating an epilepsy workup. The purpose of the evaluation is to *confirm* the diagnosis of epilepsy and, in cases of drug resistance, select options for surgical intervention. Often magnetic resonance imaging (*MRI*) of the brain will have already been completed at the time of diagnosis of the cerebral palsy and doubles as an important step in the evaluation of epilepsy as well. Routine video electroencephalogram (*EEG*) is typically the next step in diagnostic examination to evaluate for interictal evidence of epilepsy in the form of focal background slowing, interictal epileptiform discharges, or other abnormal findings. After a single unprovoked seizure in an individual with known cerebral palsy, the predicted recurrence risk is high enough that treatment with anti-seizure medication would usually be warranted [15].

16.5.1 Oral Medication

The goal of *medical therapy* in epilepsy is to achieve complete seizure remission without intolerable adverse effects. Anti-seizure medication selection is based on many factors, *including* type of electroclinical syndrome, medical comorbidities, the patient's age and childbearing potential, potential adverse effects, avoiding interactions with other medications or allergic reactions, and regional medication availability, among other factors [6, 16]. A list of *medications* and the corresponding year of their introduction is found in Fig. 16.1. Medical therapy with anti-seizure medications is considered first-line treatment in cases of epilepsy, and treatment should be individualised to the patient's unique individual medical circumstances (see also Chap. 27).

In many cases of individuals with epilepsy, *seizures* can be prevented with appropriately chosen and dosed anti-seizure medications. Some will continue to have seizures despite optimal medical management with anti-seizure medications. Drug-resistant epilepsy is defined as the 'failure of adequate trials of 2 tolerated, appropriately chosen' anti-seizure medications to achieve sustained seizure freedom [17–20]. Once it is determined that an individual has drug-resistant epilepsy, the patient should be referred to an epilepsy centre for further diagnostic studies to explore possible surgical treatment options. The *overall prevalence* of drug-resistant epilepsy is approximately 32.4% of all epilepsy cases [19]. There are fewer studies on drug-resistant epilepsy specifically evaluating individuals with both cerebral palsy and epilepsy [20]. Those with cerebral palsy and a *neonatal seizure* history have been found to have higher rates of developing epilepsy and a higher rate of poor epilepsy prognosis [8]. Similarly, in at least one study, findings of neonatal distress in the form of a low APGAR score of 1–4 at 5 min of life as well as a focal-onset epilepsy and focal background slowing on EEG were all predictive of future development of drug-resistant epilepsy [20] (see Chap. 9). No studies have demonstrated a significant difference in the prevalence of drug-resistant epilepsy in the cerebral palsy population as compared to the general epilepsy population.

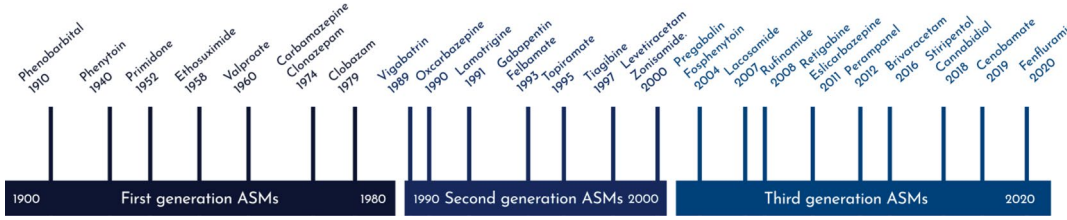


Fig. 16.1 Timeline of antiseizure medications and their year of introduction

16.5.2 Other Methods

Individuals with drug-resistant epilepsy should be referred to evaluate options for epilepsy surgery. This is particularly important in cases of CP, as many of these will have an identifiable *anatomical lesion* that may or may not serve as a surgical target (Fig. 16.2). Initial workup typically includes high-resolution magnetic resonance imaging (MRI) of the brain and video electroencephalogram (EEG) monitoring [21]. In order to confirm and localise an *epileptogenic zone*, other ancillary tests such as positron emission tomography (PET), neuropsychiatric testing, functional MRI (fMRI), Wada test, ictal single-photon emission computed tomography (SPECT), magnetoencephalography (MEG), and others can also be used (Table 16.1) [22, 23]. If further localisation is required or if precise identification of eloquent cortex and epileptic cortex is needed, invasive monitoring can be performed with stereotactic EEG or with conventionally placed subdural or depth electrodes.

The goal of *epilepsy surgery* is to improve seizure control by resection, ablation, or neuromodulation by electrical stimulation of epileptogenic tissue while preserving brain tissue to prevent significant neurologic deficits [24].

Leisonectomy, or surgical resection of what is thought to be the ictal onset zone, is still considered the most effective surgical intervention in terms of the number of patients with an outcome of seizure freedom. The success of this intervention depends on the location of the ictal onset zone and the aetiology of the lesion being resected.

Other alternatives include stereotactic *radiosurgery* with radiofrequency thermocoagulation, focused ultrasound, or gamma knife [25]. *Laser interstitial thermotherapy* (LiTT) is an increasingly used minimally invasive technique for ablating pathologic soft tissues. However, foci amenable to *LiTT* are quite limited, as this is an emerging therapy with limited data to support its use [26]. Particularly when combined with magnetic resonance-guided stereotactic methods of localisation, there may be a reduced risk of surgical comorbidities [27].

Neuromodulation using devices that provide electrical stimulation is another surgical option for patients with drug-resistant epilepsy. The first of these devices that was introduced is the vagus nerve stimulator (VNS), which has been demonstrated to increase seizure-free time by electrically stimulating the left vagus nerve [27, 28]. *Responsive neurostimulation* (RNS) has been studied and found to be effective in reducing seizures for adults with drug-resistant epilepsy by

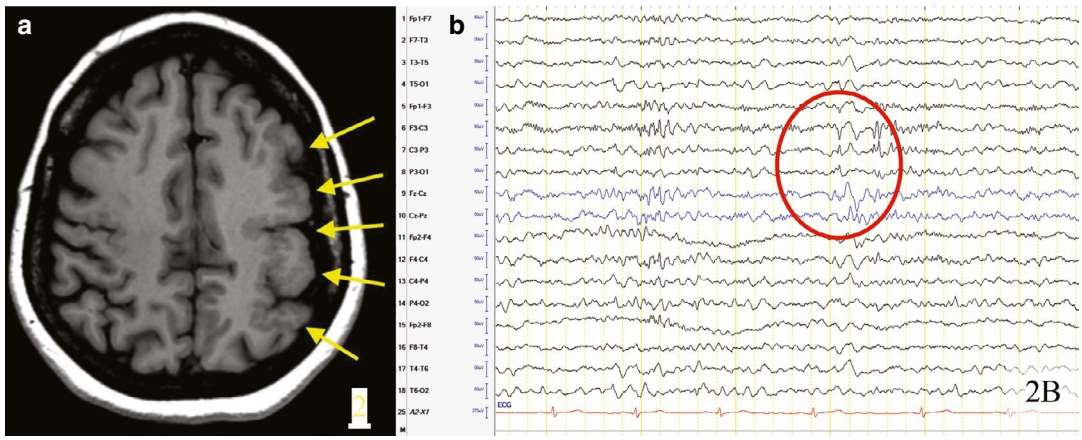


Fig. 16.2 Patient with extensive cortical migration defects over the left hemisphere, clinically with right spastic hemiparetic subtype of cerebral palsy as well as drug-resistant epilepsy. (**a**) Shows an MRI brain with axial T1 weighted sequencing shows extensive polymicrogyria. (**b**) Shows an interictal epileptiform discharge (spike/wave) with phase reversal maximal at C3, corresponding roughly to the left post-central gyrus, indicating an area of cortical irritability from which a seizure is more likely to arise

Table 16.1 Studies used in the pre-surgical evaluation of epilepsy

	Utility	Disadvantages
Brain magnetic resonance imaging (MRI)	General anatomic survey of potentially epileptogenic lesions Widely available	No structural lesion can be identified on MRI in many cases of drug-resistant epilepsy An identified anatomic lesion may not correlate to the ictal onset zone
Video scalp Electroencephalogram (EEG)	Neurophysiologic identification of irritative zone and possibly the ictal onset zone	Deep epileptogenic foci may be difficult to localize precisely
High-resolution EEG (HD-EEG)	Deliniation of the irritative zone	Not widely available
Interictal magnetoencephalography (MEG)	Deliniation of the irritative zone	Not widely available
Interictal electrical source imaging (ESI)	Deliniation of the irritative zone	Not widely available
Interictal functional MRI (fMRI)	Deliniation of the irritative zone Localization of eloquent cortex to predict post-surgical language and memory outcomes	Not widely available
Interictal 18-F-fluoro-deoxyglucose positron emission tomography (FDG-PET)	Localize the functional deficit zone	Not specific in localizing an irritative or ictal onset zone
Ictal single-photon emission computed tomography (SPECT)	Localize the ictal onset zone	Not widely available Technically challenging
Ictal HD-EEG	Localize the ictal onset zone with increased accuracy and specificity compared to conventional EEG	Not widely available
Ictal ESI	Localize the ictal onset zone	Not widely available Technically challenging
Ictal EEG-fMRI	Localize the ictal onset zone	Not widely available Technically challenging
Wada test	Lateralization and localization of language function Prediction of postoperative memory decline	Invasive procedure that carries an inherent risk of harm
Tractography	Assess risk of postoperative visual field deficits	Not widely available
Intracranial EEG via open craniotomy (cEEG)	Precise pre-surgical treatment localization of ictal onset zone	Invasive procedure that carries an inherent risk of harm
Stereotactically placed intracerebral depth electrodes (sEEG)	Precise pre-surgical treatment localization of ictal onset zone	Invasive procedure that carries an inherent risk of harm

implanting leads directly into the seizure-onset zone and providing electrical stimulation in response to abnormal electrical activity [29–31]. Deep brain stimulation (DBS), which has been available for other neurologic indications such as *Parkinson's* disease and *essential tremor* for several years, has also been found to reduce seizures for *adults* with drug-resistant epilepsy by electrically stimulating the anterior nucleus of the thalamus [31, 32]. Additional surgical targets such as the cerebellum, the centromedian nucleus of the thalamus, the pulvinar of the thalamus, and several others are under investigation for neuromodulation, a novel approach of targeting aberrant neural networks rather than epileptogenic foci [32].

The *ketogenic diet*, a high-fat, low-carbohydrate diet, is meant to induce the formation of ketone bodies. There is some evidence for seizure freedom and seizure reduction, though published studies are not always scientifically rigorous [33, 34]. Additionally, this intervention is *difficult* for many patients to implement, and

many adverse effects can be caused, including gastrointestinal symptoms, metabolic abnormalities, nephrolithiasis, cardiomyopathy, and cardiac arrhythmia with prolonged QT interval. It remains an option in selected cases of drug-resistant epilepsy if the proper support is locally available to the individual [34].

Transcranial magnetic stimulation is not widely used to treat epilepsy due to a lack of optimised treatment paradigms or identification of patients who could benefit. However, there have been favourable results in some trials, and studies are ongoing to determine its utility in cases where individuals have not reached desired levels of seizure freedom with pharmacologic treatments and are not candidates for epilepsy surgery [35].

16.6 Prognosis

In the seminal study by Kwan and Brodie, which studied epilepsy diagnoses of all causes, 63% of patients remained seizure-free either on or off anti-seizure medications [36]. By *comparison*, and probably reflective of the diverse aetiologies of cerebral palsy itself, data on seizure remission varies widely in single-centre studies, with reports of seizure freedom as low as 21% and as high as 67% [8, 37–39]. However, over time, remission rates do increase for patients with cerebral palsy and epilepsy, and anti-seizure medication discontinuation can be considered for some patients. In one study, remission of epilepsy by 11 years occurred in 47% of patients, and of those, approximately one-third had sustained seizure freedom after discontinuation of anti-seizure medications [40]. Of course, there are countless factors that may impact sustained seizure *freedom* on or off medications and with or without surgical or other interventions, making specific prognostication quite difficult in individual cases.

16.7 Conclusion

Epilepsy is a common comorbid condition with cerebral palsy. Due to the nature of CP, the associated epilepsy syndrome is often focal-onset. *However*, there are situations where a generalised-onset epilepsy syndrome can also be seen in an individual with CP. Similar to cerebral palsy, epilepsy is a phenotypic rather than aetiologic diagnosis, and so there are a variety of presentations, prognoses, and treatment factors for each condition that will depend on the specific cause. Treatment of epilepsy consists of anti-seizure medications as *first-line* pharmacotherapy. If a trial of two or more appropriately chosen anti-seizure medications fails to achieve seizure freedom, a diagnosis of drug-resistant epilepsy is given, and additional workup for potential surgical interventions is initiated. *Surgical options* include resection, ablation, and neuromodulation, and less commonly, non-surgical options are employed as well. Seizure freedom is the goal in cases of epilepsy, and is achievable in a sizable percentage of patients with epilepsy and CP if seizures are treated with appropriate *pharmacologic* and *non-pharmacologic* interventions. In a smaller percentage of cases, some patients may eventually maintain seizure freedom without anti-seizure medications.

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Early Diagnosis and Differential Diagnosis of Cerebral Palsy

17

Rudolf Korinthenberg and Christos P. Panteliadis

Abstract

Cerebral palsy (CP) is a disorder with diverse causes that include early residual brain damage and non-progressive genetic disorders. Early *treatment* with multimodal, task-oriented rehabilitation has been shown to improve daily *functioning* and *integration* of affected children. However, *early diagnosis* is a prerequisite for early treatment. If, especially in preterm infants, the perinatal history was severe and brain damage was documented, early diagnosis of CP is straightforward. However, because more than 50% of CP patients had an unremarkable perinatal period after a full-term birth, valid risk predictors and clinical procedures for early diagnosis are needed in these cases. In *addition* to traditional testing for *persistent* primary neonatal reflexes and impaired muscle tone, a number of *standardized* tests have been developed that have high sensitivity and specificity for predicting impending CP and atypical development even in the first months of life. Neurodegenerative and metabolic disorders that progress slowly and have predominantly motor symptoms can mimic CP. Although rare, they should not be overlooked because of their importance in genetic counseling, treatment, and prognosis. The *present* chapter has been extensively revised with regard to early diagnosis, diagnostic workup, and differential diagnoses.

Keywords

Cerebral palsy · Early diagnosis · Developmental testing · Ataxia · Dystonia · Neurodegenerative and neurometabolic disorders

17.1 Introduction

The diagnosis of cerebral palsy (CP) is a *phenomenological* diagnosis based on clinical assessment. CP is an "umbrella term" for various clinical pictures with predominantly motor symptoms that originate in the pre-, peri-, or early postnatal period. *Depending* on the location and severity of the underlying brain injury, cognitive impairment, sensory perception disorders, and epilepsy often occur simultaneously. It is a non-progressive disorder, although symptoms change as the child ages and develops (see also Chaps. 2 and 12).

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Regarding *etiology*, authors have historically used the term CP only for cases with acquired early brain damage due to infection, hypoxic-ischemic, cerebrovascular, or traumatic events (see also Chaps. 5 and 6). However, the consequences of early brain damage are often indistinguishable from primary brain malformations, and several genetic mutations and syndromes have a similar clinical picture to cerebral palsy [1]. Therefore, it is more appropriate to use a purely phenomenological definition of CP and define the etiology at a separate level [2].

It is *assumed* that early intervention already in the first months of life improves the developmental outcomes of affected children, at least in terms of daily functioning and social integration [3]. Because such early treatment first requires early diagnosis, two large population-based epidemiological studies in the second half of the twentieth century, among others, examined *risk factors* for the later development of cerebral palsy and other disabilities [4]. A study in the United Kingdom (1970) was able to predict disability based on a combination of pre- and perinatal risk factors in a cohort of 14,862 children that were followed from birth up to the age of 7 years. *Similarly*, Ellenberg and Nelson in the United States followed a cohort of 32,000 children from birth to the age of 7 years. They *demonstrated* that striking neurologic findings of increased tone in the neck, arms, legs, and trunk at 4 months of age were predictive of the development of later motor disabilities, particularly in association with a delay in motor milestones [5]. Such *epidemiological* findings, although statistically convincing, are not very useful for predicting the need for early treatment in individual infants. Validated tests with clear thresholds are needed here and are presented in this chapter.

At the same time, CP must be *distinguished* from other neurological diseases that worsen over time, such as brain tumors, neurodegenerative and neuromuscular diseases, and inborn errors of metabolism. In *addition*, CP must be distinguished from spinal cord disorders and disorders with purely intellectual dysfunction (mental retardation). Early diagnosis must therefore take into account both the etiology of CP (acquired or genetic) and the differential diagnoses that mimic CP [6].

17.2 Early Diagnosis

17.2.1 The Objective of an Early Diagnosis of CP

Early diagnosis of CP followed by early treatment is thought to improve the expected treatment effects by taking advantage of the higher *plasticity* and regenerative capacity of the brain in early childhood [7]. However, until recently, reviews and meta-analyses concluded that better treatment effects were only described in *methodologically* inadequate studies but never confirmed in properly designed clinical trials. In addition to an actual lack of efficacy, a variable definition of *early* treatment, variable interventions, and varying disease severity could be responsible for these disappointing results. Therefore, as recently as 2015, Scandinavian authors concluded that there was a large unmet need for research in the field of early intervention for cerebral palsy [8].

However, this has changed in recent years. In 2021, an *international* working group published evidence-based practice guidelines that provide clear recommendations and caveats for the management of young children with CP aged 0–2 years. These *guidelines* are based in part on sufficient scientific evidence and in part on expert consensus. It should be noted that traditional passive-motor and physical-only interventions have not been shown to be effective and resulted in little change in motor performance. In contrast, task-based *motor training* and restricted-use techniques, as well as cognitive, sensory, and social training, significantly improved daily living skills, cognitive development, social interaction, and family integration [3, 7] (see also Chaps. 18, 19, and 20). Although many questions remain unanswered, the call for early diagnosis of CP has become more urgent again due to these recent developments [9].

However, *early diagnosis* of CP can be difficult. Infants with a history known to be associated with increased risk of CP, such as prematurity, severe asphyxia, cerebral hemorrhage, or meningitis, are usually monitored closely by pediatricians and specialized clinics, at least in economically advanced countries [4]. If they

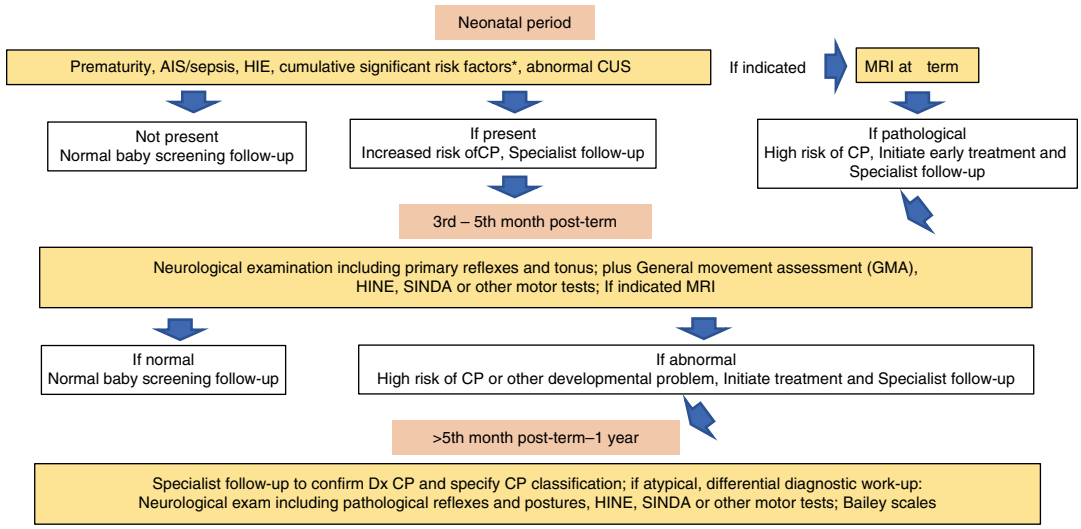
have suffered neurologic damage documented by clear *pathology* on neuroimaging, the likely diagnosis of CP can be made early, and treatment is usually initiated before discharge from the neonatal unit. However, more than half of the neonates who later developed CP did not have such obvious brain damage [2]. In *these* infants, early clinical diagnosis may be difficult because of slowly developing symptoms. In a Danish study of 1291 children born between 1995 and 2003, the median age for diagnosis of CP was 11 months [10]. In less economically developed countries, the age at diagnosis is often much higher [2].

17.2.2 How to Make an Early Diagnosis in CP

Obstetric and perinatal *risk factors* and optimality scores have been identified for decades to predict a newborn's risk of later developing cerebral palsy [4]. In a recent publication, 3250 former full-term newborns from the Canadian Cerebral Palsy Registry were compared with children from the Alberta Pregnancy Outcomes and Nutrition Study. A model with *12 variables* (tobacco use, drug use, diabetes, preeclampsia, chorioamnionitis, prolonged rupture of membranes, male sex, number of pregnancies, number of miscarriages, 5-min Apgar score, weight, and gestational age) was calculated that predicted cerebral palsy with a sensitivity of 56% (95% CI 52–60) and a specificity of 82% (95% CI 81–84) [11]. The effect of these variables is additive and contributes significantly to prediction of CP more than hypoxic-ischemic encephalopathy. Thus, using the published calculator, an increased risk for CP can be predicted already in the neonatal period, giving reason to enroll the child in an appropriate screening program [11, Supplement 2].

Following an infant with increased risk of CP, an algorithm as depicted in Fig. 17.1 can be recommended.

The *first clinical symptoms* of developing CP are disturbances in muscle tone (either hypotonic or hypertonic), persistence of primitive reflexes (e.g., Moro, ATNR), abnormal postures and movements, and delayed motor milestones (see Chap. 9). Epileptic seizures may occur as a comorbid feature. However, these symptoms and findings are not CP-specific (see Chap. 15). They can also be observed in other disorders of brain development, but also as a transient phenomenon



Explanations: AIS= amnion infection syndrome, HIE= hypoxic ischemic encephalopathy, CUS = cranial ultrasound, MRI= magnetic resonance imaging, CP= cerebral palsy, HINE= Hammersmith Infant Neurological Assessment, SINDA= Standardized Infant NeuroDevelopmental Assessment, *further significant risk factors: tobacco use, drug use, diabetes, pre-eclampsia, prolonged rupture of membranes, male sex, no of pregnancies, number of miscarriages, birth weight, gestational age, 5-minute APGAR [11]

Fig. 17.1 Flow-chart from an increased risk of CP to an early diagnosis in the first months of life

with benign outcome, even after premature birth [12]. It is not until the third and fourth trimesters of life that more specific signs usually appear, such as a spastic hemiplegia pattern or hypertonic patterns in the upper and lower limbs with leg scissoring and increased deep tendon reflexes (see Chap. 12). Therefore, early treatment in the first months of life is often based on a still relatively nonspecific diagnosis of impending CP (*high CP risk* [7]), whereas the definitive diagnosis of CP, including correct classification, may be made later [2]. However, once CP or *high CP risk* is confirmed, treatment with the recommended task-oriented and interactional interventions should not be delayed [2, 3].

The first *important question* to ask when examining an infant is whether an observed delay in developmental milestones or postural dysfunction is severe enough to suspect CNS pathology. For *example*, is a neurologic problem present in an infant who is not yet crawling or a toddler who cannot yet walk independently, or are they merely demonstrating borderline development or a normal variant such as "dissociated motor maturation" [13]? To *approach* this question, one must consider the wide variability of normal development in all developmental domains, e.g., motor, adaptation, perception, hearing, vision, and social contact, ideally relying on standardized developmental tests. Not only the quantity of motor development should be considered, but also the quality of movements.

A *number* of such developmental tests have been developed and validated to objectively assess neurological function and predict outcome in infants. The Hammersmith Infant Neurologic Examination (*HINE*) has been validated for low- and high-risk neonates, infants, and preterm infants from birth [14, 15]. Its predictive value for cerebral palsy has been shown to be high throughout the first year of life, and the most predictive items are those assessing movement quality and quantity [16]. However, a recent analysis has shown that an abnormal HINE score in the first year of life is also predictive of significantly abnormal cognitive function at 2 years of age (MDI < 70 in Bailey II scales). Thus, like other tests, the HINE is not specific for CP [17]. The infant motor profile (IMP) is applicable to children aged 3–18 months. It has been shown to differentiate between infants with normal neurological status, simple and complex mild neurological dysfunction, and abnormal neurological conditions [18]. The *General* Movement Assessment (GMA) is based on gestalt perception of spontaneous movements in infants. Its predictive value for normal or abnormal development is very high in infants with various developmental risks and underlying diseases [19] (see also Chap. 11).

Another recently validated and published screening system for neurodevelopment is the standardized infant neurodevelopmental assessment (*SINDA*). It consists of three scales (neurological, developmental, and socioemotional) to be used at 6 weeks to 12 months of age. Intrarater and inter-rater reliability were reported to be good. Two *consecutive* studies of the predictive value of SINDA were conducted at a German center for pediatric neurology, involving 181 (validation of the neurological scale) and 223 (validation of all three scales) infants who were suspected by their pediatricians to be at risk for a developmental disorder. All infants were followed until at least 24 months of age, when a complete neurological examination and *Bailey* II test were performed. A *Bailey* Mental Developmental Index or Psychomotor Developmental Index of less than 70 or a diagnosis of cerebral palsy was considered an atypical outcome. In the first study, low neurological scores ≤21 predicted an atypical outcome and CP with a sensitivity of 89% and 100% and a specificity of 94% and 81% [20]. In the second study, atypical neurological scores again predicted an atypical outcome (sensitivity 83%, specificity 96%). Atypical developmental scores predicted intellectual disability with a sensitivity of 77% and specificity of 92%, and atypical emotionality and atypical self-regulation were associated with behavioral and emotional disorders [21]. SINDA is *described* as a relatively easy-to-use, sensitive, and specific indicator of impending disability in at-risk children, but like all other tests, it does not lead to a specific neurological diagnosis.

Together with these standardized tests, a developmental neurologic examination by an experienced examiner can detect or exclude neurologic signs *pathognomonic* of cerebral damage, such as increased tone, abnormal reflexes, ataxia, or dystonic posture [22, 23]. However, despite these investigations, the initial diagnosis sometimes remains only a provisional one. In these cases, the patient must be followed up at regular intervals.

In infants with severe perinatal conditions, cranial *ultrasound* (US), *EEG*, and *MRI* examinations of the brain may be helpful in predicting the risk of cerebral palsy in addition to the above scores and clinical findings. In a cohort of 102 preterm infants born with a gestation of <32 weeks or a birth weight of <1500 g, the predictive value of cranial ultrasound examinations at 12 months of age was even higher than that of an abnormal HINE score performed at the same age [24]. In a group of 1053 NICU patients with regular ultrasound examinations in the neonatal period, 44% of children with ventriculomegaly and 52% with abnormal echolucencies on US developed cerebral palsy at prospective neurologic follow-up at 2 years of age. In *contrast*, neonatal ultrasound findings were normal in 43% of children with cerebral palsy [25]. In neonates with hypoxic-ischemic encephalopathy, an abnormal background EEG pattern was highly predictive of an abnormal neurologic outcome (positive predictive value 0.88), which was even increased by an abnormal ultrasound or MRI finding (positive predictive value 1.0). *Abnormal* signal in the posterior part of the internal capsule and diffuse cortical gray matter damage were the most predictive MRI findings [26]. In addition, newer MRI techniques such as diffusion tensor imaging and fiber tracking can predict the severity of periventricular leukomalacia and neurologic impairment [27, 28].

In a *systematic review* of early diagnostic methods for predicting CP risk published in 2017, the authors concluded that Prechtl's GMA (98% sensitivity) and HINE (90% sensitivity) were the best predictive tools before the corrected age of 5 months, and after 5 months of age, HINE (90% sensitivity) and the Developmental Assessment of Young Children [29] (83% sensitivity of the C index) were the best. The value of these clinical scores was consistent with the predictive value of an MRI scan at birth (86–89% sensitivity) and at 5 months (86–89%) [7]. The authors at Nationwide Children's Hospital/Columbus, Ohio, investigated the feasibility of these criteria in their follow-up clinic in the neonatal intensive care unit. Every member of the multidisciplinary staff in their clinic had received training in GMA and HINE. By *comparing* cases before and after implementation, they demonstrated that the measures were feasible and that the new procedures resulted in greater investigator competence and shorter time to diagnosis of CP [30]. A Delphi conference with a multiprofessional expert panel of cerebral palsy researchers and clinicians defined the following three main tasks for physicians seeking early diagnosis of CP: (i) referral for GMA testing, (ii) referral for HINE testing, and (iii) appropriate communication of the diagnosis and counseling of the family. While these publications highlight the feasibility of the procedures in a high-level clinic setting, it seems questionable whether this would also be the case in a more general pediatric setting and in less economically developed regions and countries.

17.3 How to Approach the Etiology of CP and its Differential Diagnoses

When the presence of a pathological condition is confirmed, the question of its cause arises. Clarifying the *etiology* contributes to the long-term prognosis, helps to under-stand genetic risks for the family, and, in the case of some differential diagnoses, may open a window for etiologically oriented treatments. Last but not least, knowing the cause of their child's disability is one of the most important factors in family coping. *However*, clarifying a yet unknown etiology is usually not one of the most important tasks of early diagnosis in CP. It can often be postponed until more clinical information has been gathered over a few months and a relationship of trust has developed

between the investigator in charge and the family. The *exception*, of course, is when there is a strong suspicion of a genetic etiology with a risk of recurrence in siblings or when there are reasons to suspect a treatable disease (see Chaps. 5 and 7).

In *etiologic* workup, it is essential to obtain a detailed personal and family history and to perform a complete pediatric and neurologic examination. Acute neonatal onset of hemiplegia, usually accompanied by focal seizures, is a hallmark of perinatal brain infarction; however, in most cases with hemiplegic CP the onset is prenatal and the symptoms develop over several weeks. *Neuroradiological* examinations for CP children are recommended by many authors, but sophisticated laboratory investigations are only necessary if a genetic etiology or metabolic disease is suspected.

In many patients, *prenatal* or *perinatal factors* known to be associated with increased risk of brain damage and cerebral palsy can be identified [4, 11, 31, 32]. However, evaluating such potential risk factors and distinguishing acquired CP from genetic disorders are often problematic. Although *neonates* with perinatal asphyxia may present with CP later in life, most do not. Therefore, a critical approach is needed when obtaining the perinatal history (see Chap. 9). To assume asphyxia as the cause of CP, clear signs of acute neonatal hypoxic-ischemic encephalopathy must be present, e.g., somnolence or coma, neonatal multifocal seizures, abnormal muscle tone). In *addition*, a 5-min Apgar score < 5, a markedly abnormal umbilical cord pH (<7.0), and signs of multiorgan failure such as renal failure, hepatopathy, and cardiac failure are signs of asphyxia severe, enough to cause long-term disability [32]. However, it is important to remember that, conversely, preexisting neurologic disease and genetic syndromes can also lead to prematurity and severe asphyxia.

The *static* nature of the underlying brain damage and motor disability is one of the main features of CP. Therefore, one of the most important diagnostic features of the diseases to consider as a differential diagnosis is their usually progressive course. However, *recognition* of progressive neurologic disease in infants and young children can be much more difficult than expected. Most CNS disorders in children result in a delay in brain maturation 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 more apparent to parents and medical personnel. This may suggest progression even when no true regression of function has occurred. To obtain a reliable indication of a diagnosis of progressive disease, one must look for an obvious loss of functions and abilities that have already been acquired, or at least a stagnation of development. On the other hand, secondary feeding and respiratory problems, orthopedic complications, and epileptic encephalopathy in children with CP may also lead to the false impression of progressive disease (see Chaps. 25, 34, and 36). On history taking and clinical examination, certain signs suggest genetic, neurometabolic, or space-occupying disorders rather than CP (Table 17.1).

Neuroradiological *examinations* such as cranial ultrasound (in the first year of life), MRI, and CCT can be extremely helpful in the etiologic workup and differential diagnosis of CP (see Chaps. 10 and 13). In more than 80% of CP cases, an MRI scan of the brain reveals pathologic findings and contributes to the etiologic diagnosis. Damage to the brain during the first trimester of pregnancy results in dysplastic findings such as agenesis of the corpus callosum, migratory disorders such as pachygyria, cortical heterotopia, and schizencephaly. Later, polymicrogyria, periventricular leukomalacia, and the remnants of intraventricular hemorrhage are characteristic (see Chap. 4). From 37 weeks, typical findings include selective neuronal necrosis with cerebral atrophy and ulegyrias, parasagittal watershed infarcts, multicystic encephalopathy, and localized infarcts leading to porencephaly [33, 34]. Apart from these findings, malformations, brain tumors, and patterns specific for certain metabolic syndromes can also be identified. Subependymal and parenchymal calcifications are indicative not only of prenatal infections

Table 17.1 History and clinical findings suggestive of a disease other than CP

• Positive family history for CP: Genetic background
• Progressive neurological symptoms: Tumor, inflammatory, neurodegenerative/-metabolic
• Psychomotor regression, i.e., loss of already acquired abilities: Neurodegenerative/-metabolic
• Relapsing-remitting or diurnal variability of symptoms: Metabolic or neurotransmitter disorders
• Acute symptoms after fasting: Disorders of energy metabolism
• Lack of risk factors for CP: Think of alternative etiologies
• Primary microcephaly (head circumference < third percentile, already apparent at birth): Familiar, genetic/primary hereditary, intrauterine infection or dystrophy, fetal alcohol abuse syndrome)
• Secondary microcephaly (decreasing percentile, apparent only after birth): Perinatal and postnatal injuries, neurometabolic disorders, Rett syndrome, Cockayne syndrome
• Macrocephaly (>97) or rapidly increasing size of skull: Space-occupying lesions (hydrocephalus, tumor, hygroma), craniofacial dysplasia, leukodystrophies, neurocutaneous disorders, neurometabolic disorders with abnormal accumulation of lipids, glutaric aciduria type 1
• Specific or unspecific malformations and stigmata: Suggesting a genetic etiology when multiple
• Prominent ataxia or hypotonia without spasticity or dystonia: Rather genetic than acquired
• Peripheral nervous system involvement: Neurodegenerative/-metabolic
• Corneal clouding, cataract, atrophy of the optical nerve and retinopathy: Multiple metabolic and syndromic disorders
• Eye movement abnormalities (oculogyria, oculomotor apraxia, paroxysmal saccadic eye movements)
• Skin lesions such as depigmentation or hyperpigmentation: Genetic neurocutaneous syndromes such as tuberous sclerosis complex, incontinentia pigmenti, hypomelanosis of Ito, and many others
• Hepatomegaly and splenomegaly: Metabolic disorders with accumulation of metabolites, chronic infections
• Cardiomegaly and cardiomyopathy: Pompe disease, neuromuscular diseases
• Severe muscle weakness, absent tendon reflexes: Spinal muscular atrophy, congenital myopathies, and muscular dystrophies
• Blindness, deafness, other sensory deficits: Multiple genetic syndromes and metabolic disorders

(cytome-galovirus, toxoplasmosis) but also of some neurodegenerative diseases (Cockayne syndrome, Aicardi-Goutieres syndrome) [6, 35].

A waking and sleeping *electroencephalogram* are required when epileptic seizures or developmental regression/stagnation due to subclinical continuous epileptic activity is suspected. Certain waveforms (giant evoked potentials on slow visual stimulation) are indicative of ceroid lipofuscinosis. Auditory and visual *evoked potentials* are performed when a sensory deficit is suspected. Nerve conduction studies, *electromyography*, and a muscle biopsy are performed to detect or rule out the presence of peripheral neuromuscular disease or peripheral involvement in multisystem disease. Metabolic and genetic testing can be performed as screening when suspicion is low (amino acids, organic acids, chromosomes), but should usually be performed selectively based on a clinically justified diagnostic hypothesis [36].

17.3.1 Clarification of a Genetic Etiology of CP (See Chap. 7)

According to the current definition of CP, not only *acquired* but also genetic cases with non-progressive symptoms are included in this diagnosis. While CP in preterm infants is most often the result of pre- or perinatal brain damage, more than 50% of newborns do not have pre-, peri-, or postnatal brain damage. In these cases, a genetic etiology must be considered. These *include* genetic disorders with dysmorphic syndromes, isolated brain malformations, non-syndromic static abnormalities of motor and mental development, and, last but not least, syndromes that progress so slowly that they are misdiagnosed as static, e.g., Pelizaeus-Merzbacher disease, see Sect. 17.4.8 [1, 37] (see Chap. 7).

The presence of similar symptoms in other family members as well as consanguinity of the parents is a clue to suspect a genetic disease. A

complete family history must include at least three generations. The *timing* and depth of molecular genetic diagnosis depend on the degree of suspicion, the general and local availability of the required genetic tests, and the family's desire to have further children. If a specific disease or syndrome is suspected, direct testing of the corresponding gene(s) is sufficient. For more nonspecific symptom complexes, one of the methods of next generation sequencing (NGS) with parallel investigation of several candidate genes is now more useful than sequential investigation of many genes [1, 37, 38] (see also Chap. 7). However, it should be noted that the commonly used whole-exome sequencing (WES) method is not able to detect lager CNVs, deletions, and duplications; if one of these is suspected, MLPA analysis of the corresponding chromosomal region is indicated (e.g., in SMA, DMD, or CMT1A).

17.4 Differential Diagnoses and Mimics of CP

In most cases, the *diagnosis* of cerebral palsy can be confirmed by history (e.g., pregnancy, childbirth), clinical findings, and possibly additional neuroradiologic studies after an adequate observation period. However, many disease groups, usually rare, can be clinically confused with a CP diagnosis [39, 40]. Therefore, the absence of identifiable risk factors should lead to a more thorough investigation for other possible causes. Sometimes, the definitive diagnosis of CP can only be made by excluding these diseases (Table 17.2).

Table 17.2 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

17.4.1 Neuromuscular Disorders

These are a broad group of disorders that affect the lower motor neurons, nerves, or muscle fibers and do not usually affect the brain. The *diseases* most commonly seen in infancy are spinal muscular atrophy types I and II, congenital myotonic dystrophy, and congenital muscular dystrophies. Less common are the so-called congenital structural myopathies and congenital myasthenic syndromes. *Differential* diagnosis can be difficult, especially in the first months of life when CP is still in the hypotonic phase [41, 42].

Atypical of infants with a brain lesion, these severely hypotonic and weak infants are mentally alert with the absence of deep tendon reflexes. Excessive muscle weakness can lead to respiratory and swallowing difficulties. The congenital muscular dystrophies often have early contractures (Figs. 17.2 and 17.3). The presence of *mental* retardation is usually indicative of a central



Fig. 17.2 Young infant with congenital muscular dystrophy showing both hypotonia and contractures

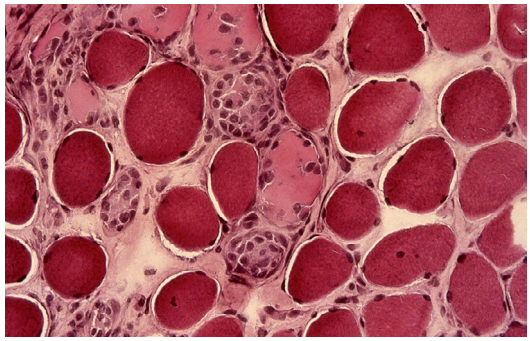


Fig. 17.3 Muscle biopsy in congenital muscular dystrophy, HE stain showing variable fiber size, centralized nuclei, necrotic fibers infiltrated by mononuclear cells, and increased interstitial connective tissue

nervous system lesion; however, it should be remembered that some of the neuromuscular diseases also have CNS involvement (myotonic dystrophy, the congenital muscular dystrophies with CNS changes including Walker-Warburg syndrome, mitochondrial cytopathies).

Diagnosis of neuromuscular diseases requires CK serum testing and possibly electroneuromyography. For most of these diseases, direct molecular genetic diagnosis is now available and should be performed if clinically suspected (e.g., spinal muscular atrophy, congenital myotonic dystrophy). In *addition*, NGS methods can be used to include entire disease groups in genetic testing. Muscle biopsy with histochemistry, immunohistology of gene products, and electron microscopy is indicated only in otherwise unclear cases [41].

17.4.2 Severe Psycho-Intellectual Delay

Primary *mental* retardation is more often the cause of delay in motor development in children than CP. The problem of distinguishing these two conditions is obvious, considering that CP is often associated with mental retardation. However, in pure mental developmental delay, motor retardation is usually mild or moderate and improves toward the end of the first year of life, whereas cognitive difficulties (including language problems) are more prominent. At the same time, the child with CP develops the typical signs of spasticity. *Therefore*, follow-up is often required to distinguish the two disorders. Modern molecular genetic diagnostic methods, including WES, can also contribute significantly to the etiological understanding and diagnosis of these disorders [38, 43].

17.4.3 Diseases of the Spinal Cord

Depending on the neurologic level and *extent* of damage, these patients present with partial or complete spastic paraplegia or, less commonly, tetraplegia associated with loss of sensation with a sharp upper border and bladder dysfunction. *Brain function* is normal. Tumors of the spine and spinal cord, including paravertebral neuroblastoma, traumatic perinatal damage (usually at the junction of the cervical and thoracic spine after breech delivery), or transverse myelitis, must be considered as possible causes. Due to the different therapeutic approaches and rehabilitation plans for these conditions, an early differential diagnosis to CP is essential [44].

17.4.4 Brain Tumors

Brain tumors are the second most common neoplasm in childhood. They *present* with progressive neurologic and visual symptoms and often with increased intracranial pressure. Manifestation in the first 2 years of life is possible and typical for some tumor entities. Symptoms tend to be nonspecific at this very early age, and misdiagnosis of CP over a long period of time is possible, especially in slow-growing tumors such as supratentorial astrocytoma [45, 46].

17.4.5 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 [31]. However, there are several rare genetic neurodegenerative diseases, the *group of primary dystonias* that frequently begin in childhood and lead to progressive disability (Fig. 17.4). Their symptoms can be purely dystonic, but also combinations with parkinsonism and other neurological and sensory symptoms exist. An increasing number of these diseases can be confirmed by genetic testing [47, 48]. Especially in the most frequent pure dystonia with an autosomal dominant TOR1A-mutation (*DYT1*), deep brain stimulation has been proven to be of high therapeutic value in adults, but also already in large number of children and adolescents.

Of greatest importance in the differential diagnosis of CP is *Segawa syndrome*, as it offers unique therapeutic opportunities. This is a hereditary disorder of dopamine synthesis due to an autosomal dominant mutation in the GTP cyclohydrolase gene. Symptoms can be completely controlled by lifelong administration of L-DOPA + carbidopa at low doses. In early publications, the characteristic symptom was described as progressive, generalized dystonia with diurnal fluctuations: Symptoms improved markedly after sleep and worsened during the day. However, it is well documented that not all patients with the demonstrated genetic defect and response to L-DOPA exhibit these diurnal variations. In addition, some patients did not present with dystonia but with parkinsonian symptoms and increased reflexes or even just equinovarus. Cognitive functions and MRI findings were normal [49]. Therefore, any child with suspected CP and normal MRI findings and unknown etiology should undergo *CSF HVA* and biopterin testing or/and sequencing of the GTP cyclohydrolase gene. Also, in unclear cases, treatment with L-DOPA + carbidopa (starting at 25 mg/day and increasing to 200–300 mg/day) should be tried. Autosomal recessive *tyrosine hydroxylase deficiency* is an alternative but less common cause of another type of DOPA-responsive dystonia.



Fig. 17.4 Dystonic posture in a school-aged boy with primary torsion dystonia

Some of the syndromes with dystonia have been shown to be secondary to a metabolic defect. These include (see Tables 17.4 and 17.5) *panthotenate kinase-associated neurodegeneration* (PKAN, now classified as juvenile type of neurodegeneration with brain iron accumulation NBIA) (Fig. 17.5). The disease usually begins in childhood but may occur earlier and lead to a mistaken diagnosis of dyskinetic CP. A genetic diagnosis is available. Anecdotally, vigabatrin and high doses of panthetonate have been reported to have some effects [48].

Glutaric aciduria type 1 is initially characterized by an abnormally growing head circumference and nonspecific developmental delay. However, after an acute metabolic crisis due to fever and/or a catabolic state, irreversible basal ganglia damage with static severe dystonia dominates the clinical picture. A lysine-controlled diet and supplementation with riboflavin and carnitine have been shown to prevent these metabolic crises [48].

Further metabolic defects include other disorders of neurotransmitter metabolism. Unlike Segawa disease, these children usually cannot be cured, but their symptoms and quality of life

can be significantly improved by special diets and treatment with neurotransmitter precursors [50].

17.4.6 The Hereditary Spastic Paraplegias

Hereditary spastic paraplegias (HSP, in OMIM: SPG) are a group of genetically and clinically heterogeneous disorders. Several genes have been described as causative, 70% of which have autosomal dominant mutations. An autosomal recessive and X-linked inheritance is also known [51].

Clinically, these diseases are characterized by progressive spasticity of the lower limbs. The absence of additional neurological signs characterizes non-complicated or simple HSP. Disease onset varies from early childhood to adulthood, as does the rate of progression and ultimate prognosis. Cases with *additional* neurologic symptoms, dementia, ataxia, ichthyosis, optic nerve atrophy, deafness, or axonal neuropathy are classified as "complicated" forms of the disease. In 10–20% of patients, the disease begins before the end of infancy, making the differential diagnosis to CP difficult [52]. Genetic diagnosis is best made using NGS methods (Table 17.3).

17.4.7 The Ataxias

Non-progressive ataxia is often referred to as *ataxic CP* [9]. With this diagnosis, it is important to realize that exogenous, nongenetic damage to the cerebellum in early life is very rare and that most of these cases are due to developmental abnormalities, which are often hereditary. Intellectual development is also abnormal in many cases. This *type* of CP is characterized by a great heterogeneity both in terms of etiology and clinical presentation. Mutations of the reelin and *VLDL* receptor genes have been shown to be causative in some affected families [53].

However, *progressive ataxia* is due to cerebellar or brainstem tumors or neurodegenerative syndromes. In children, the autosomal recessive ataxias (Friedreich's ataxia, ataxia-telangiectasia, ataxia with vitamin E deficiency, ataxia-oculomotor apraxia 1 and 2) are more common than the later autosomal dominant ataxias (spinocerebellar ataxias type 1–18) [54, 55]. Progressive or fluctuating ataxia is also a symptom of various neurometabolic disorders that require thorough diagnostic workup (Tables 17.4 and 17.5).

17.4.8 Neurometabolic Diseases

Neurometabolic diseases are inherited metabolic disorders with predominantly neurological symptoms [6, 36]. They can lead to various progressive neurological symptoms and signs, including vision loss, dementia, epilepsy, spasticity, dystonia, and ataxia (Table 17.4). It is of great *clinical* importance that these inherited disorders be diagnosed. Otherwise, the opportunity for genetic counseling and prenatal diagnosis in future siblings will be lost. Emerging treatment options include enzyme replacement therapy in infantile NCL, substrate inhibition with *miglustat* in Niemann Pick Type C, or bone marrow transplantation, but there is not yet a cure for most of these diseases.

In particular, the subgroup of leukodystrophies (e.g., metachromatic leukodystrophy, Alexander's disease (Fig. 17.6), Krabbe's disease, Canavan's disease, and mitochondrial cytopathies (e.g., Leigh's syndrome)) that present in infancy or early childhood with spasticity and ataxia may initially be confused with CP. Developmental

Table 17.3 Hereditary spastic paraplegia genes implicated in inherited forms of cerebral palsy to date [1]

Gene	Function	Inheritance
NIPA1 (SPG6)	Bone morphogenetic protein receptor	Autosomal dominant
SPAST (SPG4)	Microtubule-severing	Autosomal dominant
SPG34	Thyroid transporter	X-linked
AP4B1 (SPG47)	Endolysosomal trafficking	Autosomal recessive

Table 17.4 Common metabolic and genetic disorders that mimic CP according to the prominent motor dysfunction [6, 35]

Disorders with prominent spasticity
• Hereditary spastic paraplegia
• Arginase deficiency
• COL4A1-related spastic CP
• Biotinidase deficiency
• Aicardi-Goutières syndrome
• Sulfite oxidase deficiency/molybdenum cofactor deficiency
• Holocarboxylase synthetase deficiency
• Leukodystrophies, such as metachromatic leukodystrophy, adrenoleukodystrophy, Sjoegren Larsson syndrome
Disorders with prominent dyskinesia
• Dopa-responsive dystonia
• Sepiapterin reductase deficiency
• Glutaric aciduria type 1
• Pelizaeus–Merzbacher disease
• Glucose transporter deficiency type 1
• Neurodegeneration with brain iron accumulation (NBIA)
• Cerebral creatine deficiency syndrome
• PDH deficiency and other mitochondrial disorders, Leigh syndrome
• Lesch–Nyhan syndrome
• Cerebral folate deficiency
• Hyperekplexia
• Rett syndrome
• ADCY5-related dyskinesia
• Juvenile neuronal ceroid lipofuscinosis
• PCDH12-related dyskinesia
• NKX2–1-related ataxic dyskinetic CP
• TSEN54 gene-related pontocerebellar hypoplasia type 2
• 3-methylglutaconic aciduria
• 3-methylcrotonyl CoA carboxylase deficiency
Disorders with prominent ataxia
• Glucose transporter deficiency type 1
• Ataxia telangiectasia
• Pelizaeus–Merzbacher disease
• Hereditary ataxias
• Joubert syndrome
• Mitochondrial cytopathies (mainly NARP mutation)
• Pontocerebellar hypoplasia
• Cockayne syndrome
• Niemann–pick disease type C1 and 2
• Angelman syndrome
• Carbohydrate-deficient glycoprotein syndromes
• Gangliosidosis type 1, juvenile and adult forms
• Non-ketotic hyperglycinemia
• Maple syrup urine disease
• X-linked spinocerebellar ataxias
• NKX2–1-related ataxic dyskinetic CP
Disorders with apparent or real muscle weakness
• Duchenne/Becker muscular dystrophy
• Congenital muscular dystrophies
• Congenital myopathies with structural peculiarities
• Spinal muscular atrophy
• Infantile neuroaxonal dystrophy, infantile NBIA
• Joubert syndrome
• MECP2 duplication syndrome
• Mitochondrial cytopathy
• Prader–Willi syndrome

Table 17.5 Initial biochemical and genetic studies to consider, when in a child with suspected CP mimic MRI findings are normal or unspecific [35]

Developmental delay, mixed syndrome	Spasticity	Dystonia/chorea	Ataxia
Serum TSH	Serum ammonia	Serum TSH	Serum AFP
Serum uric acid	Serum lactate	Serum uric acid	Serum lactate, pyruvate
Serum amino acids	Serum amino acids (including arginine, serine)	Serum AFP	Serum biotinidase activity
Serum lactate, pyruvate	Urine organic acids	Serum lactate, pyruvate	Urine organic acids
Serum acylcarnitine	Serum biotinidase activity	Serum acylcarnitine	Mitochondrial genetic analysis, CoQ10 level
Serum biotinidase activity	Genetic testing for HSP	Urine organic acids	SNP-CGH microarray
Urine organic acids	SNP-CGH microarray	Urine purines, pyrimidines	
CSF studies[a]		Urine creatine, GAA	
SNP-CGH microarray		CSF studies[a]	
		Genetic testing for NKX2.1	
		SNP-CGH microarray	

[a]CSF studies: glucose (+serum glucose), lactate, pyruvate, neurotransmitter metabolites (biogenic amines + GABA), pterins, 5-methyltetrahydrofolate

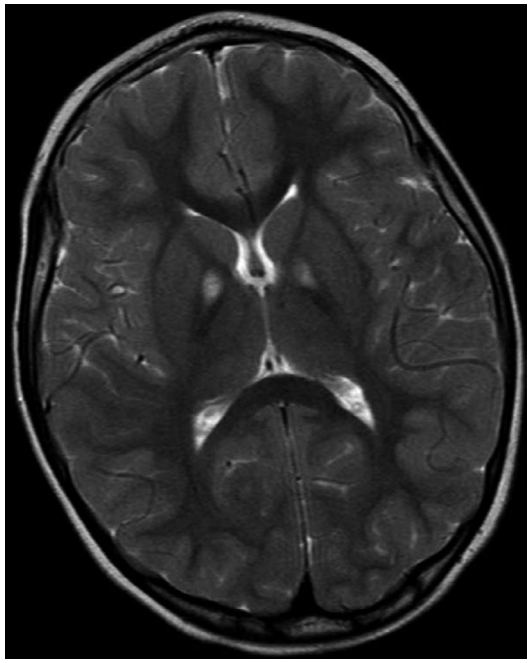


Fig. 17.5 Eye-of-tiger sign in T2-MRI in PKAN: gliosis and increased iron content in pallidum

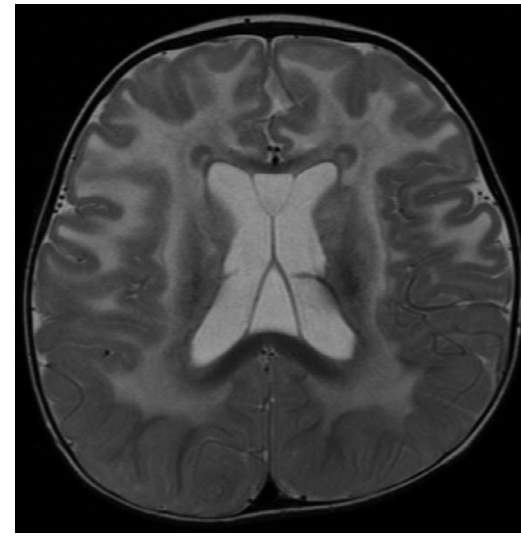


Fig. 17.6 T2-MRI: frontally accentuated leukodystrophy and macrocephaly in GFAP-mutated Alexander disease

regression after early normal development followed by a highly progressive course allows the correct diagnosis in most cases [56, 57].

However, in *slowly* progressive syndromes such as Pelizaeus-Merzbacher disease (*PMD*), diagnosis may be delayed for decades. PMD is due to a lack of CNS myelination caused by X-linked recessive mutations in the proteolipid protein (*PLP*) gene. A *similar* phenotype can also

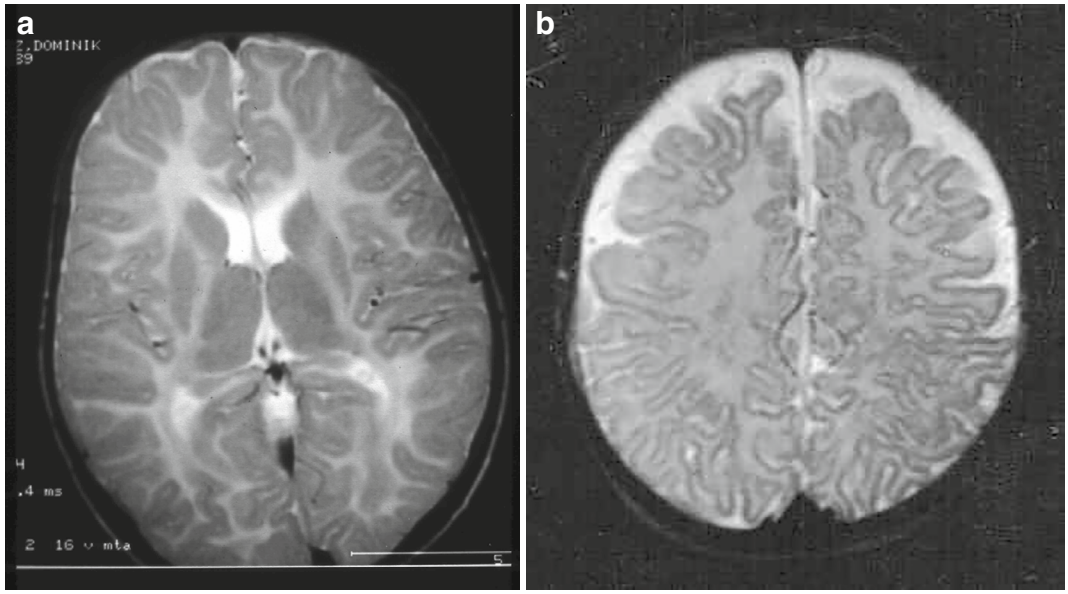


Fig. 17.7 Pelizaeus-Merzbacher disease, T2-MRI at the level of thalami (left) and above ventricles (right): severe hypomyelination, in normal brain white matter should be hypointense (darker) as compared to gray matter/cortex

be inherited autosomal. In the classic form of the disease, the first symptoms appear in early infancy with nystagmus, hypotonia, and weakness. Spasticity, dystonia, and cerebellar symptoms develop much later. Cognitive functions are not significantly impaired. Magnetic resonance imaging of the brain shows a characteristic finding with an absence of myelin detectable from 1 year of age. The barely detectable course in the first years of life often leads to the misdiagnosis of CP, unless previous cases have been diagnosed in the family [58].

Some guidance on the initiation of metabolic diagnosis in these disorders is provided in Table 17.5 and Fig. 17.7.

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Early Intervention for Children with Cerebral Palsy

18

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Abstract

Over the past decades, there has been a substantial increase in the number of trials and quality of evidence for early intervention for infants with and/or at risk of cerebral palsy (CP). *Critical* to commencing intervention early, during key periods of brain plasticity and *prior* to maladaptation of the musculoskeletal and central nervous system, is identifying and referring children with and/or at high risk to cerebral palsy specific interventions. Following the *publication* of international guidelines on early detection of cerebral palsy, there are now *international* guidelines for early intervention for children with and/or at high risk of CP aged 0–2 years which incorporate evidence from within the field of cerebral palsy and beyond. Whilst CP is *primarily* a motor impairment, it is essential for early intervention to focus not only on motor function but also on cognitive skills, communication, eating and drinking, vision, sleep, tone, musculoskeletal health for the child and parental capacity for attachment and support for parents and caregivers. The *present* chapter has been in all fields revised.

Keywords

Cerebral palsy · Early intervention · General movements · Motor learning · Infant development

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 [1–3]. The *lifelong* ability of both the brain and the body to change is largely activity dependent, and there is increasing evidence that environment and experience shape development [4–6]. When an infant is born, they have to learn how to move outside the mother's womb in an antigravity environment. This *involves* opportunities for intensive self-initiated practice that enables the fundamental characteristics of motor control in the upper and lower limbs. These *processes* normally result in the infant learning to roll, sit, crawl and ultimately walk, usually within the first 18 months of life.

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However, when 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. Not only does the resultant maladaptive movement result in muscle disuse and changes to the muscle function but can also affect central nervous system organisation [7, 8]. 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 ultimate aim to optimise the child's function [5, 9, 10]. Whilst CP is primarily a motor disorder by definition [11], children may also have a range of co-morbidities from cognitive impairments to pain. The number of *co-morbidities* and severity of motor impairment are related to intervention efficacy, with children with the involvement of fewer limbs (i.e. unilateral CP) and fewer co-morbidities having a better response to intervention [9] (see Chaps. 12 and 31). It is essential that early intervention is individualised to the child and the family, and that all aspects of life are taken into account, not just the motor development of the child.

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, minimize developmental delays, remediate existing or emerging disabilities, prevent functional deterioration and promote adaptive parenting and overall family function. In this *chapter* we will focus on early intervention applied in the first 2 years of life. Traditionally, early intervention for children with CP commenced after a confirmed diagnosis typically 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 the appearance of specific motor impairments or delay in developmental milestones, such as crawling and/or walking. Many early intervention clinical trials now commence prior to 6 months [9, 12, 13].

18.3 Early Detection

Early, accurate diagnosis of CP is crucial to ensuring timely referral to early intervention [14]. Clinical *signs* and *symptoms* of CP such as spasticity and dystonia emerge and evolve later in infancy; however, infants with CP often show signs of atypical spontaneous movements within the first few weeks following birth [15–17] (see Chap. 12). These changes in function are often related to structural changes in the brain which may be evident on cranial ultrasound and/or magnetic resonance imaging depending on the time of the injury [7, 14]. Many infants with CP are *identified* as "high risk" in early development, due to risk factors in the new born period, such as brain injury along with neurological findings assessed with a combination of standardised tools [14, 18]. 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 [14, 18, 19] (see Chap. 11). Since the publication of International *Guidelines* for early, accurate diagnosis of CP in 2017 [14], there has been a worldwide shift in clinical practice to implement early detection of cerebral palsy with the ultimate goal of ensuring children and their families are referred to early intervention and parents access appropriate support [19–21]. As expected, many parents do experience grief at time of diagnosis and report that receiving the diagnosis early in development allows them to start intervention for their child earlier but also enables the parent themselves to be supported [9, 22].

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 on 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 [23], 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 but defining participation in infants remains a challenge [24]. 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, whilst for infants their participation will be highly correlated to caregiver involvement. *Focus* on early infant participation includes play, opportunities for social interactions, eating and sleeping and should include activities that not only involve caregivers but opportunities for the infant to be independent.

Many *factors* impact upon children's participation in activities including functional skills, activity preferences, attitudes and the environment. Whilst *participation* for infants is not as well understood and there is a lack of outcome measures, from an early intervention perspective, it seems prudent to focus on targeted play activities, the involvement of families and enrichment of the environment as described below.

18.5 Environmental Enrichment

Neuroplasticity has been the subject of both basic science and clinical research for several decades (see Chap. 4). 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 is critical to recovery [5, 25]. 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 or experience-dependent *plasticity* is the basic mechanism that rehabilitation interventions try to harness 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 [4, 26]. In *addition*, recovery after brain injury has been shown to be significantly enhanced by an enriched environment (EE). EE is typically *defined* as one containing complexity and variability, and that includes cognitive, sensory, social and motor stimuli and challenges. Gains documented in animal studies of EE *include* improved memory and motor recovery [27]. 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. Systematic *review* and meta-analysis data show a small but favourable effect of EE interventions over standard care for improving motor outcomes in infants at high risk of CP [28]. These *findings*, along with the ICF inclusion of environmental factors as influential to child activity and participation, *should* lead clinicians to deliberately

attend to the various aspects of environmental enrichment when planning early intervention. Strategies used should be customised to the child and family context.

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) [29]. 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 (see Chap. 11). There is an increased focus on 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 [9, 30, 31] (see Chap. 13). 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 by small sample sizes [29].

18.6.1 Traditional Approaches to Early Intervention

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 (see Chaps. 9 and 20). These *approaches* focus on the normalisation of movement patterns and strategic use of facilitation techniques as well as positioning and handling. 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. The *Bobath* Clinical Reasoning Framework has recently been proposed as a contemporary framework, which has evolved with understanding of the neuroscience regarding motor control and neuroplasticity, to also address a person's goals and functional capacity [32] (see Chap. 11). Core techniques and strategies, however, have remained the same particularly the central place of therapeutic handling including facilitation and inhibition. This *new* framework has yet to be examined in clinical trials, with previous systematic reviews showing NDT shown to be inferior to activity-based and body structure and function interventions in infancy and at school age [33–35]. The *second* widely used approach, the developmental skills approach, is largely focused on sequential milestone attainment across all developmental domains [36].

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 [35]. One quasi-controlled study that compared the two approaches found no between-group differences in motor outcomes [37]. In *contrast* the study by Palmer and colleagues in 1988 demonstrated significant between-group differences in favour of the *LearningGames* programme over NDT in a homogenous group of infants with spastic diplegia [38] (see Chaps. 12 and 19).

18.7 Current Guidelines for Early Motor Interventions in CP

The evidence base for effectiveness of early motor interventions for infants with CP is slowly gaining ground as earlier detection is increas-

ingly becoming standard of care. There has been a shift away from traditional passive approaches, such as NDT (*neurodevelopmental* therapy) with increasing evidence from clinical trials that activity-based and body structure and function interventions are more effective than NDT for improving motor function [33] (see Chaps. 19 and 20). A *comprehensive* clinical guideline summarised the best available evidence and made four recommendations for motor training in CP [9]. This *guideline* was developed using the Grading of Recommendations of Assessment, Development and Evaluation (GRADE) framework and *Appraisal* of Guidelines, Research and Evaluation (AGREE) II tool. Recommendations include:

- starting very early: children diagnosed with or at high risk of CP should be referred for CP-specific, age appropriate early intervention,
- focus on task and context-specific training, at the "just right" challenge for the child. Therapists should coach and educate parents/caregivers to support their involvement in early intervention for their child,
- building parental/caregiver capacity and expertise to enhance the parent–child relationship and ensure intervention can be part of daily activities including play,
- the use of modified Constraint Induced Movement Therapy or Bimanual therapy for children with unilateral CP and,
- recommendation against the use of more traditional passive approaches.

18.8 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 [34]. Numerous *systematic* reviews have shown that interventions such as goal-directed training or functional training produce improvements in gross motor function and performance of daily activities in young children and toddlers with CP [9, 35, 39]. 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 [35]. However, in the past decade, there has been a shift to new early motor protocols based on the principles of experience-dependent plasticity which yielded some promising results:

- **GAME** (goals, activity, motor enrichment) is a goal-oriented therapy intervention delivered in a parent partnership model [12]. 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. Parent interviews reveal high levels of satisfaction with the customised and home-based nature of GAME intervention [22].
- **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 (see Chap. 20). Good quality evidence indicates children with hemiplegia who had received mCIMT (modified CIMT) during infancy had better functional ability at 2 years [40] and have enhanced motor skills [41]. In a recent study of early constraint versus early bimanual therapy for infants with hemiplegia, both approaches were similarly effective reflecting findings in older children with unilateral CP [42] (see Chaps. 12 and 20).

- **HABIT-ILE** (Hand-Arm Bimanual Intensive Therapy Including Lower Extremities) has been shown to be effective in older children with unilateral CP, with increasing evidence in young children aged 1–4 years with unilateral CP [10, 43] (see Chaps. 1 and 20). HABIT-ILE is an intensive intervention based on motor skill learning principles which focuses on a bimanual use associated with postural and/or gross motor stimulation. This intervention is now being trialled in infants aged 6–18 months, known as Baby HABIT-ILE [44] and will use the same model of day camps (5 h/day for 2 weeks, 5 days/week = 50 h) with intensive motor training led by a therapist.

18.9 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 [45, 46]. Table 18.1 describes characteristics of experience-dependent neuroplasticity from which motor interventions can be devised and applied to infants and toddlers with CP.

Table 18.1 Principles of neuroplasticity in practice for infants

Origin	Principle	Application for therapy design
Neuroplasticity	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
Neuroplasticity	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
Neuroplasticity and motor learning	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
Motor learning	Feedback	
Neuroplasticity and motor learning	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
Neuroplasticity and motor learning	Intensity/ practice	Practice needs to occur at an adequate intensity. Daily practice will be more effective than weekly therapy sessions. Practice schedules can be organised into massed or distributed models
Neuroplasticity	Timing	Training ought to begin as soon after the injury as feasible; therefore early detection of CP is vital
Neuroplasticity and motor learning	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
Neuroplasticity	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
Neuroplasticity	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
Neuroplasticity	Interference	Plasticity can also be maladaptive. The formation of compensatory strategies might inhibit the development of preferred skills

18.10 Parental Involvement

Within the context of the ICF, infants and young child are most often dependent on a parent or caregiver for activity and participation [24]. Further, *targeting* the parent–infant relationship and parental well-being is essential for early intervention to be effective [22, 29]. *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 [47, 48]. 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 [22, 49]. *Higher* rates of anxiety, depression, grief and stress are reported in parents of children with CP for many reasons [50]. It is important to support parents to optimize their child's development, by coaching them to scaffold their child's abilities, a commitment to supervision, patience, compassion and behavioural management skills whilst also taking care of their own well-being [12, 51]. To *date* there have been very few studies that have focused specifically on parenting interventions for parents of children with CP in infancy. The clinical *guidelines* looked beyond the CP literature and report that *cognitive* behavioural therapy (CBT) and *interventions* that incorporate acceptance and commitment therapy may have the potential to improve mental health [9].

Supporting parent well-being and the parent–child relationship is key to early motor interventions, as intervention environments and professional input alone are not sufficient to achieve goals of early intervention programmes.

18.11 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. We *know* 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. It is *important* that the essential ingredients of effective interventions are identified. To do this it is critical that fidelity and implementablity of clinical trials are well understood [46].

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 but we can learn from the literature beyond CP [9]. It's essential that we consider the individual needs of the child and family and target interventions to their diverse needs including comorbidities (see Chaps. 31 and 38). In a historical review the whole spectrum of CP and the therapeutic interventions is described [52].

18.12 Conclusion

Early *intervention* for infants and children with CP or at high risk of 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 should *focus* 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. Clinical *guidelines* are available to support health professionals and parents on effective motor interventions which should be start early, focus on task-specific and context-specific goals and focus on building parent capacity.

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19 Physiotherapeutic Interventions: Bobath, Vojta and Motor Learning Approaches

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Abstract

This chapter describes different approaches to physiotherapy in children with cerebral palsy and the neurophysiological and neuropsychological 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 avoid and improve the abnormal neurophysiological function in patients with cerebral movement disorders by early therapy. Several controlled studies designed to evaluate this therapeutic approach failed to prove effectiveness of such approaches for later motor function. Current knowledge suggests that motor learning is more likely to improve the children's motor abilities. 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.

Keywords

Physiotherapy · Vojta · Bobath · Therapy to day

19.1 Introduction

Physiotherapy, like occupational therapy, involves promoting sensorimotor development, improvement of abnormal posture and movement control in all activities, such as prevention of deformities and finding the best possible position when standing, sitting and lying. There are *various* therapeutic approaches, which are based on different theoretical principles and use different techniques and methods.

One main symptom of cerebral palsy (CP) is abnormal muscle tension impaired coordination and posture control. According to the *type of CP* abnormal muscle tension can be identified in the assessment of Passive Range of Motion (*pROM*)—partly depending on the speed of movements—or only with active or intended movements. It also *affects posture*, e.g. 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, depending on the setting in which the child lives. Disorders of the sensory circuit and sensorimotor and cognitive deficits are found simultaneously.

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19.2 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 no longer appear appropriate. Their prior acceptance was based on presumed plausibility of the underlying theory by patients and therapists, and easy learning and implementation for therapists. One concept, e.g. in the *Vojta* approach is the 'neurological reorganisation', which is based on the hypothesis of Fay [1]:

- approaches to modify the neurophysiological basis,
- approaches based on the principle of motor learning,
- approaches to treat specific symptoms of the disease,
- alternative and complementary approaches.

19.3 Vojta Approach

Vojta [2] developed his ideas from observation of therapeutic interventions for children of average intelligence with CP. By 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 predictive changes of posture assumed to be beneficial for development and useful movement-patterns. From this he concluded that there had to be a complex reaction pattern affecting the whole body. This *Koordination complex* of Vojta [3] was seen as an element of locomotion, in the sense of *reflex locomotion*. Vojta postulated that these are innate patterns of movement (central pattern generator) (vojta.com/Reflex Locomotion). This reflex movement is activated through 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 set by the therapist to limit and reduce active movement and generate isometric muscular activity is considered as important. Stimulation of each of the ten zones then leads to activation of different muscle patterns of the entire body. Hok et al. [4] confirmed these findings. They found hints to changes in blood flow in parts of the brain caused by prolonged manual pressure of different body regions in the respective somatosensory areas of the CNS but no influence on motor control.

Vojta *assumed* that in children with CP a blockade of motor development at the function of a 6-week-old infant exists. 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. It is assumed that the regulation and control of the coordination complexes on the supraspinal level happen through frequent repetitions and will eventually become permanent. The goal of this therapy was to improve the highly differentiated posture of the spine as a basis for the function of extremities.

Vojta *refused* to allow sitting or standing unless the child has attained sufficient control of posture, as this would unnecessarily trigger 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 surrounding and improve the child's motor abilities; 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* was additionally considered to impact not only on the musculoskeletal system but also on other areas, such as swallowing, chewing, breathing and autonomic functions. Nowadays the Vojta concept may be considered for treatment of a range of conditions including

neuromuscular disorders and diseases of the peripheral nervous system, e.g. *plexus paresis* and *myelomeningocele*.

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, for example *Landau* or *Peiper-Isbert* reactions. If there are six to seven abnormal postural reactions or five abnormal reactions and a hemiparesis, treatment is immediately indicated.

Vojta's ideas of physiotherapeutic treatment on a neuro-physiologic basis are in many aspects contrary to Bobath's concept. Although the *treatment* techniques differed substantially, both were originally based on some shared theoretical ideas about motor control and neurological development, however. Both are based on a hierarchical reflex-oriented model of motor control in accordance to the knowledge of the 1940s and 1950s. In view of the recent knowledge on the importance of motor learning the Vojta concept is currently only considered in special conditions, such as significant physical limitations and considerable mental deficits.

19.4 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 the treatment session. The posture of the hand as well as minimal voluntary movements of the fingers could be observed, and the patient felt improved sensation in his hand.

The patient with CP shows not only *persisting* primitive motor patterns and insufficiently developed postural reflex mechanisms, but also an abnormal postural tone. The development of postural reactions, such as head control, equilibrium reactions, and many other adaptive and protective postural reactions, is 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.

Berta and Karel Bobath [6] extended earlier concepts and described their therapeutic approach to children's normal sensorimotor development as neurodevelopmental treatment (*NDT*). Paediatricians have used the terms Bobath and NDT synonymously. In young children with infantile CP, no prior motor experience exists. Thus, matching normal motor development should guide the motor development and treatment goals. 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' (p.373) [6]. 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) 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, 8] it is possible to diagnose severe movement disorders already in the first 3 months of life through the assessment of general movements (see Chaps. 9, 11 and 17).

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 elements [9]. 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.

Stimulation of motivation and 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. Stimulation and guidance by the therapist will be reduced stepwise allowing the patient to take an active part in the setting. Facilitation is an active process that seeks to influence sensory information through therapeutic handling, environmental and verbal cues; the client's response to facilitation informs the clinical reasoning process (https://ibita.org/Theoretical Assumptions and Clinical Practice/Bobath Concept-Definition) [10]. Priority is given to the accomplishment of everyday tasks, largely independent of the quality of the movement sequences. *Particularly*, with increase in age pathological movements are increasingly 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.

19.5 Motor Learning Approaches

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 programmes, a process known as closed loop control.

Further concepts about the learning process and the neurophysiological correlates of information processing and action planning were developed in the sixties: Adams Closed Loop Theory, Schmidt's Schema Theory and Ecological Theory and Bernstein's Dynamical Systems Theory (reviewed in https://www.Physio-pedia.com/motor control_and_learning). More recent postulates point to involvement of more complex, interdependent linked systems. Leech et al. [11] distinguish: (1) Use-dependent motor learning resulting from repeated practice, requiring time and patience: Progress may be accelerated by (2) instructive motor learning, which involves multiple cognitive processes to understand, commemorate and amplify the learning process (mediated by structures in the prefrontal cortex), (3) reinforcement motor learning involved in selecting movements that result in task success, related to nondirectional external feedback, resulting in the child's perception of errors in the movement process or finding solutions (mediated by reward-based dopamine signalling, involving basal ganglia and the primary motor cortex) and (4) sensorimotor adaptation-based motor learning: changing the motor behaviour because of prediction errors. Sensory prediction errors are perceived in the nervous system when the actual sensory consequence of a movement (*most* commonly detected by visual, auditory or proprioceptive feedback) differs from the predicted sensory consequence of that movement [11]. According to the current understanding this mechanism of motor learning is primarily dependent on the cerebellum. In case the progress during therapy is less than expected, the plan for therapy should be

adapted accordingly prior to modifying the targets (https://cpsn.org.au/news-and-events/news-index/new-recommendations-aim-improve-physical-function-children-and-young).

As *prerequisites* for the therapeutic work on the basis of motor learning, the following topics 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 and,
- 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.

19.6 Selected Studies on the Evaluation of Treatment Effects of Physiotherapeutic Approaches

19.6.1 Vojta

The effects of Vojta's therapy were evaluated in two Japanese studies with control groups. A retrospective study carried out by Kanda et al. [12] 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) Hayashi [13] 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. In contrast, 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, however. 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 were poorly designed as the children on therapy and the control children had unequal risks and because the number of children was inadequate for the detection of small but potentially meaningful effects [14–16]. The control group without preventive therapy had a significantly slower motor development, but CP was not observed in either group. On an overall basis the evidence, these studies comply with level 3, which is the maximum according to 'The Oxford 2011 Levels of Evidence'.

19.6.2 Bobath/NDT

Since the 1970s, studies on the effectiveness of Bobath/NDT physiotherapy in children with CP were published, most however, without an appropriate control group. Butler and Darrah [17], in a meta-analysis of methodologically more appropriate studies commissioned by the American Academy for Cerebral Palsy and Developmental Medicine (*AACPDM*), did not find 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 [18–21]), whereas in two studies with nonrandomised control groups (level II) a difference was found. A systematic review of different intervention categories confirmed the results [22].

In further studies with closer analysis of some of the studies details Ganley [23], Thomason et al. [24] and Damiano [25] point to great individual differences in the study populations regarding symptoms, aetiology and living conditions. Considering these individual factors in stratified analysis might help to answer the ques-

tion 'what works best for whom'. 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' [20, 21]. The studies by Palmer et al. [18, 19] compared the effects of NDT (*group A*) with intensive support of the gross and fine motor, cognitive and linguistic development (*group B*). After 6 months the children of group A with NDT showed less motor progress than group B. However, the NDT followed a former concept of the Bobath Therapy.

Jackman et al. [26] published a recent international clinical practice guideline for training and facilitating motor function in children with CP based on a detailed and extensive review on therapeutic concepts and their evaluation (Table 19.1). They recommended client-chosen goals, whole-task practice within real life settings, support to empower families and a team approach. The potential contribution to achieve these aims by different concepts was assessed (Appendix S2: Body structure and function intervention). Essentials of the NDT/Bobath therapy are supposed to constitute facilitation to reduce the muscular tonus to allow for active movements. The impact on activities of daily living is less focused. This does neither meet the definition von IBITA (www.ibita.org/Bobath/Concept-Definition) nor standard therapy in many countries.

Decades of discussion about the optimal refinement of Bobath therapy as to the importance of manual support and the child active efforts yielded different activity therapy concepts over time with marked differences between different schools and countries. The division between activities with manual support and self-guided activities of the patient including activities of daily living varied. Meta-analyses of even high-quality studies are therefore difficult to compare because of heterogeneous interventions, which appears to be a general problem with reviews and meta-analyses in physiotherapy and occupational therapy [27].

Any results of even well-designed Randomised Control Trials (*RCTs*) may be valid only for the specific treatment and patient group studied. External validity for other settings regarding contextual factors such as the psychosocial family conditions and individual counselling may preclude generalisability. Since it is important to adapt the intervention to the individual child's needs and circumstances, in which they live [28]. Prediction of probable effects based on studies in different populations and with different interventions is limited (see Chap. 18). Stratification in accordance to ICF may help, but cannot account for subtle differences in the interventions [29].

Table 19.1 Features of relevant effect studies (modified Table 16.1 of third edition)

Term.	Vojta approach	Bobath NDT approach	Motor learning approach, e.g. treadmill
Up-to-date concepts	Encouraged using reflex locomotion to foster motor development	The original Bobath approach based on facilitation has shifted to the task-oriented motor learning concept	Gait training integrated in motor learning approaches
Methodology	Repetitive triggering of reflex creeping and reflex turning	Depending on the individual goals which should be achieved different techniques are used	Repetition, using functional/ economical principles to achieve a desired goal
Setting/ therapists	One to two times per week by physiotherapist and two to three times per day reflex locomotion at home	One to two times per 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	One to two times per week, beginning with overground training and depending on the client and the success; in clinical settings progression to treadmill training (offered during defined periods of intensified treatment)

19.6.3 Motor Learning and Motor Development

19.6.3.1 Occupational Therapy

The approaches such as hand-arm bimanual intensive training (HABIT) and constraint-induced movement therapy (CIMT) improve targeted and fine motor learning of arm and hands: HABIT and CIMT (for more see Chap. 20) are also based on motor learning [30–32]. Goal-directed or task-oriented interventions 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 for children with both different disabilities and cerebral palsy [33, 34].

19.6.3.2 Physiotherapy

In physiotherapy gross motor development is in focus which may be supported by technical devices supporting standing, balance and walking. The most important goal for children with CP is to learn walking with or without ortheses. This aim is achieved by about 75% of the children depending on the severity of disease, and often only by the age of 5–6 years.

Considering the updated concepts of neurodevelopmental therapy, the study by Bar-Haim et al. [35] (level 2 evidence according to The Oxford 2011 Levels of Evidence on children aged 6–12 years (Gross Motor Function Classification System (GMFCS) level II and III (see also Table 1.1)) 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 decreased. This does not automatically lead to the conclusion that NDT is ineffective and not advisable, particularly taking into account that the actual NDT concept and the therapeutic techniques overlap with those of task-oriented motor learning (see Chaps. 11 and 20).

Progress in motor development and function appear to be achievable with both methods. The choice between these approaches (NDT or motor learning) should be based on the child's ability to cooperate and the therapeutic progress.

Learning of walking may be supported by overground gait training and adequate head and spine control. If insufficient, external support by various devices is possible but should be withdrawn during the therapeutic process in accordance to the progress attained. If unable to support its weight, weight relief may be useful for the child.

During treadmill training with advanced technology more effective muscle extension may be achieved to avoid muscle contractures and vegetative functions are activated. Therefore, treadmill training may also be advantageous for adolescent CP who lose previously attained motor functions (see Chap. 20).

Chiu et al. [36] reviewed the results of controlled outcome studies on mechanical assisted walking training in children with cerebral palsy (GMFCS level I–IV, mean age range 4–14 years). The size of the effect of mechanically assisted training on gross motor function appeared higher than for overground walking training (with broad 95% CIs, however; these studies therefore provide moderate evidence only). Mechanical assisted training with body weight support improved gross motor function more compared to overground walking training but the effect sizes were small with broad 95% CIs.

Modern devices may also use electric muscle stimulation triggered by surface electrodes regu-

lating gait rhythm and speed by robotic technology (robotic assisted gait training, RAGT). Exoscelet devices may also be applied. There is no consensus as to the strength of the effects of robotic assisted gait training (RAGT) compared to other forms of gait training including studies with devices with electric stimulation pool [37, 38]. Supplementing treadmill training with virtual reality may improve effectiveness by improving the children's motivation. As yet the evidence for the additional effect is limited [39, 40]. For the effectiveness of the ankle foot ortheses (AFO) to improve standing and walking see Chaps. 20 and 25.

Several studies 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, with the scientific evidence of level 2 have been reported. Thus, confirmation on further RCT studies is needed as pointed out by Brogren [41]. A more recent RCT study [42] compared a task-specific physiotherapist-led 1-week training approach to a non-specific parent-led home programme for attaining bicycle-riding goals in 60 ambulant children with cerebral palsy (GMFCS level I or II). Children in the task-specific training group were ten times more likely to attain the goals than those in the parent-led home programme at 1 week after intervention (odds ratio [OR] 10.4, 95% confidence interval [CI] 2.8–38.6), with evidence for superiority by a factor of 4 at 3 months (OR 4.0, 95% CI 1.3–12.5). This study provides clear evidence for the higher effectiveness of task specific physiotherapist-led training to achieve prespecified goals than a non-specific parent-led home programme.

Myrhaug et al. [43] published a literature analysis regarding the extent as to how intensity and context influence the therapeutic effects on fine motor function. 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 studies had a high risk of bias, except for two older studies (again with therapeutic techniques following the earlier Bobath concept) regarding gross motor function (Bower et al. [44, 45]) and three CIMT studies.

19.6.4 Clinical Relevance of the Evaluation Studies

Clinically relevant improvements can possibly only be achieved with therapies adapted to individually agreed objectives that are relevant for the child Mayston [46]. The indirect effects of each therapeutic intervention setting for well-being of parents and child may further contribute to improvement during therapy (Table 19.2). 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 [47] 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, nor is mental performance. Also basic objections are raised against the strict methodological requirements regarding studies for therapy evaluation and their classification according to conventional 'levels of evidence', as was stated by Rosenbaum [48] 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.

Table 19.2 Therapy indication of relevant effect studies and experience (modified Table 16.2 of third edition)

	Vojta therapy	NDT/motor learning	Motor learning, e.g. treadmill training
Spasticity distribution:			
Diparesis	(+)	+	+
Tetraparesis	+	+	+
Hemiparesis	(+)	+	+
Choreoathetosis		(+)	+
Ataxia	(+)	+	+
Contractures	+	(+)	+
Scoliosis	+	+	+
Mental status:			
Normal	(+)	+	+
Severely abnormal	+	(+)	(+)
Motivation:			
Normal	(+)	+	+
Severely abnormal	+	(+)	
Psychosocial resources:			
Normal	(+)	+	+
Severely abnormal	(+)	(+)	+

+ recommended, (+) possible, but not recommended

19.7 Therapy Today

Therapists have to be an analyst, catalyst and family adviser. They should have knowledge about normal and abnormal motor functioning and the mechanism of the motor learning as well as mental capacity and availability of potentially appropriate compensatory devices. The therapist and the physician work together to achieve the main goal: autonomy depending on the extent of disability. The therapist does not treat CP but '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.

19.8 Conclusion

The concept of Vojta to stimulate reflexes in order to improve active mobility has not been proven effective. It may be useful for treatment of closely defined aspects of tetraparesis or scoliosis as part of a comprehensive therapeutic concept. In children with severe spastic CP and significant mental retardation Vojta may offer a therapeutic option to achieve predefined targets. The concept of Bobath or NDT based on facilitation has been widely modified during recent decades. The most important element is consent on therapeutic targets for the patient and family. Therapists have to select from a huge variety of different methods and techniques: an individual selection is necessary and crucial.

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20 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, build activity competence or minimise body structure or function impairments of children with cerebral palsy. The strength of evidence is in the surveillance to minimise the effect of impairments and intense delivery of goal-focused, activity-based interventions to promote activity performance. There is also a growing body of evidence supporting participation-focused interventions to improve participation outcomes as well as build skills.

Keywords

Physiotherapy · Occupational therapy · Goal focused · Surveillance · Children-adolescents · Evidence-based

20.1 Part I. Principles and Practices of Occupational Therapy and Physiotherapy

20.1.1 Introduction

20.1.1.1 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

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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, 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 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 and participation [2].

20.1.1.2 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) Physical therapists 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 systems 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 and physical activity is essential to maximising potential and outcomes [7].

20.1.2 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 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. 20.1). 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 occurs as a consequence of a dynamic interaction between the person with a health condition's 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

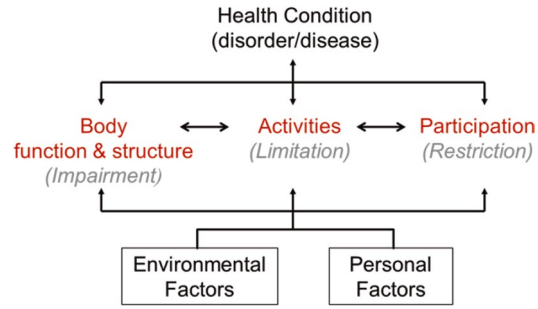


Fig. 20.1 The International Classification of Functioning, Disability and Health [8]Reprinted with permission from Towards a Common Language for Functioning, Disability and Health: ICF The International Classification of Functioning, Disability and Health (Geneva: WHO, 2002). WHO/EIP/GPE/CAS/01.3 http://www.who.int/classifications/icf/icfbeginnersguide.pdf?ua=1

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].

20.1.3 Evidence-Based Practice

Evidence-based practitioners integrate research evidence with clinical expertise, client values and preferences and service-level resources [10]. 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 [11], it is 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. It is time to focus on contemporary evidence-based therapies which are goal directed and task related and provide structured opportunities for intense practice of desired skills and abilities [12, 13]. In addition, new evidence supports provision of therapies in the natural contexts of everyday life of children and youth—for example, at home, school and recreational settings—that provide the right accommodations to assure attendance and involvement in the activities [14]. 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 [15]. The levels of evidence related to intervention effectiveness range across Level 1: systematic review of randomised controlled trials (*RCTs*) 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; and Level 5: mechanism-based reasoning [15].

20.1.4 Family-Centred Care

Family-centred care is the best practice in paediatric health care and rehabilitation [16, 17] 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 values and prioritises the family and child's preferences and choices [16]. In developing a family-centred partnership for practice, therapists aim to learn about and consider the family's values, supports and routines; assist them in accessing appropriate resources to achieve their goals; and provide inter-professional services in ways that consider the health and well-being of the whole family, in particular the primary caregiver [16].

20.1.5 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 [18]. Table 20.1 provides an overview of how therapy focus might change over time for children with CP.

20.1.6 Complexity of Motor Change in Cerebral Palsy

Cerebral palsy is defined 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, often centring on their potential to be able to walk [7, 19]. The development, validation and longitudinal evaluation of the Gross Motor Function Classification System (*GMFCS*) [20] 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 more functional *GMFCS* level, but intervention can prevent the person from deteriorating and being reclassified at a more severe *GMFCS* level [7, 21, 22].

Table 20.1 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 Early mobility and communication supported with equipment	Rehabilitation—Focus on activity and participation; focus on establishing life-long habits and healthy lifestyle preferences Monitor muscle length changes and contracture carefully Use of aids and equipment	Rehabilitation—Establishment of life habits to prevent effects of inactivity on premature aging; 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 developing autonomy Mutual parent/child goals, focus on family lifestyle habits, building fitness for health Family and caregiver Well-being	Individual autonomy—Independence/interdependence with 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 PA
Individual characteristics	Child parent bonding Temperament, family and child values and preferences	Gradual disengagement—Developing individual preferences for activity types Adaptive behaviours	Preferences, strengths, motivation, personal 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↑

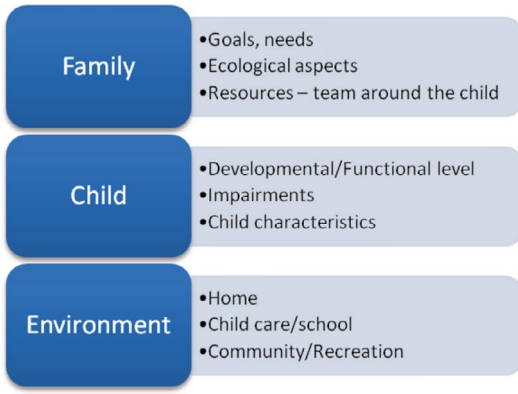


Fig. 20.2 Assessment at all levels of the child's ecosystem is critical

20.1.7 Embedded Assessment

Embedding assessment into practice at the level of the family, child and environment (or context) ensures that interventions are guided by current need, are goal directed and individually tailored and address the wide-ranging factors that promote function (Fig. 20.2).

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. They also need to be feasible and useful—for the child and family and the therapist.

20.1.7.1 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 crucial contribution to clinical reasoning. It is an internationally accepted standard that all therapists and other healthcare providers know and use. 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 and appropriate goal setting [23].

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 related to the functional area of the classification system. 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 [24, 25].

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. Five 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.

20.1.7.2 Gross Motor Function Classification System

The Gross Motor Functional Classification System (*GMFCS*) classifies gross motor function with emphasis on a child's self-initiated

movement and need for mobility aids [26]; for more, see Chap. 22. The GMFCS is applied within four age bands: 1. before the second birthday, 2. between the second and fourth birthdays, 3. between the fourth and sixth birthdays and 4. between the sixth and 12th birthdays. Evidence supports the validity and reliability of the GMFCS [20, 27, 28], its clinical utility [22, 29], its stability over time [28, 30] and its prognostic ability [31]. The updated, extended and revised GMFCS (GMFCS E & R) includes an additional age band of 'between the 12th and 18th birthdays' [32]. The five levels of the GMFCS are:

Level I:	Walks without limitations
Level II:	Walks with limitations
Level III:	Walks using a handheld mobility device
Level IV:	Self-mobility with limitations; may use powered mobility
Level V:	Transported in a manual wheelchair

20.1.7.3 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

20.1.7.4 Eating and Drinking Ability Classification System

The Eating and Drinking Ability Classification System (*EDACS*) [38] has been 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

20.1.7.5 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, the 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

20.1.7.6 Visual Functioning Classification System

The Visual Functioning Classification System (VFCS) classifies a person's use of their visual ability in daily life. It was designed for toddlers and youth aged 1–19 years [41]. The classification should be made by someone familiar with the child or youth and is based on performance in typical settings and everyday life. The VFCS does not measure visual impairment: it is intended to account for the impact of various visual impairments common in CP, including those due to peripheral or cortical damage to the visual system. As a new tool, there is emergent evidence for its validity and reliability, with high levels of inter-professional agreement and test-retest agreement being reported and lower levels of professional-parent agreement [41].

The five levels of the VFCS are:

Level I:	Uses visual function easily and successfully in vision-related activities
Level II:	Uses visual function successfully but needs self-initiated compensatory strategies
Level III:	Uses visual function but needs some adaptations
Level IV:	Uses visual function in very adapted environments but performs just part of vision-related activities
Level V:	Does not use visual function even in very adapted environments

20.1.7.7 Individualised Goal Setting Tools

Setting goals is both part of an effective intervention and an evaluative approach [13]. 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 [42].

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

20.1.7.8 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 are displayed in Table 20.2. Standardised measures that identify

Table 20.2 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)	Abilhands-kids	Fitness • Aerobic with modified shuttle test [120] • Anaerobic with muscle power sprint test
Participation and environment measure for children and youth (PEM-CY)	Activities scale for kids (ASK)	Hip surveillance
Child engagement in daily life measure (CEDLM)	Agility (10 × 5 m sprint test)	HOUSE assessment of thumb deformity
	Ambulatory capacity • Timed up and go (TUG) • Functional mobility scale (FMS) • 6-minute walk test (6MWT) • 10-meter fast walk test (10mFWT) • 1-minute walk test • Gillette functional ambulation questionnaire (FAQ)	Joint measurement/muscle lengths • Active range of movement (AROM) • Passive range of movement (PROM)
	Assisting hand assessment (AHA)	Functional strength test (30-second sit to stand, 30-second lateral step-up, 30-second ½ kneel to stand)
	Caregivers functional use survey (CFUS)	Muscle strength • Grip strength dynamometry • Handheld dynamometry for lower limb strength • Oxford scale
	Children's hand-use experience questionnaire (CHEQ)	Spasticity measures • Australian spasticity assessment scale (ASAS)
	Gross motor function measure (GMFM) 88 or 66	Spinal alignment and range of motion measure (SAROMM)
	High level mobility assessment tool (HiMAT)	
	Melbourne Assessment-2	
	Pediatric balance scale	
	Pediatric evaluation of disability inventory: Computer adapted test (PEDI-CAT)	
	Quality of upper extremity skills test (QUEST)	

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 [46].

20.1.8 Theory-Driven Practice: Top-Down Approaches

Figure 20.3 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 describes 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

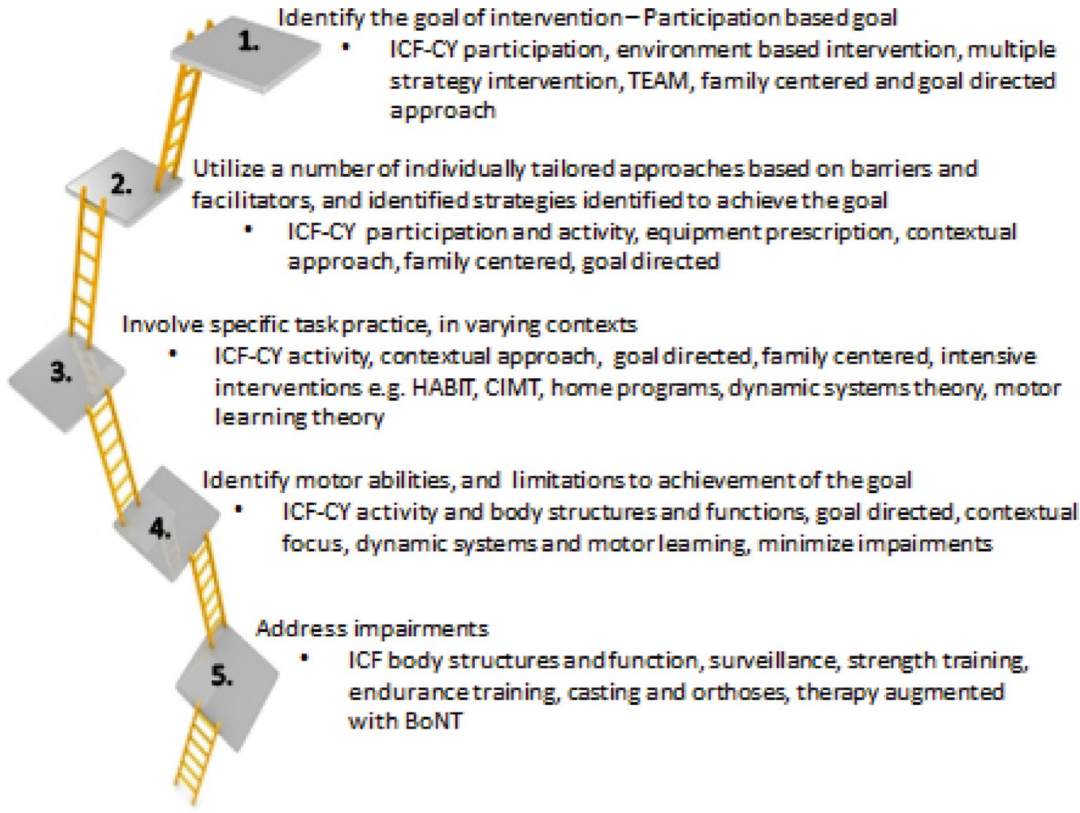


Fig. 20.3 Top-down approach to therapy in cerebral palsy

worsen with age in children with CP, and therefore assessing and intervening to ensure no loss of function are important. However, the strongest evidence to date suggests that effective treatments are those that are directed at the activity level [13, 47].

20.1.8.1 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 that the child spends sufficient time practicing an activity in natural environments is important for learning [48].

In Part II, the time frames 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.

20.2 Part II: Interventions

20.2.1 Optimising Participation

Since the publication of the ICF in 2001, there has been a strong interest in enhancing participation outcomes following health interventions. Interventions that focus directly on changing participation outcomes, rather than aspects of body structure or functions, or activity performance,

are more likely to be effective [47, 49]. Effective interventions included group and individualised approaches and often involved coaching. All occur in the natural settings in which the activity of interest takes place.

There has been a growing body of evidence about how to optimise and assure participation in children and youth with disability, including CP over the past 5 years. Recent studies reinforce the importance of starting early with a participation focus and 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. A knowledge translation paper has been published to guide therapists in how to take a participation-focused approach to practice [14].

20.2.1.1 Pathways and Resources to Engagement and Participation

Definition: Anaby et al. [50, 51] developed 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. The programme is called Pathways and Resources for Engagement and Participation (PREP), and since its development, it has been applied in rehabilitation and educational settings, including children and youth from 4 to 25 years of age [52].

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 adapting the activity (rather than trying to 'fix the impairment') will enable increased participation of youth with impairments.

Evidence: Eleven studies [52] using interrupted time series, pre-post evaluations or single-case experimental designs provide a growing body of evidence of the effect of the intervention. A recent systematic mapping of the effects of PREP on transient, enduring or ultimate participation outcomes demonstrated that individual goals can be achieved (measured using the COPM [44]) and that frequency of participation and involvement can be improved (measured using the Participation and Environment Measure-Children and Youth (PEM-CY) [53]). There is also some evidence that this participation-focused intervention can positively impact body function outcomes [54].

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) [50].

Who the intervention was designed for: The intervention was originally designed for adolescents (but has been evaluated in people aged 4–25 years) of any MACS/GMFCS level and is implemented in the home and community setting most appropriate for the goal. People with cognitive and communication impairments require greater engagement and support of a family member or support person during implementation [50].

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 that the goals are articulated as participation-based goals (rather than activity performance or skill-based goals).

Therapist training requirements: Training is recommended via an online self-directed module available via the CanChild website: www.canchild.ca.

20.2.1.2 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 [55]). 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 the theoretical work that supports the importance of self-awareness, goal setting and self-monitoring in participation outcomes. The programme takes a cognitive skill development approach, teaching adolescents to apply the meta-cognitive strategy of goal-plan-do-check [56] in 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) [55, 57].

Evidence: Project TEAM has undergone a range of studies to test it during development [55, 58] and an evaluation of effects using a quasi-experimental repeated measure, two-group design [57]. The comparison group participated in goal setting only. Findings demonstrated that knowledge about environments and strategy use could be increased (measured using a knowledge quiz) and that more youth in the project TEAM group attained their participation goals (measured using GAS [43]) than the comparison group at 6-week follow-up. Further research is required to establish a firmer evidence base.

How to, volume of therapy: Project TEAM involves a 14-week manualised programme: (a) initial assessments and goal setting, (b) 9 weeks to deliver 7 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: Young people aged 12–22 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 that further development of the materials was needed to support adolescents with less cognitive ability [55].

How you know it is working: The intervention explicitly involves pre- and post-assessment of goal achievement—using Goal Attainment Scaling (*GAS*) [43]—and has been evaluated using the Child Occupational Self-Assessment (*COSA*) [59]. In addition, a specific knowledge test has been developed to evaluate change in environmental knowledge and strategy use.

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

20.2.1.3 FitSkills

Definition: *FitSkills* was designed to promote participation in gymnasium-based exercise of young people with disability (aged 13–30 years) by addressing two key barriers to participation: the need for social support to exercise and the lack of inclusive programmes [60]. *FitSkills* involves matching a mentor (typically a healthcare university student) with the young person with disability and the pair exercise together in their local gymnasium. The young person with disability receives a physiotherapist (or other exercise specialist)-designed exercise programme tailored to their needs. The therapist does not supervise the exercise programme in the gymnasium but provides follow-up support as needed.

Theoretical rationale: Exercise has well-established benefits for physical and mental

health; however, there are known restrictions to participation in exercise and high levels of sedentary behaviour in young people with disability, including those with CP. The aim of *FitSkills* is to improve participation in community-based exercise by addressing the known environmental barriers and building self-efficacy in the young person through experiences of success.

Evidence: Following evidence of positive effect in early pilot studies [61] (Level 4), *FitSkills* was evaluated for feasibility of scaling up across a community and measurement of effectiveness in a stepped-wedge cluster randomised trial (Level 2) involving 163 participants (effectiveness results pending) [62].

How to, volume of therapy: *FitSkills* matches a young person with disability with a mentor from their community and the pair exercise together at their local gymnasium. The programme involves two 1-h sessions per week for 12 weeks. The exercise programme is prescribed by a physiotherapist tailored to the needs of the young person with disability.

Who the intervention was designed for: Young people with child-onset disability aged 13–30 years who can follow simple instructions and take part in moderate-to-intense physical activity. Young people with acute or concurrent medial conditions that make them unfit to take part or significant psychological or behavioural problems have been excluded in the research studies to date. In the *FitSkills* trial, 36% of participants had CP, with most classified at GMFCS Levels I–III.

How you know it is working: Participation outcomes are measured using the Adolescent Physical Activity Recall questionnaire, the Children's Assessment of Participation and Enjoyment and the Young Children's Participation and Environment Measure. Activity level and body function level outcomes can also be measured.

Therapist training required: Physiotherapists or exercise specialists do not need additional training to prescribe the individual's exercise programme. A detailed protocol has been developed to support the selection, orientation and training of peer-mentors. In addition, excellent communication between the young person, peer mentor, community gymnasium and therapist supporting the exercise prescription is needed.

20.2.2 Environment-Based Interventions

20.2.2.1 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 is 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 have received relatively little research attention with many published studies lacking robust methodological quality [63, 64]. There is Level 2 evidence that adaptive seating and adaptive technology can improve activity and participation in the home environment [63, 65] and that devices should be provided as an intervention early in life [65]. 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 [66, 67].

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 bike, modified strollers, and 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 include mobility devices and positioning equipment [68]. Frequency, duration and equipment use schedules are individually determined based on the gaol 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 [63, 68] and those with dyskinetic movement disorders for computer access modifications [63].

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.

20.2.3 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]. 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) [69]. Standard care does not appear to provide sufficient intensity of training.

20.2.3.1 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 [42].

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 [70]. 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 [71]. Meaningful goals harness the engagement of the family, thus increasing opportunities for practice of activities [47].

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 [47, 70, 71].

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 and opportunities to practice 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 are 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 that 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 [72] or PEDI-CAT [73] 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. Best practice principles on goal setting to improve functional outcomes in CP have been published including a series of detailed infographics [47].

20.2.3.2 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 that the child uses both hands together in bimanual tasks. 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 [74].

Evidence: A strong body of RCT evidence (Level 2) and a systematic review (Level 1) [75] support the effectiveness of bimanual training both when provided as HABIT and as intensive occupational therapy [76–78].

How to, volume of therapy: In research, bimanual training has been provided either in 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 [77]. Day camp models have been conducted for 2- or 3-week periods, in which 6 h of daily training is provided for 5 days per week [74, 79]. 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 and 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 [80–82], 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 is under development. Additional bimanual activity measures, such as Abilhands-Kids [83], 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.

20.2.3.3 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 [84]. In a recent consensus-based guideline related to CIMT, four forms of CIMT were described: forced use, modified CIMT, signature CIMT and hybrid CIMT [85]. In all forms, the less impaired limb is constrained from use for some period within the intervention programme.

- 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 [85].

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 [85, 86]. In addition, in the hybrid CIMT, there is an assumption that the 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 [87, 88].

Evidence: Level 1 (systematic review) and Level 2 evidence (randomised controlled trials) supports the positive effect of modified CIMT, CIMT and hybrid CIMT to improve skill development [13, 89]. The 2019 systematic review provides a comparison between CIMT and comparisons (e.g. occupational therapy, bimanual training) provided at either low (<25 h) or high (>25 h) doses. There was evidence that CIMT was more effective than low-dose comparisons, but not more effective than high-dose or dose-matched comparisons for improving unimanual capacity [89].

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 [85].

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 that 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 with the systematic review finding a mean of 129 h (range 20–504 h) [89]. The key recommendation from this review was that the effects of CIMT are supported when the affected hand is constrained, and blocks of intense structured training are provided. Intensive training can be 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 (10–12 *weeks*) less frequently (1–2 times per week) [78]. 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 [90].

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 Assessment is valid, reliable and responsive and is available for children across a wide range of ages [81, 82]. For unimanual performance, outcome measures used in research include the Melbourne Assessment 2 (formerly called the Melbourne Assessment of Unilateral Upper Limb Function) [91], the Box and Blocks [5] and the Jebsen-Taylor Test of Hand Function [92].

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.

20.2.3.4 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 complement direct intervention and to assist in achieving the necessary intensity of practice to effect the desired outcome of the intervention [69, 93]. Dose of therapy, which includes the intensity and duration of therapy [94], is closely related to clinical outcomes [78], with evidence suggesting that the dose of therapy may be just as important as the type and context of therapy [95]. In children with CP, home exercise programmes can account for 50–80% of the total therapy received [78]. 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 [93, 96].

Evidence: A systematic review [95] demonstrated that interventions that included home programmes to increase the 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 [90].

How to, volume of therapy: Adherence to home programmes is necessary to attain the level of practice required to achieve goals. To be effective, home programmes must involve parent education and active involvement in training [93, 95, 96]. 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), are not too complex and minimise disruption of the affective or recreational family relationship and the programme addresses the real needs of family [96]. More recently, mobile health apps (mHealth) have been developed to improve engagement and adherence to home programmes [97].

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 [96]. 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 the 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, adherence or engagement can be recorded using a programme diary or logbook or, if using mHealth technology, can be collected with the Web or app interface.

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.

20.2.3.5 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 [98]. 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 [98].

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 [98].

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 [99].

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 [98]. In the RCT, a 6-month period of intervention was offered, in which 18–24 sessions were held [99].

Who the intervention was designed for: The RCT [99] included young children (aged 12 months to 5 years) who were classified at all levels of the GMFCS [26], 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 [72] or PEDI-CAT [73].

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 that 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 [99].

20.2.4 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 [100, 101]. Therefore, surveillance to detect pro-

gressive musculoskeletal impairment is a critical role of therapists to ensure that interventions occur early [102, 103]. Secondary impairments include contracture and pain which impact 80% of children with CP. Those at greatest risk are children with spasticity [64, 104].

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 of complex lower limb surgical intervention in the school-age years [105]. 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 [106]; for more, see Chap. 22.

20.2.4.1 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 [102].

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 section on deterioration of gait). Self-reported causes of deterioration are pain, fatigue and lack of adapted physical activity, while strong predictors are severe neurological involvement [104, 107]. Pain and fatigue levels are higher in people with CP compared with their typically developing peers [108, 109]. Nearly 70% of adolescents with CP self-report some pain over a typical week [104]. A key barrier to engaging in physical activity in children with CP is the presence of pain during exercise [104]. 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 [110]. Increasing physical activity levels in children with CP have been found to be effective at improving pain and fatigue levels [108].

Children with CP are at risk of hip displacement [111]. 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 [103]. Hip dislocation can lead to pain, difficulty with positioning and seating, loss of function and decreased quality of life [103]; for more, see Chap. 19.

The incidence of scoliosis in CP has been reported as 15–65% in school-age children with CP [112]; see Chap. 20. Age is the most important factor predicting progression, and in most children, scoliosis was diagnosed after 8 years of age with progression most prevalent after 12 years of age [113]. Risk of scoliosis is also associated with GMFCS level: the risk of developing scoliosis increases with GMFCS level and age [113, 114]. 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 [114].

The prevalence of respiratory comorbidities 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 [115, 116]. 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 [115, 116]. 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 physiotherapist (for more, see Chap. 30).

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 [117]. There is population-based evidence to show that hip surveillance can prevent progression to hip dislocation by identifying timely intervention [117], and multi-level surgery for muscle contracture can be prevented by identifying timely intervention [105].

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 [118–121]. 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 [103]. 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 [103, 111, 117].

There are no evidence-based guidelines for timing and frequency of surveillance to detect changes in ROM, muscle strength and 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 [105, 122].

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 [123].

Respiratory surveillance guidelines in CP are being developed [124]. 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 [124]. Until evidence-based guidelines are available, it is recommended 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. Respiratory risk should be assessed at a minimum annually and more frequently for those at highest risk.

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. For respiratory surveillance, a reduction in healthcare use and hospital admissions is a major factor.

Therapist training required: For musculoskeletal surveillance, 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 [125].

20.2.4.2 Strength Training

Definition: Strength training should be more correctly termed resistance training, and it refers to the use of progressively more challenging resis-

tance 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.

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 [126]; 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 [127].

There is limited evidence of a relationship between upper limb function and strength [128]. 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 [129]. 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) [130] training guidelines of training, type, intensity and time for inducing strength changes in children [127, 129].

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- to 15-repetition maximum, which is the number of repetitions that can be completed before fatigue.
4. Incorporate an increase in the amount of resistance as strength increases.
5. Be performed 2–3 times per week for a minimum of 12 weeks [130].

Who the intervention was designed for: The majority of evidence for positive strength gains in CP is for ambulatory children with spasticity (GMFCS Levels I, II and II) [127]. There is limited evidence for upper limb training [129]. 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 [130].

How you know it is working**:** Change in strength is 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 [119].

Therapist training required: Therapists who use resistance training with children with CP should know the US NCSA for children [130] and incorporate these recommendations with those provided by Verschuren et al. (2011) for resistance training in CP [127].

20.2.4.3 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 [131]. 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 programme, orthoses and serial casting, augmented with botulinum toxin A if indicated. See also the sections on casting, orthoses and strength training and Chap. 22.

Deterioration of gait has been identified around the age of 12 years [132] and can progress to be a pronounced problem in adolescents and adults with CP [107, 133]. The most common gait deviations are in-toeing, excessive knee flexion, stiff knee, hip flexion, internal rotation, adduction and equinus [134]. Strong predictors of deterioration are age at commencement of walking [107, 132] and increasing gait disability, with those at GMFCS Levels IV and V showing greater deterioration [107, 134]. 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 [133]; 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 is effective [21].

Evidence: There is Level 1 evidence that endurance training is effective in the short term in improving aerobic capacity, anaerobic capacity, muscle strength, agility and oxygen uptake with limited information on the effectiveness on activity and participation [135]. 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 [127]. Reason for poor translation of strength improvements to walking capacity is that strengthening exercises are prioritised for the knee extensors and flexors, despite their relatively minor role in human walking [136]. Further consideration of the specificity of strength training may provide greater translation of strength gains to improved walking outcomes.

Hand Arm Bimanual Intensive Therapy Including Lower Extremities (HABIT-ILE) is an intensive task-specific training of upper and lower limbs with an RCT demonstrating improvements in motor performance and daily life activities in children with unilateral CP [137].

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. A recent systematic review evaluating the effectiveness of treadmill training in CP has shown improvements in walking speed and endurance, with only a slight favour towards efficacy of treadmill training to overground walking [138].

Rehabilitation robotics and computer-assisted systems are being trialled to complement physiotherapy in CP. Well-designed randomised controlled studies in children are lacking [139]. The theoretical rationale is based on repetitive practice, intensity and maintaining motivation. Apart from the intensity of practice, robotic assisted therapy does not provide the other key factor involved in motor skill learning: 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. A systematic review of FES in children with CP has shown small improvements in gait speed while the FES device is in use; however, whether the effects are maintained once the device is off and long-term outcomes are unknown [140].

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. 17.8). 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.

Strength training to improve walking capacity and running gait needs to consider task specificity [136]. 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. 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 skill training may be used before undertaking this approach, as has been conducted successfully in adults with acquired brain injury [141]. Orthoses may also have a role to play in minimising gait deterioration. See section on casting and orthoses.

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-minute walk test [142], timed up and go [143] and high-level mobility assessment tool [144].

Therapist training required: No formal training is required, but knowledge and use of the NSCA guidelines [130] are recommended. For guidance in training endurance in CP, we recommend the protocol described by Vershuren et al. (2007; 139), for specificity of training published by Williams et al. [136], and for training in running, see Gibson et al. [145].

20.2.4.4 Casting and Orthoses

Definition: Orthoses (or splints) are removable external devices designed to support a weak or ineffective joint or muscle. 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. 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 tissue's increased 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 (>12 months) following orthosis use with people with CP [146]. More

recently, a randomised controlled trial (Level 2) of rigid wrist-hand orthoses in children aged 5–15 years found evidence of incremental benefit in the orthosis group (n = 38) compared to control (n = 36) at 6 months of 13.15° (95% CI: 0.81° to 25.48°) in wrist extension with fingers extended, and at 12 months 20.94° (95% CI: 8.20° to 33.69°) [147]. There is Level 3 evidence supporting functional orthosis use in the upper limb in children with CP. There is Level 3 evidence that orthosis improves 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 [148].

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 the 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 [149]. 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, 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 are repeated every 4–5 days for a minimum of 2 weeks and continued 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 cast, history of non-union fracture or recent fracture, decreased bone density at the extremity to be cast, 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, orthosis donning and doffing techniques, and 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 is also 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 [150], 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 re-application 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 be done through either formal professional development activities or mentoring with colleagues experienced in the area.

20.2.4.5 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 that 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 [13, 121] (see Chap. 22).

20.3 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 the surveillance to minimise the effect of impairments; intense delivery of goal-focused, activity-based interventions to promote activity performance; and emergent evidence for participation-focused interventions to improve participation outcomes. Surveillance of body structures and functions remains critical in the growing child with CP and adulthood. Future directions should focus on building strong evidence about how to sustain positive outcomes that are typically evaluated for only short periods of time in most studies.

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Muscle Biology of Contractures in Children with Cerebral Palsy

21

Sudarshan Dayanidhi and Richard L. Lieber

Abstract

Muscular contractures are routinely observed in children with cerebral palsy (CP). 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 our understanding of 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 required for myonuclei during postnatal development and repair of skeletal muscles throughout life. The satellite cell population is significantly altered in contractured muscles. Overall, these findings suggest that impaired muscle *growth* and *contractures* in children with CP may be related to alterations in muscle stem cell function during postnatal development.

Keywords

Contracture · Skeletal muscle · Cerebral palsy · Muscle stem cell · Satellite cell · Sarcomere

21.1 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*) 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, use of assistive devices for walking, and use of wheelchairs for mobility (for more, see Chap. 25). *Spasticity* is the largest subcategory, and 70–80%

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of 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 flexor and hip flexor contractures that limit knee extension and hip extension [5] (Fig. 21.1). 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 until the age of 4, after which there is a steady decline in muscle tone [7], and older children show limitations in range of motion presumably associated more 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 and 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 the development of contractures in the long term (for more, see Chap. 29). 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.

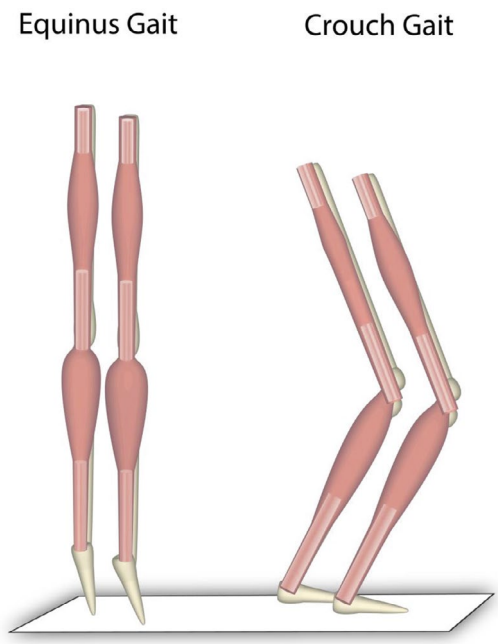


Fig. 21.1 Contractures in gait impairments. Equinus and crouch gait are common gait patterns seen in children with CP, which are associated with muscular contractures of the plantar flexors, hamstrings, and hip flexors. The contractures limit the available excursion at the hip, knee, and ankle joints

The natural *progression* of walking in children with CP over a 2–4-year period, without surgical intervention, leads to a gradual reduction in permissible joint excursion and a crouch gait pattern [12]. 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) [13], even in children 15 months of age [14]. Longitudinal bone growth is also reduced in children with CP [15]. 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 III. In addition, abnormal torsion along the femur and tibia

is reported, either due to failure of typical postnatal developmental changes such as in femoral anteversion or acquired due to muscle force abnormalities [4]. *Consequently*, most clinical treatments for children with CP are focused on 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.

21.2 Longitudinal Growth and Sarcomere Addition

Skeletal muscles are structural 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 [16]. *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 leads to reduced force while an optimal sarcomere length, reflecting a maximal overlap between the actin and myosin filaments, produces maximal force [17].

21.2.1 Postnatal Development

Postnatal muscle development is characterized by both longitudinal and cross-sectional myofiber growth [18]. Longitudinal growth increases the range over which a muscle functions, while cross-sectional growth increases muscle contractile force [19]. It is important to note that during *postnatal* development, in mammalian muscles, the number of myofibers does not increase [20]. In a series of seminal murine studies [21, 22], 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 [18] that between postnatal days 1 and 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 [18].

Longitudinal myofiber length increases by the addition of sarcomeres in series such that the force-length relationship is maintained (Fig. 21.2). This increase using mouse models has shown that there is a fivefold increase in sarcomere number during the postnatal period [21]. Sarcomere addition is difficult to measure directly in humans, but a clinical case showed, in a child undergoing distraction osteogenesis, that there was a corresponding sarcomere number increase with bone growth [24]. In this case, with a twofold increase in fiber length, there was nearly a twofold increase in sarcomere number, showing that the fiber length increase was not purely just a case of stretching existing fibers and creating fibers with increased sarcomere length (Fig. 21.2).

21.2.2 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 optimum [22]. Similarly, if a muscle is maintained in a shortened position, myofiber length will reduce over several weeks and will lose sarcomeres such that the sarcomeres are no longer in a shortened

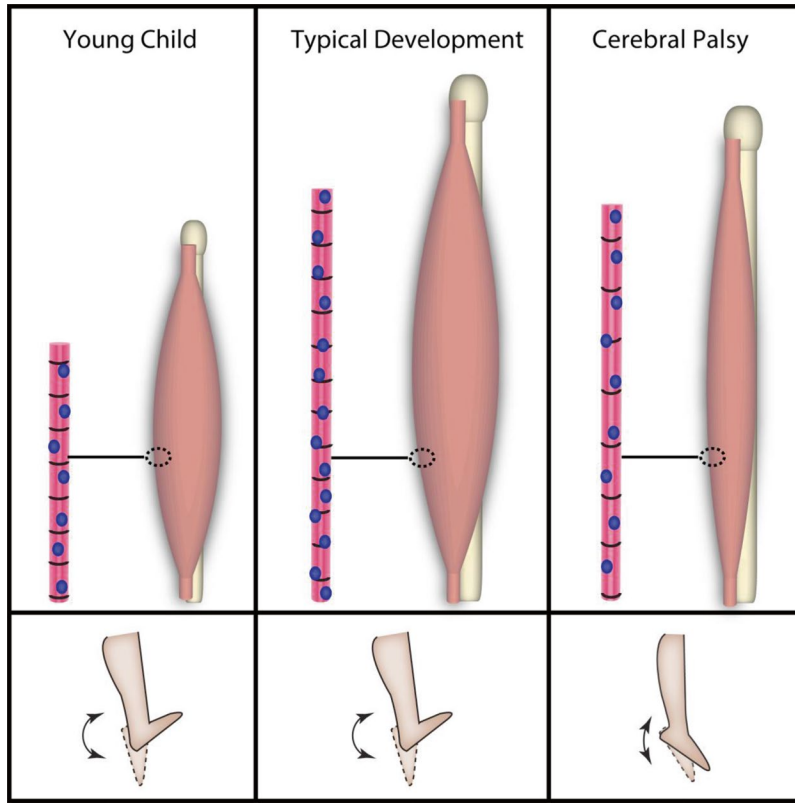


Fig. 21.2 Muscle growth and contractures. During postnatal development as a young child's muscle (left) grows, in typical development (*middle*), there is an increase in the myofiber length associated with an increase in the serial sarcomere (distance between the black bands) number and myonuclei (*blue*). This allows for the 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 the 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

position [22]. 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 [22] by removing the immobilization, subsequent stretch and growth result 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 [25].

21.2.3 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., have markedly reduced range of motion at the joint. The sarcomere length of the flexor carpi ulnaris was increased ~45% compared to non-contractured muscles in control subjects [26]. *Intraoperative* sarcomere length is highly correlated with the degree of contrac-

ture, i.e., maximal permissible passive range of motion such that the children who have the worst contractures also have the longest sarcomere lengths [27]. 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 joint adaptation.

Sarcomere length measured in contractures in lower limb muscles (*gracilis*, *semitendinosus*, and *soleus*) was also increased by 20–50% [28, 29]. The popliteal angle, measuring the degree of hamstring contracture, is negatively correlated with sarcomere length. Similar to the finding in wrist flexion contractures, sarcomere lengths were the longest in children who had the more severe contractures [28]. These results in *upper* and *lower* extremity muscles suggest an inability of the growing contractured muscle to add sarcomeres in series to increase the fiber length but rather stretching of existing sarcomeres to increase fiber length. 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 [29]. 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. 21.2). 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. 21.2) and development of contracture (Fig. 21.1). 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 [30, 31], routinely not seen during later postnatal development [18]. This implies either a reduction in overall muscle development or impaired muscle regeneration that could be related to contracture development.

21.3 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 or how force interaction and transmission occur from contractile proteins to tendon and bone [32]. The microstructure and function of normal ECM are 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 [32]. Briefly, collagen is the major protein of the ECM with *type* I and III being the major components although other types such as type IV, glycoproteins, and proteoglycans are also present in significant amounts.

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 [28]. Quantitative analyses for collagen using hydroxyproline assays also showed a significant increase in extracellular matrix content in *contractured* muscles [28]. However, histological evaluation, which may not have the resolution to detect differences, has not shown such changes in intramuscular connective tissue in contractured muscles of the upper extremity [33]. Interestingly, there is some evidence to suggest that children with moderate-severe spasticity have a greater collagen content [34]. At the level of transcription, contractured muscles of both the lower and upper extremity demonstrate an increased gene expression related to the ECM, *specifically* in collagens and laminin [30, 31]. In 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.

21.4 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* [35]. 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 (*for example*, the giant intracellular protein titin, which secures the myosin filament to the Z-disc of the sarcomere). Increased passive stiffness could contribute to the 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 [36]. 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 combining different types of muscles [28]. 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 that 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 that there are differences in children with CP compared to children with TD, it is not clear how they are related to contractures. As *mentioned*, in the previous section, even in healthy muscles, there is a poor understanding of how all these components combine to transmit passive force from the muscle to the tendon as well as overall muscle excursion capabilities.

21.5 Muscle Stem Cells, Postnatal Development, and Contractures

Satellite cells are the primary resident muscle stem cells responsible for postnatal muscle development, repair, and regeneration throughout the lifespan [37]. By *definition*, an adult tissue stem cell has two properties—the ability to differentiate to create new tissue and the ability to self-renew [38]. The ability to self-renewal is a critical feature that allows 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 in the 1960s, but it was not until the 2000s, after new molecular markers such as the Pax7 transcription factor were identified [39], that it was convincingly shown that the satellite cells are indeed the primary muscle stem cell capable of self-renewal and differentiation [40]. Satellite cells were so named initially, based on their peripheral location in the myofiber, sand-

wiched between the sarcolemma and basal lamina [41] (Fig. 21.3). In *contrast*, multiple myonuclei are present within the sarcolemma for each myofiber (muscle cell). *Adult* (mature) myonuclei are terminally differentiated, i.e., unable to divide, proliferate, or regenerate. During postnatal development, skeletal muscle myofibers accrue numerous postmitotic myonuclei from satellite cells [42].

21.5.1 Role of Satellite Cells

Satellite cells are normally quiescent but become activated during growth or, in case of repair, proceed down the so-called myogenic pathway of proliferation, differentiation, and fusion of new *myoblasts* to existing myofibers. As previously mentioned, during early postnatal development, skeletal muscle myofibers accrue thousands of postmitotic myonuclei from satellite cells [42]. There are numerous ways to activate satellite cells [43] including mechanical stretch, which are important in the postnatal period during bone-mediated muscle growth. *Postnatal* muscle development is critically dependent on satellite cells [44]. Pax7 null mice demonstrate a dramatic reduction in both myofiber size and satellite cell number during the postnatal period. Using a transgenic mouse that conditionally inactivates Pax7, it was shown that myoblasts from Pax7 lineage fuse into myofibers and are indispensable during the postnatal period. Conditional satellite cell inactivation during the postnatal period results in severely compromised muscle regeneration after injury. Recent studies show that, in the postnatal period during the growth of myofibers, beyond providing myonuclei, satellite cells also

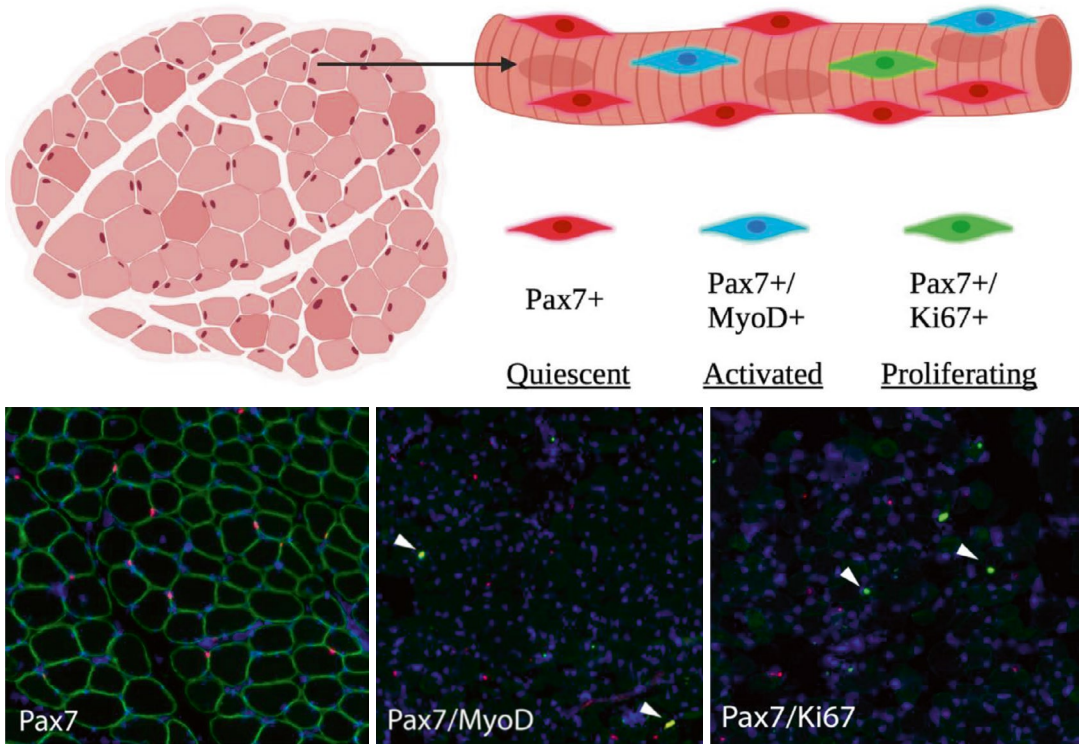


Fig. 21.3 Muscle stem cells and contractures. Satellite cells are muscle stem cells located in their niche between the basal lamina of the extracellular matrix and the sarcolemma of the myofibers. They are the source for myonuclei and are indispensable for growth and regeneration throughout life. They are identified by the canonical marker Pax7 expressed even during quiescence. During growth and repair, they get activated (Pax7/MyoD), proliferate (Pax7/Ki67), and differentiate, as indicated by the arrowheads

change dynamically to establish a stem cell pool, the loss of which leads to impaired growth [45]. During *postnatal development*, there is a reduction in satellite cell abundance, but there is an interaction between quiescent, activated, and proliferating cells to ensure that an appropriate stem cell pool is established by the end of the developmental period [46]. A number of studies [47, 48] 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 [49].

21.5.2 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 speculated that contracture formation may, in part, be due to satellite cell dysfunction. Using flow *cytometry* of muscle biopsies obtained during surgery from children with CP [50], we showed that, compared to typically developing (*torn knee ACL*) children, children with CP had a significantly reduced (~60%) satellite cell population. 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 CP muscle. *Consequently*, we used a more rigorous in situ immunohistochemistry (IHC) method to quantify satellite cells using antibodies for satellite cells (anti-Pax7), basal lamina (anti-laminin), and a nuclear stain (*DAPI*) (Fig. 21.3) [51]. By systematically sampling a large number of fibers, we quantified satellite cell number in situ without significant tissue manipulation. The satellite cell abundance quantified from these sections similarly showed a 70% decrease compared to age-appropriate TD controls. Significant *reduction* (~40%) in satellite cell number has also been reported in upper extremity biceps muscle contractures (see 60). The exact reason for reduction of satellite cell abundance in contractured muscles reported in prior studies is unknown. They possibly reflect an exhaustion of the satellite cell pool, a failure to establish an appropriate pool, or an alteration in satellite cells following ACL injury in children with TD [52]. The exact *postnatal* developmental timeline of establishing a mostly quiescent satellite cell pool is also unknown in human studies. Based on animal studies, it is known that satellite cell abundance is greatest during early stages and reduces as myonuclei are established and as the mostly quiescent pool is established [46].

As a complementary approach, we recently used IHC to evaluate in situ myogenic characteristics in both contractured muscles (*gastrocnemius*, *adductors*) and non-contractured muscles (*vastus lateralis*) in muscle biopsies obtained during surgery [53]. We found that in children with CP, contractured muscles showed impaired muscle growth, i.e., smaller fiber size and higher frequency of smaller muscle fibers compared to non-contractured muscles and atrophic muscles in children with typical development (torn knee ACL). In situ contractured muscles had a greater abundance of satellite cells, particularly in type 1 fibers compared to non-contractured muscles. However, contractured muscles showed lower percentage of activated (Pax7+/MyoD+) and proliferating (Pax7+/Ki67+) cells, indicating reduced myogenic characteristics (Fig. 21.3). Myonuclear number, i.e., number of myonuclei per fiber, was not statistically significantly different among muscles, suggesting that myonuclear accretion that comes from satellite cells early in life occurred even in muscles that later develop contractures. However, both myonuclear number and domain were lowest in the contractured muscle that had the most impaired growth ($p = 0.06$). *Myonuclear* number between fiber types was different in contractured muscles. Correspondingly, positive associations were observed between satellite cell abundance, myonuclear number, and fiber cross-sectional area only in contractured muscles, suggesting an ongoing establishment or alteration of the satellite cell pool. No significant differences were observed in satellite cells and

myonuclear characteristics in primarily ambulatory (GMFCS I, II, III) and minimally ambulatory (GMFCS IV, V) children, suggesting that early cellular development occurred prior to start of walking (see Chap. 25).

Muscle *contractures* and satellite cell exhaustion are prominent features in a common childhood myopathy, Duchenne muscular dystrophy (DMD) [54]. In DMD, due to constant bouts of injury and repair, satellite cells increase in abundance initially, but as the disease progresses, the satellite cell pool undergoes extreme exhaustion [55]. Similarly, muscle contractures are also seen in children with brachial plexus birth palsy [56]. While it is unknown what happens to satellite cell abundance in these muscles in children, a neonatal birth injury mouse model has investigated cellular aspects in these muscle contractures [57]. Muscle contractures in these mice increase abundance of satellite cells immediately after the plexus injury. Similar results are also seen in peripheral nerve injury, where there may be an increase in abundance prior to reduced abundance [58]. However, unlike the reduced myogenic characteristics we observed in children with CP [53], satellite cells in DMD muscles also show increased activation and proliferation [59], while in brachial plexus injuries, there are no differences [57]. While still limited, these studies [50, 51, 53, 60] in muscles in children with CP using different methods, different muscles, and different subjects demonstrate that it is highly likely that there are significant changes in the satellite cells in children with CP that are different from other developmental disorders. This is an ongoing area of research by many laboratories.

Satellite cells are primary muscle stem cells, but they do not act independent of other muscle mononuclear cell types such as fibroblasts and macrophages [61]. Recent evidence from animal studies suggests 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 [62]. More recently, it was seen 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 [63]. One proposed mechanism is that satellite cell activation is associated with upregulation of interstitial collagenases, which allow ECM remodeling and satellite cell migration. 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 [28]. These contractured muscles also have significantly reduced satellite cell number [50, 51], providing support for the idea that increased ECM might be related to decreased satellite cell number. In our recent study, muscle collagen content in muscles from children with CP was negatively associated with satellite cell abundance and positively associated with activation and proliferation [53]. 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 [64]. Our *preliminary* studies also show that recovery from a muscle contracture-like state (reduced serial sarcomere number) by adding sarcomeres is impaired in the presence of reduced number of satellite cells [65]. Ex vivo human studies of mechanical deformation of satellite cells in muscle contractures show similarly increasing deformation with increasing sarcomere length in response to stretch in children with both CP and TD [66]. However, as mentioned previously, the in vivo length of muscle contractures is increased compared to children with TD. Consequently, in vivo, the satellite cells may be under greater deformation at these higher sarcomere lengths, potentially leading to altered function.

Emerging evidence shows that epigenetic factors appear to play a central role in the function of satellite cells in muscle contractures and impaired muscle growth in children with CP. In vitro cell culture studies using satellite cell-derived progeni-

tor myoblasts from contractured hamstring muscles show greater proliferation rates, but an impaired capacity to differentiate, mature, and fuse to produce myotubes compared to TD (ACL-injured) children [67, 68]. These defects appear to be secondary to epigenetic factors of DNA hypermethylation, which can be partially rescued by the use of a demethylating agent. Large-scale DNA methylation patterns in both satellite cell-derived myoblasts and myotubes are distinctly different in muscles in children with CP [69]. Results in progenitor myoblasts derived from gastrocnemius microbiopsies, expanded ex vivo, in younger children report myonuclear dysregulation and impaired myotube formation [70], which may be altered across different muscles [71]. *Furthermore*, transcriptional profiles in satellite cell-derived progenitor myoblasts as well as progenitor myotubes from mostly spinal muscles show significant alterations compared to children with TD [72]. Overall, these cellular and transcription studies indicate cellular dysfunction in muscle stem cells in muscle contractures during postnatal development, which could prevent appropriate satellite cell function and muscle growth during development. *Interestingly*, there is some evidence to suggest that children with cerebral palsy show epigenetic changes of altered methylation patterns even in peripheral blood cells, which are sufficient to distinguish them from children without cerebral palsy [73]. In the near future, as our knowledge of the exact role of altered epigenetics on muscle development becomes clear, this will almost certainly lead to novel therapies.

21.6 Metabolic Properties

Skeletal muscles require significant amounts of energy to power muscle contraction. Sarcomere force generation is highly energetic and requires constant replenishment of ATP for the cross-bridge cycle. Evolutionarily conserved metabolic pathways are utilized to break down carbohydrates, fats, and proteins systemically [74]. The substrates from this process then enter cells such as muscles where glucose and fatty acids are oxidized to create metabolites for the majority of energy production within mitochondria. *Human skeletal* muscle fibers have three primary fiber types: type I, type IIA, and type IIX (slowest to fastest/oxidative to more glycolytic), associated with different isoforms of myosin heavy chain, which demonstrate differing metabolic properties [75], with majority of energy production being dependent on mitochondria (Fig. 21.4).

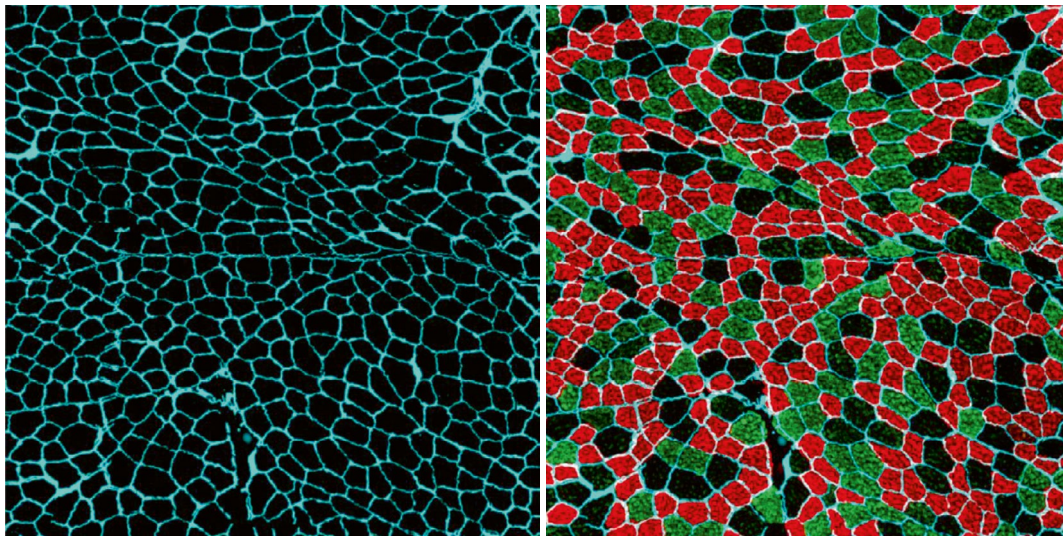


Fig. 21.4 Extracellular matrix and fiber types in muscle. Representative image showing laminin labeling for the basal lamina (left) and three primary fiber types (type 1 in red, type 2A in bright green, and type 2× in dark green, right) from semitendinosus muscle section in a child with cerebral palsy. (Data from Zogby et al. [79])

Mitochondria are subcellular organelle networks located within all cells that provide most of this cellular energy by *oxidative phosphorylation*; muscles in particular have large amounts of mitochondria in and around muscle fibers. Two key processes of energy production in muscles and other tissues under aerobic conditions occur within the mitochondria: the *tricarboxylic* acid (TCA) cycle (for breaking down food substrates) and the electron transport chain (ETC)-ATP synthase (for creating ATP). Carbohydrates and fatty acids are partly broken down outside the mitochondria and then broken further down within the mitochondria using the TCA cycle to NADH and succinate. For example, (anaerobic) glycolysis occurs within the cells, outside of the mitochondria, and yields a small fraction of ATP and pyruvate. Pyruvate, in the presence of oxygen, is then broken down to acetyl CoA that enters the mitochondrial TCA cycle and generates a small amount of ATP, NADH, and succinate that then feed into the ETC-ATP synthase to generate the majority of ATP by oxidative phosphorylation. Each mitochondrial network has numerous ETC-ATP synthase units that have five complexes: CI (NADH-ubiquinone oxidoreductase), CII (succinate-ubiquinone oxidoreductase, also known as succinate dehydrogenase, SDH), CIII (ubiquinol-cytochrome c oxidoreductase), CIV (cytochrome c oxidase), and the ATP synthase, located along the inner mitochondrial membrane, and intermediaries coenzyme Q (ubiquinone) and cytochrome c. The transport of the electron passes through CI-CIII-CIV or CII-CIII-CIV with NADH and succinate being the starting substrates, respectively. The electron transport flux through the complexes creates a proton gradient across the inner mitochondrial membrane. The ETC is indirectly coupled to the *ATP synthase*, such that the proton gradient facilitates energy production at ATP synthase to provide energy to the working muscle. This uses oxidative phosphorylation, i.e., ATP phosphorylation from ADP by the ATP synthase requires oxidation by the ETC. During *postnatal muscle* growth, and in response to exercise training, mitochondria markedly increase the abundance of ETC units by biogenesis, and increase in network size by fusion, and maintain functional mitochondria by mitophagy, to meet the energy requirements of the developing muscle [76].

The metabolic properties of muscle contractures have primarily been studied in the context of skeletal muscle fiber type. Prior to the discovery of individual myosin heavy-chain isoforms, fiber types were classified on the basis of myofibrillar adenosine triphosphatase (*ATPase*) activity, which distinguishes between slow (*type 1*) and fast (type 2) contracting muscle fibers. Lower extremity muscles from children with CP show a strong preference for one or the other fiber type, with a shift towards type 1 muscle fibers [28, 53], whereas TD children show a greater balance between fiber types [77]. Similar changes in having a predominance of one fiber type, with a shift towards type 2X, have been observed in upper extremity muscles in young adults with contractures [78]. However, there are significant alterations in myofiber size, heterogeneity, and fiber-type distributions in the muscles from children with CP [53], and even the newer techniques do not fully capture their metabolic capacity fully. Our recent work using histochemical succinate dehydrogenase (SDH) staining shows that while the hamstring muscles in children with CP are significantly smaller than in TD children, the metabolic activity per unit of type 1 fibers is greater than type 2A muscle fibers, but is similar between the two groups [79]. However, taken as a whole, these muscles appear to be in poorer metabolic health. At a *transcriptional* level, gene expression for oxidative metabolism is significantly reduced in both wrist flexor and hamstring muscles of children with CP [30]. The metabolic machinery within the muscle also depends on the appropriate delivery of oxygen to the mitochondria through appropriate development of the capillary network. Reduced capillary density has been reported in wrist flexor contractures in young adults compared to control subjects, suggesting that it may play a role in reduced metabolic capacity [78]. Exercise studies have shown that young adults with cerebral palsy do get exhausted at lower exercise intensities, but they are able to dynamically increase muscle vascularization in response to exercise [80].

Our *recent study* directly measured mitochondrial electron transport capacity using spectrophotometric assays in gracilis muscle biopsies obtained during surgery from independently ambulatory children [81]. Maximal *enzyme activity* assays were performed for CI, CII, CIII, and CI + III by using specific substrates with associated electron acceptors, and reduction/oxidation rates of either substrate or electron acceptor, depending on the assay, were measured. Maximal rate of individual electron transport complexes CI, CII, CIII, as well as CI + CIII combined was 45–80% lower in children with CP compared to TD children. Citrate synthase activity, a mitochondrial matrix enzyme and part of the TCA cycle, is considered a robust marker of mitochondrial content, at least in healthy young adults. Skeletal muscles in children with CP had similar citrate synthase rate as TD children. Mitochondrial DNA (mtDNA): genomic DNA, also referred to as mtDNA copy number, was increased fourfold in children with CP, although this was not significant ($p = 0.061$). These data suggest that, at least in the hamstring muscle, alterations in mitochondrial function are not simply due to a reduction in content but are probably reflective of poorly functioning electron transport chain, similar to what has been reported with aging.

In a *complementary*, comprehensive, and larger study, Von Walden et al. [82] measured mitochondrial electron transport chain, ATP synthase complexes' protein abundance, and gene expression of mitochondrial biogenesis genes; performed secondary analysis of transcriptomics in CP; and compared it to aging and chronic inactivity using publicly available gene expression datasets. They obtained biceps biopsies during surgery from children with CP, along with typically developing control samples, obtained postmortem. Protein abundance for mitochondrial electron transport chain complexes CI, CIII, CIV, and ATP synthase was 20–40% lower in children with CP, but not significantly lower for CII ($p = 0.07$). *Correspondingly*, the mtDNA copy number was ~25% lower in children with CP, suggesting an overall reduction in mitochondrial content in these muscles. They also evaluated changes in gene expression of peroxisome proliferator-activated receptor gamma coactivator (PGC1) α, considered the "master regulator" of mitochondrial biogenesis, although mitochondrial biogenesis is complicated and requires multiple pathways, players from both mtDNA and genomic DNA, as well as transporter proteins into the mitochondria since mtDNAs by themselves are unable to create the whole of any of the complexes. Interestingly, they reported that the total PGC1α gene expression was ~25% lower in children with CP, along with 35–65% reduction in splice variants PGC1α1 and PGC1α4. Although this is not a measurement in response to a single bout or a program of exercise, this does suggest that the capacity for mitochondrial biogenesis may be reduced in children with CP. A *secondary* transcriptomic analysis of publicly available gene expression dataset [31] was performed to evaluate any changes in gene ontology and pathways in the hamstring (gracilis and semitendinosus) muscles between children with TD and CP. Their *analyses* revealed that both glycolytic and mitochondrial transcriptomic networks were significantly altered and associated gene sets were downregulated. Their experimental and secondary analysis results indicate that there is a significant downregulation of mitochondrial physiology in children with CP. To further test if these alterations were metabolically similar to conditions known to reduce mitochondrial capacity—chronic inactivity or aging—they compared transcriptomics across these three conditions—CP, aging, and bed rest datasets. *Downregulated* genes were common between CP and aging (332 genes), between CP and inactivity (109 genes), and across all three (28 genes). Overall, these data show that muscles in children with CP have a significant reduction in metabolic capacity, which is not purely explained by disuse and might have more in common with aging, secondary to living with a chronic disability. To understand how mitochondrial physiology is altered, direct mechanistic studies measuring mitochondrial respiration are needed to tease apart differences in mitochondria in muscle contractures due to poor growth from those associated with increased disuse, as well as in response to exercise.

21.7 Conclusion

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 *functionality* of muscle stem cells, responsible for postnatal development, repair, and regeneration, is significantly reduced in contractured muscles. Mitochondrial activity and quantity appear to be reduced in muscle contractures. *Future* studies will utilize regenerative medicine to provide novel therapeutics for improving the muscle health to prevent the development of contractures.

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Hip Dysplasia in Children with Cerebral Palsy

22

Amelia M. Lindgren, 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.

Keywords

Hip · Dysplasia · Osteotomy · Subluxation · Dislocation

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22.1 Introduction

Hip dysplasia represents a common and debilitating orthopedic problem seen in children with neurodevelopmental disabilities such as cerebral palsy (CP). *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 with ambulation, sitting balance, and perineal nursing care and may increase the risk for developing decubitus ulceration.

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22.2 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 [4, 5]. Population-based studies show a marked trend toward hip displacement in *nonambulatory* children and recommend close surveillance beginning from age 1 to 2 [3]. Additionally, a recent study found that 22% of nonambulatory CP patients had *progressive* hip displacement after skeletal maturity and recommends continued surveillance in patients with migration percentage over 35% at the time of triradiate cartilage closure and in those with pelvic obliquity [6].

22.3 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 presence of pelvic obliquity; as such, it deserves close scrutiny in children and adolescents with CP [7]. This is especially true in *nonambulatory* adolescents (GMFCS IV and V) [7]. Assessment of hip flexion deformity can be made using the *Thomas test*. Hip abduction as well as rotation, popliteal angles, and 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 (see Chap. 21).

22.4 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 [8, 9].

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.

22.5 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, it does not prevent the need for surgery [10]. Boyd and Hays [11] showed the rate of surgical intervention at the 3-year follow-up point in patients who received botulinum toxin A in addition to bracing, which was significantly less with 27% needing surgery compared to 47% in the non-Botox group [11]. A recent study found a 3-degree change in neck shaft angle in those treated with an abduction brace compared to controls after 1 year of treatment [12] (see Chap. 25).

Picciolini et al. [13, 14] 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 postural exercises and a control group undergoing only NDT (see Chaps. 11 and 19). 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. 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 [15].

Botox is a common treatment for spasticity in the CP patient population. A large cohort study of 1405 CP patients found no difference in the incidence of *hip dislocations* and scoliosis, nor the surgical rates of hip or spine surgery in the Botox cohort versus the control cohort [16]. Selective dorsal *rhizotomy* (SDR) is another treatment that aims to reduce lower extremity spasticity (see Chap. 29). In a long-term follow-up study, Miller et al. found that it had no effect and the incidence of hip displacement post-SDR was consistent with population-based studies at an average of 5 years, with an MP over 30% in 46%, 72%, and 78% of GMFCS III, IV, and V patients, respectively [17].

22.6 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.

22.7 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 to be 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].

Temporary medial *hemiepiphysiodesis* of the proximal femur with an eccentrically placed transphyseal screw has been shown to improve MP and neck shaft angle (NSA). An *initial* case report of nine patients demonstrated a decrease in MP from 52.2 preoperatively to 37.1 at 2 years postoperatively. The HSA decreased 10.6 degrees [21]. *Another* study of 56 hips found that the NSA decreased by 14 degrees, AI decreased by 6 degrees, and MP decreased by 10.3% at 5 years postoperatively. Younger patients had more improvement in NSA. Although nine hips grew off the screws, there were no complications [22]. When *comparing* soft tissue releases to soft tissue releases combined with guided growth, there is a much lower rate of recurrence of hip displacement in the guided growth cohort compared to the soft tissue cohort (5% vs. 39%) at 1 year postoperatively [23]. Another study found that in patients with a preoperative MP over 50%, the addition of guided growth increased the likelihood of an MP under 40% at 2 years *postoperatively* (73% vs. 41%) than in the soft tissue-only cohort [24]. This is a *procedure* that should be considered in the young CP patient (2–6 years old) with an MP over 40% to augment soft tissue releases and offers a less invasive option than proximal femoral osteotomy.

22.8 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 <45°. When possible, femoral osteotomies should be delayed until at least 4 years of age [25, 26]. 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 [27]. 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.

22.9 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. [28] 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. [28] 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.'s 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 [29].

A systematic review of salvage options (proximal femoral resection, *valgus* osteotomy, or total hip arthroplasty) in severe hip dysplasia in patients with CP [30] shows that among patients with functional levels of GMFCS IV or V, all the typical salvage procedures relieve pain better than arthrodesis, which has a significantly higher rate of complications. *Similarly*, a retrospective *review* comparing Schanz osteotomy, Girdlestone, Castle, and McHale procedures found that all four procedures provided pain relief. Proximal *femoral migration* was similar among the procedures. Heterotopic ossification was more common after the Castle procedure, while bone resorption and revision surgery were more common following the McHale procedure [31]. Arthrodesis in nonambulators is associated with a > 100% complication rate and inferior pain relief [30].

22.10 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 [32]. Typical pain control modalities include a postoperative *epidural*, regular dosing of benzodiazepines and nonsteroidal anti-inflammatory agents, including ketorolac. A recent study comparing general anesthesia, general anesthesia + epidural, and general anesthesia + lumbar plexus block found that the lumbar plexus cohort *had significantly* lower postoperative pain scores, heart rate, and narcotic consumption, while the epidural group had longer length of stay [33]. Alternatively, a *study* comparing epidural versus lumbar plexus block in patients with intrathecal baclofen pumps found lower narcotic consumption in the epidural cohort. There were no cases of intrathecal baclofen pump malfunction [34]. Good outcomes have also been reported with fascia iliaca pain blocks [35].

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.

22.11 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 [36]. One recent study found the odds of developing a major complication increase by 2.6 times for each additional *comorbidity* (gastrostomy tube, respiratory requirement/tracheostomy, history of seizures, nonverbal status) (see Chaps. 34 and 35) [37].

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 [38]. 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 an MP >50% or the requirement of subsequent surgeries (see Chap. 25).

Shore et al. 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 [39]. Five years following a varus derotational osteotomy for hip subluxation or dislocation, children show a redislocation rate of 16% [20] (Figs. 22.1 and 22.2). Similarly, Minaie found an overall failure rate of 13% after hip reconstruction. Age under 6 at the time of surgery was significantly associated with higher failure rate (26% vs. 6.3%), as was preoperative MP >70% (28.9% vs. 9.9%). *Acetabular* osteotomy was protective against failure (9.1% vs. 16.9%), especially in patients with a preoperative AI >25° (OR 0.24) [40].

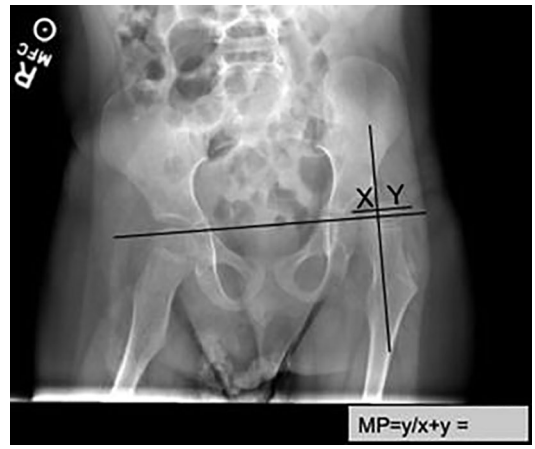


Fig. 22.1 Preoperative radiograph of a 5-year-old child with CP (GMFCS level V); migration percentage of the left hip 80%



Fig. 22.2 1-year postoperative radiograph demonstrates bilateral varus derotational osteotomies with improved coverage of both hips

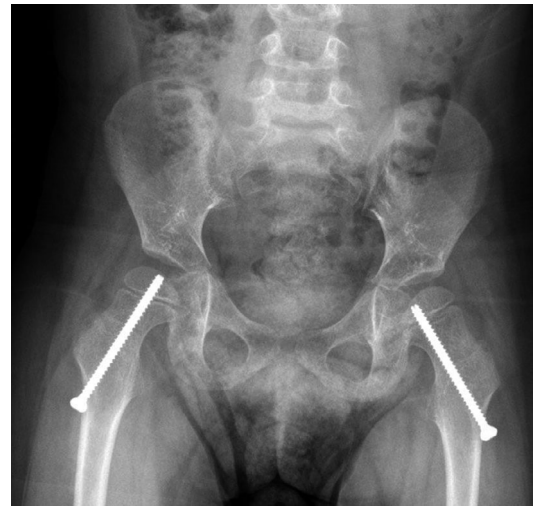


Fig. 22.3 AP Pelvis in a 3 year old with spastic quadriplegia, with proximal femoral growth modulation

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. 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% [41]. 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. One recent study found an AVN rate of 3% associated with older age (11 vs. 8.1 years) and open hip reduction [42].

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 [43]. Relative to non-neuromuscular patients with or without comorbidities, children with neuromuscular disease experience higher rates of transfusion as well as higher volumes [44].

22.12 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 [44]. Buxbom et al. evaluated stability and migration across VDRO in children with neuromuscular disorders at 5, 3, 6, and 12 months after surgery using radiostereometric analysis (RSA) and demonstrated that migration stagnates within the first 5 weeks postoperatively [45]. Even in severe spastic quadriplegia, VDRO in combination with pelvic osteotomies leads to good midterm results with stable, pain-free hips (Fig. 22.3) [46].

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. have demonstrated that reconstructive hip surgery is effective in improving health-related quality of life of nonambulatory children with CP. Each additional 1% correction in migration percentage is correlated with an increase by 0.2 points [32].

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% [47]. Braatz et al. demonstrated improvement in pain and function in children with CP and severe hip dislocations, even if the hip joint was incongruent after reconstruction [48].

22.13 Prognosis

A child's GMFCS level has a strong impact on subluxation risk, and the risk continues to the end of growth [49]. 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 [50]. 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 [51].

Recent *literature* supports the use of hip surveillance programs in improving hip morphology as well as decreasing pain [52]. 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 has also demonstrated improved outcomes with an intentional hip screening program for patients with CP. Patients in Finland who did not participate in a hip surveillance program were more likely to undergo hip surgery at an older age and to develop hip displacement and dislocation [53].

22.14 Conclusion

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 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 and 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

23

Patrick Thornley and M. Wade Shrader

Abstract

Scoliosis frequently occurs in children with cerebral palsy, with increasing incidence in nonambulatory patients (GMFCS levels IV and V). Scoliosis in this population can be *progressive* and severe and have negative consequences on the quality of life, including increased rates of pain, restrictive lung disease and possibly reduced life expectancy. When indicated, posterior spinal fusion surgery is a reliable and reproducibly successful treatment method to prevent deformity progression. With *spinal fusion*, complication rates, namely deep surgical site infection rates, are high. However, spine fusion for neuromuscular scoliosis in cerebral palsy has been durably demonstrated to improve the quality of life of patients, family and/or caretakers. This chapter has been in all fields revised.

Keywords

Scoliosis · Cerebral palsy · Spinal fusion · Spinal deformity

23.1 Introduction

Children and adolescents with *neurodevelopmental* disabilities, such as cerebral palsy (CP), frequently experience spine deformities. While a number of possible spinal deformities may occur in patients with CP, neuromuscular scoliosis, hereafter referred to as scoliosis only, is the most common [1, 2]. Cerebral palsy patients with greater GMFCS levels (IV and V) experience scoliosis at a *prevalence* of up to 90% [3]. While patients with lower GMFCS level scores (I and II) may experience scoliosis, their risk of progression to a surgical threshold is similar to a non-CP patient [2]. Though it is important to recognize the possibility of *scoliosis* in any CP patient, management of scoliosis in the ambulatory CP population is different, following more similar guidelines to the adolescent idiopathic scoliosis population.

Scoliosis has a significant impact on the quality of life of patients with CP in addition to that of their family and caretakers (see Chap. 38). Larger spinal deformities typically affect non-ambulatory

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patients, and often patients will present with complaints of wheelchair fitting difficulties [1, 4]. As the *spinal deformity* progresses, patients frequently experience worsened head control as significantly increased energy expenditure is required to try to maintain truncal control [4]. Scoliosis in CP classically involves large, progressive thoracic curves which can lead to cardiopulmonary insufficiency [2]. In *addition*, these deformities often drive significant lumbar deformities, which typically amplify pelvic obliquity, a horizontal misalignment of the pelvis in the frontal plane, which can impinge upon the rib cage on the high side of the pelvis [4, 5]. This in turn can increase the risk of *costo-pelvic* ulceration, and the corresponding lower hemipelvis can thus see increased seating contact pressure which increases ischial tuberosity ulceration risk [2, 4, 6].

Severe curves can not only cause skin ulceration but may worsen pre-existing restrictive lung disease as many of these children already experience respiratory compromise [1]. *Additionally*, progressive deformity can affect gastrointestinal motility, increasing rates of constipation and gastro-oesophageal reflux disease and may impact feeding abilities [7].

23.2 Pathophysiology

The overall pathophysiology of why the spine curves in children with CP is *unclear*. As it is most common in patients with GMFCS levels IV and V, it may be partly due to a lack of weight bearing, standing and walking. Scoliosis occurs with *all subtypes* of CP including hypotonia and spasticity, with spasticity being the dominant presenting phenotype. It is possible that in patients with spasticity, an asymmetric paraspinal musculature pull across the spinal column may induce true deformity [1].

While curves tend to be *flexible* in younger children, when curves exceed 50^0 in magnitude, there tends to be an exponential increase in the severity of the deformity. These effects are worsened with a child's secondary spinal growth spurt at pubertal onset, and with worsening scoliosis also come increasing rigidity and worsened pelvic obliquity [6].

23.3 Physical and Radiographic Evaluation

Most children with CP need at least annual evaluation by a paediatric orthopaedic centre with CP experience. Patients with GMFCS levels IV and V need a spine examination as part of a thorough physical exam every 6 months (see Chap. 25). This exam should evaluate the child in a seated or standing position and should also include a flexibility assessment 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 by having the child placed in a seated position with a parent or caretaker gently lifting the child under both axillae to straighten the spine.

Meanwhile, the examiner places one hand over the convexity of the major curve and a stabilizing hand on the *contralateral* hemipelvis, applying a reduction force to assess the flexibility of the deformity. If the spine deformity corrects, then the curve is still quite flexible. 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 is 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 as a baseline. 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 as these represent a spine free of axial load and will greatly underestimate the severity of any spinal deformity. A *special* radiographic chair that is radiolucent but allows for free sitting can be extremely useful so that reproducible films are done every time. This is *very important* as

surgical decisions are made on serial radiographs over time. Newer technology allows for biplanar radiographic measurements, 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 exaggerated *lumbar* lordosis or if kyphosis is the primary deformity. If that is the case, then lateral radiographs should also be included with each imaging follow-up visit.

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 around the *thoracolumbar* junction. 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, particularly in patients with lower GMFCS levels (I and II), including typical and atypical upper and main thoracic curves. Cobb *angle* measurements are the standard method of measuring the magnitude of the coronal 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. Increased 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) (see Chap. 29). This lumbar lordosis can be quite rigid and is a very important deformity to address during surgical correction [9].

23.4 Early Treatment

The early treatment of spine deformity in children with CP centres mostly on seating support and family/caretaker teaching and expectation setting. 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. It is imperative to assess the quality of the *wheelchair* fit at each clinical assessment prior to examining the patient out of the chair. Family and caregivers are often invaluable in providing their impressions of current chair fit or concerns.

Contrary to the *treatment* of idiopathic scoliosis, bracing is largely ineffective and remains quite controversial with neuromuscular curves [10]. A now historic study examining the effectiveness of a custom-moulded thoracolumbar *Wilmington orthosis* found that compliant brace wear at 23 h/day had no impact on scoliosis curve, shape nor rate of progression in neuromuscular scoliosis [11].

Bracing can be helpful for positioning, seating and comfort however. This must be weighed against the risk that 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.

However, bracing does have a positive impact on sitting function in *non-ambulatory* children with CP [12]. The use of sitting analysis with pressure mapping through your wheelchair modification associates can help to inform brace or chair adaptations that may be required [12]. The author's institutional practice with regard to the use of bracing in this population is a soft-style Boston or similar brace to assist with sitting function, removed for bathing and any time the child is not upright. We *emphasize* the imperativeness of avoiding skin pressure points to families, frequently modifying bracing if erythema does not resolve within 30 min of doffing the brace.

23.5 Surgical Planning

Once the major curve reaches 40^0 or the *paediatric* orthopaedic surgeon notices increasing stiffness to the curvature on examination, surgical discussions should begin with the patient and family. The decision for spinal fusion surgery is a significant one and often is met with hesitation from families. As such, the surgical discussion is frequently one which requires repeated discussions. If hesitation is noted during these initial discussions, follow-up intervals should be shortened as this often represents the onset of the secondary spinal growth spurt for these patients when their deformity will predictably increase rapidly. Repeated points of contact, particularly in the face of worsening deformity, enhance these discussions. It is important to inform the *families* that the best time to perform a spinal fusion is when the curve remains flexible, typically under 55^0. While *families* may wish to delay surgery until the scoliosis worsens significantly, these decisions need to be explained to families as one in which *increasing* deformity and rigidity increase surgical time, perioperative blood loss, morbidity and infection risks, in addition to lessening the ability to correct the spine. As such, extensive counselling and a shared decision-making approach are important to help families make the appropriate decisions for their child (Fig. 23.1) [9, 13].



Fig. 23.1 Surgical planning

Two *common* clinical conundrums frequently face paediatric orthopaedic surgeons caring for children with CP scoliosis. The *first* is surgical degree scoliosis in the presence of hip dislocation. Current expert opinion suggests that with significant pelvic obliquity and scoliosis, the scoliosis should be treated first [14]. However, in the absence of significant pelvic obliquity, the more symptomatic pathology should be treated first and never concurrently [14]. Importantly, spinal fusion has not been shown to influence either positively nor negatively the *progression* of hip displacement in children with CP regardless of residual pelvic obliquity, potentially suggesting a slight protective effect of spinal fusion surgery on hip displacement (see Chap. 22) [15]. For children who experience large, surgical sized curves at a young age, the decision to proceed with definitive spinal fusion can be a clinically difficult one and hard for families to reckon as well. New evidence supports definitive spinal fusion over *growing* rod constructs in patients as young as 8–10 years of age with CP and scoliosis [16]. This large database study found that definitive fusion resulted in fewer complications and unplanned reoperations in addition to better radiographic outcomes compared with growing rods as well as better quality-of-life improvements [16].

If a family is having a particularly difficult time deciding, a *consultation* with the medically complex paediatric service, paediatric palliative care or quality-of-life service team can be helpful [13]. *Multidisciplinary* team discussions involving all the medial subspecialists involved in the child's care including those who will become involved perioperatively can help with a shared decision-making model with families to identify the right candidate for surgery [13]. It is important that the family understands what the future holds if the spine deformity progresses significantly in future and that the outlined future with-

out spinal fusion needs to be acceptable if the family decides against proceeding with surgery.

Once the family has decided to pursue spine fusion, a thorough *multidisciplinary* preoperative assessment must occur [13, 17]. A survey of members of the Paediatric Orthopaedic Society of North America (POSNA) with an interest in spinal deformity identified nutrition status as an important *comorbidity* to optimize in this patient population [18] (see Chap. 31). Unsurprisingly, nutrition in addition to other perioperative optimization for these patients was highly variable across surgeons from different institutions [18]. The author's preferred optimization for these patients is outlined below.

All children receive a *preoperative* nutritional consult a minimum of 3 months prior to their planned surgery. Children who are *gastric tube* (g-tube) fed must be further examined to ensure that they are receiving adequate caloric intake. *Laboratory* values such as complete blood count, total lymphocyte count, and total protein and albumin may be obtained, but these are not reliable markers of nutrition nor have they been demonstrated to be associated with surgical site infections in spinal fusion in neuromuscular spinal deformity when abnormal [19] (see Chap. 36).

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 (see Chap. 28). While this should not influence surgical decision-making, recognition of its presence and a plan for possible catheter repair/replacement should be in place in case of iatrogenic damage during the dissection. If this does occur intraoperatively, temporary leaking can be stopped with the use of vascular clips on both ends of the damaged tubing.

All *patients* with CP who are GMFCS level IV or V should be assessed by paediatric pulmonology prior to posterior spine fusion PSF. Many of these children have restrictive lung disease, and some may have sleep apnoea. 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 post-operatively 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 post-operative 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/optimization (see Chaps. 31, 37, and 38). 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 that all of their questions are answered and everyone feels comfortable proceeding with the surgery.

23.6 Surgical Treatment

The specific surgical treatment of scoliosis in a child with CP differs 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 significantly higher risk for perioperative complications [17, 20].

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 life for both the patient and their family or caretakers (Fig. 23.2) [7].

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 and maintain a free abdomen to reduce



Fig. 23.2 Surgical experiment

venous compression and intraoperative bleeding. In the presence of significant *lumbar lordosis* or hip flexion contracture, the use of a sling for the legs can facilitate lordosis reduction and ease dissection and implant placement to the pelvis. Intraoperative traction can be utilized at the surgeon's discretion and has been described with both distal femoral skeletal and skin-based traction in addition to pelvic traction from the high side of the oblique *pelvis* with Gardner-Wells tongs or Mayfield cervical management cranial traction from the skull [21].

Intraoperative *neuromonitoring* should also be pursued as part of standard practice with these patients. While signals may be difficult to elicit, it is important to closely scrutinize available signals and work with your neurophysiologist to establish *monitoring* where possible as an iatrogenic spinal cord injury during surgery can worsen the quality of life of these patients significantly.

Up to 77% of GMFCS level IV and V patients will have monitorable signals via transcranial motor evoked potentials (TcMEPs), though higher stimulation impulses with greater latencies will be expected [22]. Importantly, no increase in seizure activity has been associated with TcMEPs [22].

Prophylactic *antibiotics* need to cover for both gram-positive and gram-negative bacteria in this patient population; typically, cefazolin and gentamicin are utilized. *Antibiotics* (cefazolin) are redosed if the procedure lasts longer than 4 h [23]. Antifibrinolytics (Amicar or tranexamic acid) are now considered standard treatment to minimize blood loss, in addition to the use of intraoperative cell-saving technologies to decrease the need for allogeneic blood transfusion.

The *surgical team* should consist of experienced paediatric anaesthesiologists, attending paediatric orthopaedic surgeons and orthopaedic-specific scrub technicians with spine experience. The *preoperative* surgical huddle should focus on each team member's role, with an emphasis on a balanced intraoperative resuscitation with efforts to minimize dilutional crystalloid fluid administration while ensuring maintenance of an elevated mean arterial pressure (MAP) >80 mmHg at least during critical components of the procedure such as during osteotomy work and deformity correction. There is evidence to support reduced surgical time, blood loss, major complications and length of stay when two experienced attending surgeons assist one another during this complex surgical procedure [24]. An *intraoperative* prone radiograph at this juncture may be helpful to assess the flexibility of the deformity as this has been shown to be the best predictive method of deformity correction in these patients [25].

The *exposure* is standard and should typically extend from the upper thoracic spine (typically T1, T2 or T3) down to the sacrum and pelvis. Care should be taken to avoid removal of the interspinous ligaments at the cephalad 3–4 levels to reduce the risk of proximal junctional kyphosis. Frequent packing assists *haemostasis*, and the use of Gelfoam and thrombin is not unusual.

It is imperative to work efficiently but diligently avoid excessive blood loss during the exposure.

The *choice* of implants is largely up to the preference of the surgeon and historically centred on sublaminar wires, now replaced by more contemporary pedicle screw instrumentation. While both have been shown to be appropriate in patients with CP, sublaminar wires require small laminotomies which may increase blood loss. Modern polyaxial pedicle screws with differing thread pitch to accommodate osteoporosis in the adult spine population can be readily utilized in these patients who frequently have very-poor-quality bone (see Chap. 32).

Pelvic *fixation* typically follows a more contemporary S2-alar screw construct as opposed to iliac bolt fixation. These S2AI screws can be placed from the sacrum outwards through the inner and outer tables of the pelvis, which better allow rods to be placed in line with the lumbar and thoracic screws without additional offset connectors and rods. S2AI fixation has also been shown to better correct pelvic obliquity than iliac screw fixation [26]. *Frequently*, these patients will have significant lumbar lordosis which may lead to screw crowding at the pelvis level and thus may necessitate not instrumenting S1. If this is the case, care must be taken to ensure that appropriate preparation for fusion of the L5/S1 joint is performed including preparation out to edges of the bilateral sacral ala before placing 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. As *contemporary* posterior spinal instrumentation technologies have improved, there has been greater movement away from anterior surgery in these patients to limit morbidity. Recent evidence supports reduced operative time, better pelvic obliquity correction and non-inferiority of Cobb angle correction with intraoperative traction and posterior-only instrumentation compared to an anterior-posterior approach [27].

Intraoperative *imaging* should be obtained prior to closure. Importantly, patients with a shunt must have post-operative imaging including the cervical spine to ensure that no damage to the shunt has occurred during correction with the significant lengthening which occurs during correction.

Meticulous sterile technique with frequent irrigation is imperative to decrease the risk of infection. Our *institution* uses morselized autograft and cancellous allograft for fusion mass, large volumes (typically 90–120 cc), along with a *calcium* sulphate pellet infused with vancomycin and tobramycin antibiotic powder. A layered watertight closure is important over a superficial drain. If available at your institution, there is evidence to support reduced deep surgical site infection with the use of a plastic surgeon-based paraspinal advancement flap and multilayered closure [28, 29]. An impervious dressing or incisional vacuum dressing is also used during the hospitalization.

23.7 Post-Operative Care

Essentially every patient with CP should be monitored in the *PICU* post-operatively. 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 if they are unable to be extubated safely at the end of the operation. Critical care *management* of blood pressure balanced with pain control is also important in those first post-operative days. Patients should be transfused as needed for symptomatic post-operative anaemia. Once transferred to a regular nursing unit, the goals then shift to getting the patients and families back to their base-

line 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 post-operative ileus and, more rarely, superior mesenteric artery syndrome.

The *patients* should be set up with a wheelchair evaluation soon in the post-operative period, since their sitting height and overall seating posture will be markedly different following a spine fusion and they will require chair modifications prior to discharge. 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.

23.8 Complications

Neuromuscular scoliosis is a known risk factor for post-operative complications following corrective spine surgery. *Comparatively*, neuromuscular scoliosis results in higher post-operative morbidity and mortality rates [30]. 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% [17, 29–32] with the overall complication rate averaging around 25% [7].

Common complications include severe bleeding, pulmonary compromise (pneumonia, effusions, pneumothorax), deep wound infection, gastrointestinal complications (ileus, gastritis, pancreatitis), urinary tract infection (UTI) and rarely spinal cord dysfunction (including paraplegia). Patients with pre-existing pulmonary compromise are at the greatest risk of major post-operative complications [33, 34].

Recent evidence has sub-stratified GMFCS level V children undergoing spinal fusion based on their risk of major perioperative complication [17, 18]. In this study, patients were sub-stratified according to preoperative central neuromotor impairments: presence of a gastrostomy tube, a tracheostomy, history of seizure and nonverbal status [17]. Those children identified as 5.3 (3 or 4 impairments) had a 50% risk of major perioperative complication in this investigation [17, 18].

Excessive *bleeding* and disseminated intravascular coagulation (DIC) are 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 [20]. *Increased* estimated blood volume loss is independently associated with experiencing a major perioperative complication [35]. Brenn et al. [36] 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 posterior spinal fusion. When *compared* with children with idiopathic scoliosis undergoing posterior spinal fusion, those with CP demonstrate significant differences in coagulation profiles at 15% total blood volume loss. As a result, children with CP who undergo spinal fusion have increased bleeding that starts earlier in the procedure than it does for patients with idiopathic scoliosis. *Additionally*, each 1° increase in coronal curve magnitude correction increases the odds of loss of blood volume by 1.03-fold [20].

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 (see Chap. 34). Children with CP undergoing scoliosis surgery have a higher rate of delayed extubation. As many as 25% develop post-operative respiratory issues, with prolonged mechanical ventilation (>3 days) required in up to 5% [4]. Preoperative pulmonary consultation will often make the management of post-operative pulmonary complications much easier for the patient and family. As mentioned earlier, efforts focused on a physiologic intraoperative resuscitation

avoiding dilutional anaemia and oedema with excess crystalloid fluids can help to minimize these risks when possible.

Gastrointestinal difficulties are also frequently encountered. A post-operative *ileus* is not unusual and usually responds to a slow resolution of normal feeding once bowel sounds are heard and flatus resumes (see Chaps. 35 and 36). Patients who are g-tube fed will usually start with continuous feeds and transition to more bolus-type feeds prior to discharge. It is important to advance diets in these patients as soon as they are able to tolerate, to minimize further muscle wasting in the post-operative hyper-catabolic state. *Pancreatitis* can occur and should be vigilantly monitored. Patients with CP who have a g-tube are 61% more likely to develop post-operative pancreatitis [8]. There is also a clinically relevant, though non-statistically significant, association with seizure disorder and post-operative pancreatitis [37]. *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 post-operative wound infection. The rate of significant infection ranges in the literature from 10% to 30% [38, 39]. 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 [30].

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. [39] 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* pre-operative WBC count and the use of a unit rod, which is no longer routine instrumentation. While a deep surgical site infection is a devastating complication for these patients and their care team, Jain et al. [38] have shown that in children with CP who developed a deep surgical site infection after spinal fusion, there was no recurrence of infection of deformity after infection treatment. However, Jain [38] and Eguia et al. [40] demonstrate that of all major complications, only deep surgical site *infections* worsen CPCHILD outcome scores post-operatively. Final curve correction is lower for patients with deep infections than those without, and a trend towards greater percentages of pain is also seen in those with infections (see Chap. 31). 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. *Radiographic* evidence of screw loosening, especially in the pelvis, without clinical loss of deformity correction is not significant and should just be monitored radiographically. Proximal junctional *kyphosis* is also frequently noted radiographically, in up to 27% of patients, and warrants close follow-up [41]. Patients with *worsened* C2 sagittal translation post-operatively as well as potential failure to maintain the upper interspinous ligamentous supports may increase this risk [41]. Significant hardware failure in terms of rod breakage and screw pull-out 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% [42].

23.9 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. Beckmann et al. [43] 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 (see Chap. 25). Posterior-only instrumentation was associated with shorter operating times and shorter ICU and hospital stays than combined surgery [43]. As the *duration* of surgery is a relevant predictor for post-operative complications, posterior-only instrumentation may reduce the overall complication burden.

Mercado et al. [44] *reviewed* nearly 200 published studies on posterior spinal fusion in neuromuscular scoliosis, providing a grade C recommendation that spinal fusion improves quality of life (QOL). At mid-range follow-up of at least 5 years post-operatively, CPCHILD domains of positioning, transferring/mobility, comfort/emotions and health are significantly improved from preoperative status following spinal fusion in these patients [45]. Children with smaller preoperative *Cobb angles* and corresponding smaller Cobb angles post-operatively demonstrate greater quality-of-life improvement with spinal fusion [46]. Perhaps the greatest evidence in support of the value of spinal fusion for a child with CP comes from Jain et al. [47]. In this retrospective review, caregivers ranked *spine surgery* as the most beneficial intervention in the patients' lives, secondary only to g-tube insertion, with durable quantitative improvements in QOL noted out to 2 years post-operatively [48].

The *overall* satisfaction rate by parents and caregivers as reported in the literature is over 90% (91.7% [48]) (92% [7]). Despite limited overall functional improvements, 8–40% of patients still perceive the results as improved following surgical correction [7] and report a high degree of satisfaction [49]. Improved health-related *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 (see Chaps. 37 and 38) [48]. Interestingly, in this study, the overall subjective improvement of health-related quality of life (HRQL) did not statistically correlate with the degree of objective radiographic changes post-operatively. The occurrence of a complication also did not correlate with the satisfaction rate of the overall outcome of the operation or HRQL.

23.10 Prognosis

While important to recognize, it can be difficult to predict which children will have *clinically* meaningful scoliosis progression. Evidence supports that patients with worsening spinal deformity experience a worsened quality of life [48, 49]. This has similarly been mirrored by worsened reported quality of life of patient's families and caregivers in the setting of more serve scoliosis [48, 49].

Parents frequently inquire about the *risk* of spinal deformity impacting a child's lifespan. 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 lead to a shortened lifespan. Our current literature on spine deformity is unclear if posterior spinal fusion 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 levels IV and V. One article does document increased longevity in ***Rett*** *syndrome*, whose spine deformities are very similar to CP [50]. *Parents* should be educated about the likelihood of spine deformity, and the spine should be discussed at early visits. It is important for a family who is struggling with the diagnosis of scoliosis to see other families who have managed their own children through spinal deformity as well as spine surgery.

23.11 Conclusion

Although spinal *deformity* can have 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 orthopaedic 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.

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Management of the Upper Limb in Cerebral Palsy

24

Erich Rutz and Jan Fridén

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, hand or plastic surgery background. Alleviating pain and preventing/treating pressure sores, particularly in hands and elbows, must always be a prioritized goal. *Interventions* are generally aimed at improving function, joint mobility and cosmesis by various combinations of motor training, muscle strengthening, spasticity, movement disorder management and prevention of contractures and other fixed deformities. *Movement* disorders may respond to oral medications but, when severe, may require *neurosurgical* approaches, such as intrathecal baclofen or deep brain stimulation. The *correction* of fixed musculoskeletal deformities requires various *combinations* of muscle-tendon releases and lengthenings, tenotomies, tendon transfers, osteotomies, arthrodeses and joint-stabilizing procedures. *Surgery* management varies according to the needs and goals of each child and family.

Keywords

Cerebral palsy · Upper limb · Surgery · Function

24.1 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, hand or plastic surgeons (see Chap. 20). The aim of treatment is to improve 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

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standard treatment and has been shown to relieve spasticity and improve function in the short term [3] (see Chap. 25). 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].

Occupational therapy and physiotherapy have limited treatment effects in isolation but are essential adjuncts to medical and surgical management. Repetitive BoNT-A treatments may allow for motor relearning, and BTX injections may also serve as a diagnostic tool prior to *surgical* intervention. The therapy with BoNT-A and its potential long-term effects are often debated although some recent data indicate beneficial impact of BoNT-A on growth.

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 proximal row carpectomy or 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 for correction of muscle-joint imbalance as well as 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. These can be performed as individual *surgica*l procedures or as multiple procedures, in a single session of upper limb surgery, single-event multilevel surgery (SEMLS).

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 level 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].

24.2 Clinical Assessment

It is important to commence assessment by classification of the overall level of bimanual function. In the lower limb, the *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 nonoperative therapies. The MACS is used to classify the child's abilities to handle objects during daily activities (Table 24.1).

Table 24.1 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

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 (see Chap. 12).

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 24.2) [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, separately, 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 24.2 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].

24.3 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 neurodevel-

opmental treatment, motor learning, conductive education, strength training and CIMT (see Chap. 20), 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. 28 and 29).
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.

24.3.1 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 [14] (see Chap. 20).

In a *systematic* meta-analysis, Jackman and colleagues (2014) evaluated the effectiveness of hand orthoses in children with CP [15]. 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. 20 and 25).

24.3.2 Spasticity Management

Over the years, many diagnostic tools and management strategies have been proposed for upper limb spasticity. *However*, evidence-based treatment guidelines are sparse. Therefore, a recently published expert consensus on the surgical evaluation and management of upper extremity spasticity was welcomed [16]. Whilst these guidelines covered UMN *syndrome* in adult patients, they also provided valuable discussions about basic diagnostic considerations and defined operative indications.

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 unilateral spastic hemiplegia, botulinum toxin A (BoNT-A) can be injected into selected target muscles in the upper and lower extremity. *Repetitive* (BoNT-A) treatments may allow for motor relearning as evidenced by the positive effect of BTX-A injections on the kinematic outcome measures for speed and performance of alternating tasks [17]. BoNT-A injections may also serve as a diagnostic tool prior to surgical intervention, for example in case of isolated spasticity in pronator teres. In our experience, *pronator* teres (PT) can be a trigger for a more widespread spasticity in the hand and forearm.

The *therapy* with BoNT-A and its potential long-term effects have been debated for years. In a recent study, muscle morphology was analysed in biopsies obtained from spastic upper extremity muscles of eight cerebral palsy patients treated with BoNT-A 5 months to 4 years prior to sampling [18]. These muscles were compared to muscles from patients who had not received BoNT-A treatment. The *most* important finding was that BoNT-A-treated muscles contained significantly larger fibres compared to untreated muscles. In *addition*, a strong correlation was observed between muscle fibre size and age in both groups although the growth rate in the BTX group was larger.

Pathological signs such as central nuclei, expression of neonatal myosin heavy chain, angular fibres and hybrid fibres (expressing both slow and fast myosin heavy-chain fibres) were *significantly* greater in (BoNT-A)-treated muscles compared to untreated muscles. Capillarization was also increased in BoNT-A-treated muscle compared to untreated muscles and was the best predictor of fibre size. It was suggested that, in *spastic muscles*, BoNT-A may block negative, atrophy-inducing pressure of the central nervous system on skeletal muscle. *Alternatively*, BoNT-A could enable a changed pattern of use that could be seen as a positive addition to current rehabilitation therapies. In other words, the fear of BoNT-A treatment interfering with growth may be unjustified.

BoNT-A *treatment* 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, 19, 20]. 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, 19–21].

SDR in the *lumbosacral* segments is used in selected children with spastic diplegia for lower limb spasticity. It is not used specifically for upper extremity spasticity, but incidental improvements in upper limb function have been reported [22]. In severe spastic quadriplegia, continuous *intrathecal* baclofen may be administered by an implantable pump (ITB) to affect a more generalized reduction of spasticity (see Chap. 28). 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 [23]. Injections of phenol to the *musculocutaneous* nerve and the deep branch of the ulnar nerve have a useful role in the spasticity of elbow flexors and the intrinsic muscles of the hand, respectively [1, 21, 23].

24.4 Surgical Treatment

24.4.1 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 careful 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. 20). As with lower limb surgery for children with CP, there is a need for detailed preoperative analysis, identification of segmental component deformities and muscle imbalances and 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 associ-

ated with both mixed tone and dystonia are more variable, less predictable and less amenable to surgical correction [11].

24.4.2 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].

24.4.3 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 [24]. 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, 24].

24.4.4 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 [25, 26]. 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 Shriners Hospital for Children Upper Extremity Evaluation (SHUEE) [27]. Kinematic analysis is developing rapidly but is not yet as standardized or as widely available as 3D motion analysis of walking [28]. 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 [29].

24.5 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, 24]. Tendon transfers can be utilized to improve hand or wrist position and function. 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, 24].

Shoulder: Dynamic adduction-inward rotation contracture can respond well to BoNT-A treatment. Fixed contractures require surgical releases. *Typically*, they include stair-step tendon lengthening of pectoralis major and transection tenotomy of subscapularis.

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. Phenolization of the musculocutaneous nerve is useful in younger children when the problem is purely dynamic, i.e. before the onset of a fixed contracture [23]. 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 [30].

Forearm pronation: The pronator teres is the first muscle-tendon unit to develop a contracture in the hemiplegic upper limb [1]. Surgical release of the pronator is often an effective means of reducing forearm spasticity, increasing the working range and minimizing trick and compensatory movements. *Following* PT release, the distribution and magnitude of any remaining spasticity can be better evaluated and more specifically addressed in subsequent surgeries. A *contracted* pronator teres can be simply released, but if it has a reasonable excursion, it can be rerouted to act as a supinator [31]. 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 [31, 32]. Some of these "benefits" have been challenged by Tonkin [33].

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 [24, 32]. 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, have often been corrected by Green transfer [31, 32]. However, we do not recommend this transfer. In a study by Patterson and co-workers [34] of 25 transfers, 12 developed a late deformity post-operatively. The *most* common deformities that developed were extension deformities and, to a lesser extent, supination and recurrent flexion deformities. Instead, we recommend transfer of ECU to ECRB [35]. The authors emphasize the causative role of the palmar subluxation of extensor *carpi ulnaris* and describe a surgical correction strategy detailing transfer of extensor carpi ulnaris to extensor carpi radialis brevis. This surgery re-establishes and maintains a more favourable muscle-tendon-joint mechanics and hand position [36]. Patient satisfaction is high, time and effort in daily care for patients and caregivers are less and incidence of complications is low.

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 (Fig. 24.1), palmaris longus and long finger flexors must be addressed at the same time. However, remember that FCU is a highly pennate muscle with short fibres and limited excursion potential (see Chap. 21). *Also*, it must be kept in mind that spasticity results in a major alteration of muscle-joint anatomical relationships [37]. Those authors hypothesize that spastic FCU muscle fibres are unable to add serial *sarcomeres* in response to growth, or alternatively, the selective loss of muscle length is secondary to the central nervous system lesion itself. In practice, this means that the stretched-out, long sarcomeres of a spastic FCU cannot generate dynamic force, whether transferred or not (see Chap. 21). Full motor control cannot be expected after transferring a *spastic* muscle although stabilization of the affected joint, via the passive tension added, is helpful for positioning.

Adolescents with severe wrist flexion contractures and limited function may appreciate the cosmetic gains and improvements in palmar hygiene from tendon lengthenings of wrist flexors (Fig. 24.1) and finger flexors or arthrodesis of the wrist, combined with soft tissue releases [24]. A dorsal wrist fusion plate provides stable fixation, permits early mobilization and has excellent

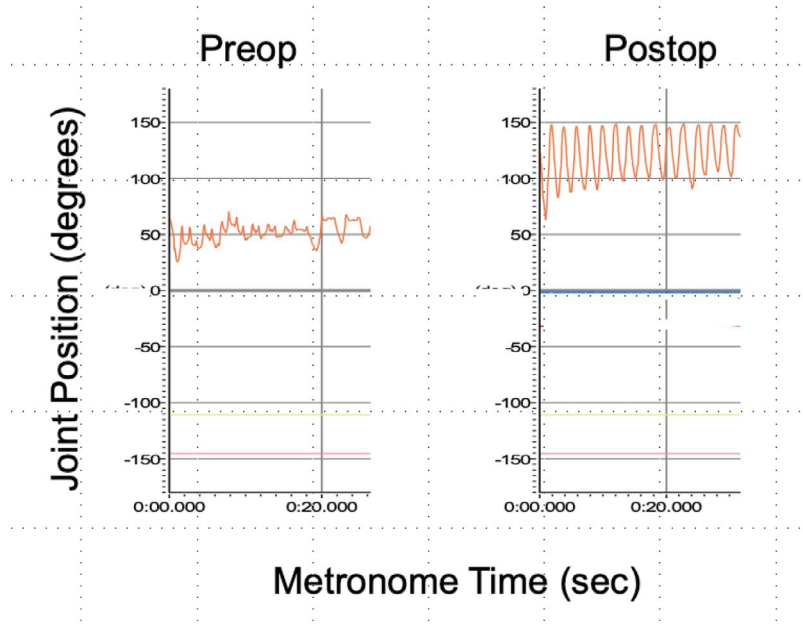


Fig. 24.1 Goniometric recording of wrist movement before and 1 year after tendon lengthening of spastic flexor carpi radialis. Note that both amplitude and regularity of wrist motion improved

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 [24]. 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 [24, 31]. 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 [24].

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 [24, 31, 38].

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 [24, 38]. 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 [24]. Rerouting 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 [24, 31]. *Alternatively*, the extensor digiti minimi may be transferred to the insertion of abductor pollicis brevis (APB) to secure a palmar abduction moment of the thumb [39].

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 [30–32, 38, 40] and [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, 19, 20]. The first high-quality, comparative study to compare therapy, botulinum toxin injections and upper limb surgery was by *Van Heest* and colleagues in 2015 [40]. 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 Shriners 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 [40].

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25

Integrated Management in Cerebral Palsy: Musculoskeletal Surgery and Rehabilitation in Ambulatory Children

Pam Thomason, Kate Willoughby, and Erich Rutz

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.

Classification of *sagittal* gait patterns in bilateral spastic CP (*BSCP*) is also useful to guide integrated management, selection of target muscles for injection of botulinum toxin A, 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 malalignment and joint instabilities in one operative session. *Rehabilitation* requires at least 1 year, and improvements continue into the second year post-operatively. The term *SEMLS* has been refined to just multilevel surgery (MLS) in acknowledgement of the need for "fine-tuning" surgery in the years following MLS, usually prior to skeletal maturity.

Keywords

Cerebral palsy · Lower limb · Gait analysis · Multilevel surgery

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25.1 Introduction

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. The 2006 definition of CP emphasises several 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. 25.1). This stage is often accompanied by musculoskeletal pain and decreased quality of life [2]. During the early, dynamic phase, gross motor function increases, and during the later fixed stage, gross motor function reaches a plateau or decreases [3, 4] (Fig. 25.2).

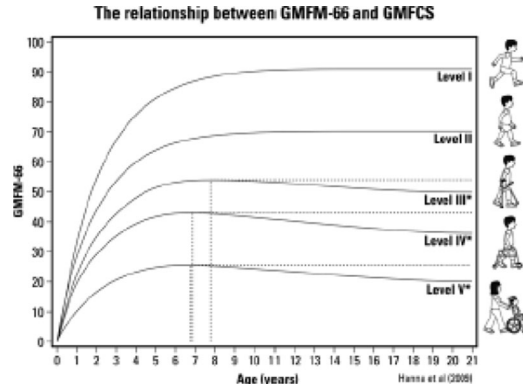


Fig. 25.2 Gross motor curves in children with cerebral palsy and the five levels of the GMFCS modified from Hanna et al. (2009) [3]. Note that gross motor function deteriorates with age at GMFCS levels III, IV and V

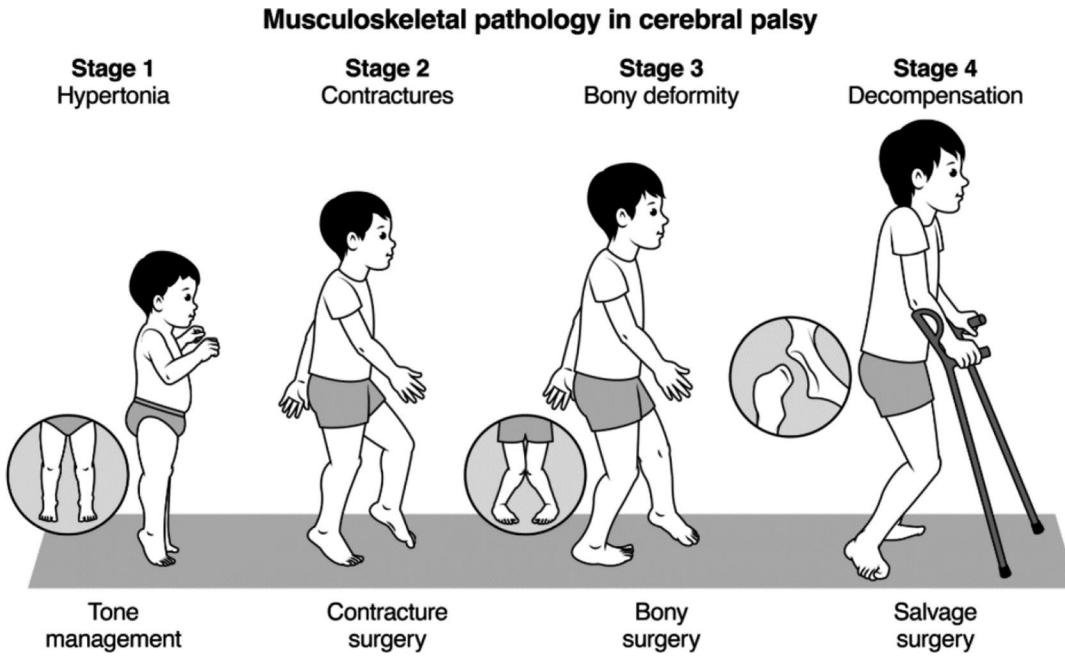


Fig. 25.1 The stages of musculoskeletal pathology (MSP) in children with cerebral palsy from birth to skeletal maturity. At stage 1, children have spasticity but no fixed contractures and should be managed nonoperatively. At stage 2, there are fixed contractures, and at stage 3 contractures and bony deformities which usually require corrective orthopaedic surgery. Stage 4 represents decompensation indicating that the MSP has progressed to a point where restoration of optimal joint and muscle-tendon function is no longer possible [8]

25.2 Classification System

The Gross Motor Function Classification System–Expanded and Revised (GMFCS E&R) 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]. Illustrations accompanying the descriptor for each GMFCS level are available for children aged 6–12 years (Fig. 25.3) and for children aged 12–18 years (Fig. 25.4). These are available from the CanChild website (https://www.canchild.ca/en/resources/42-gross-motor-function-classification-system-exnded-revised-gmfcs-e-r).

The combination of motor growth curves [4] and GMFCS provides a framework for under-

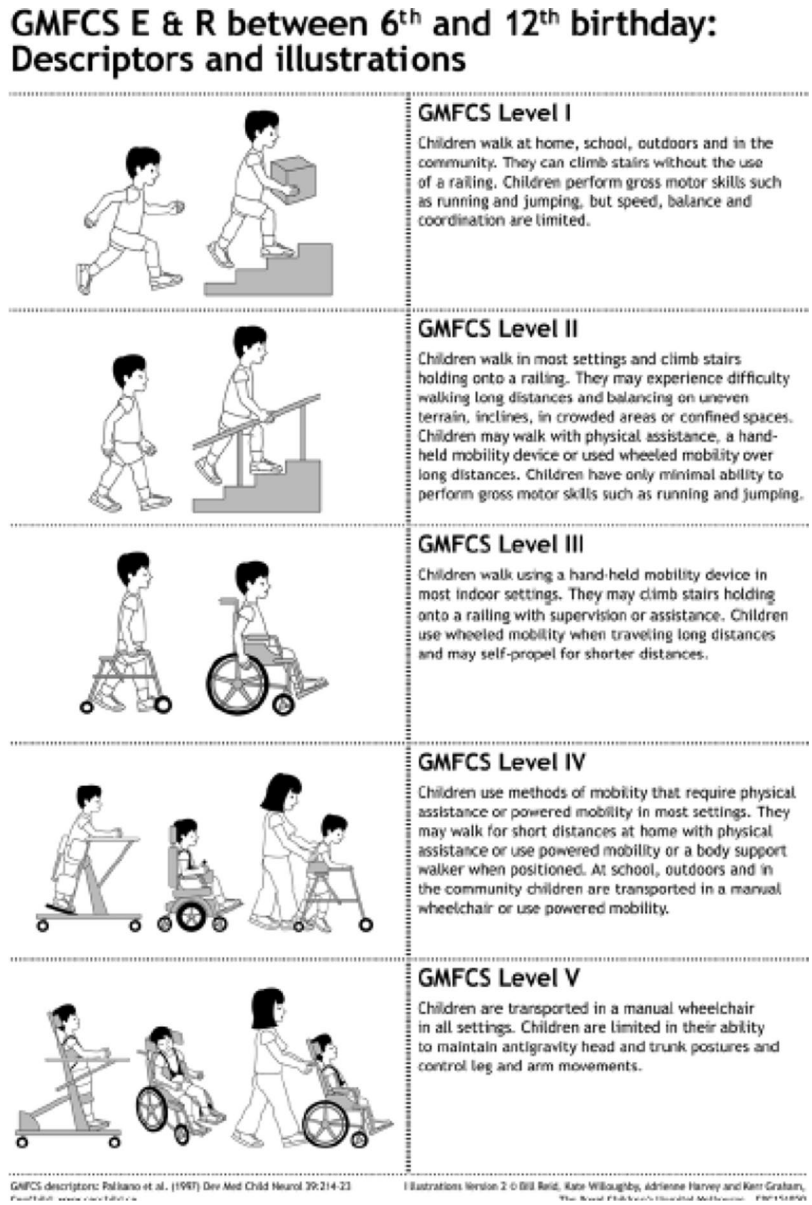


Fig. 25.3 GMFCS age 6–12 years: GMFCS E&R descriptors and illustrations between sixth and 12th birthdays. (© Reid, Willoughby, Harvey and Graham, The Royal Children's Hospital, Melbourne)

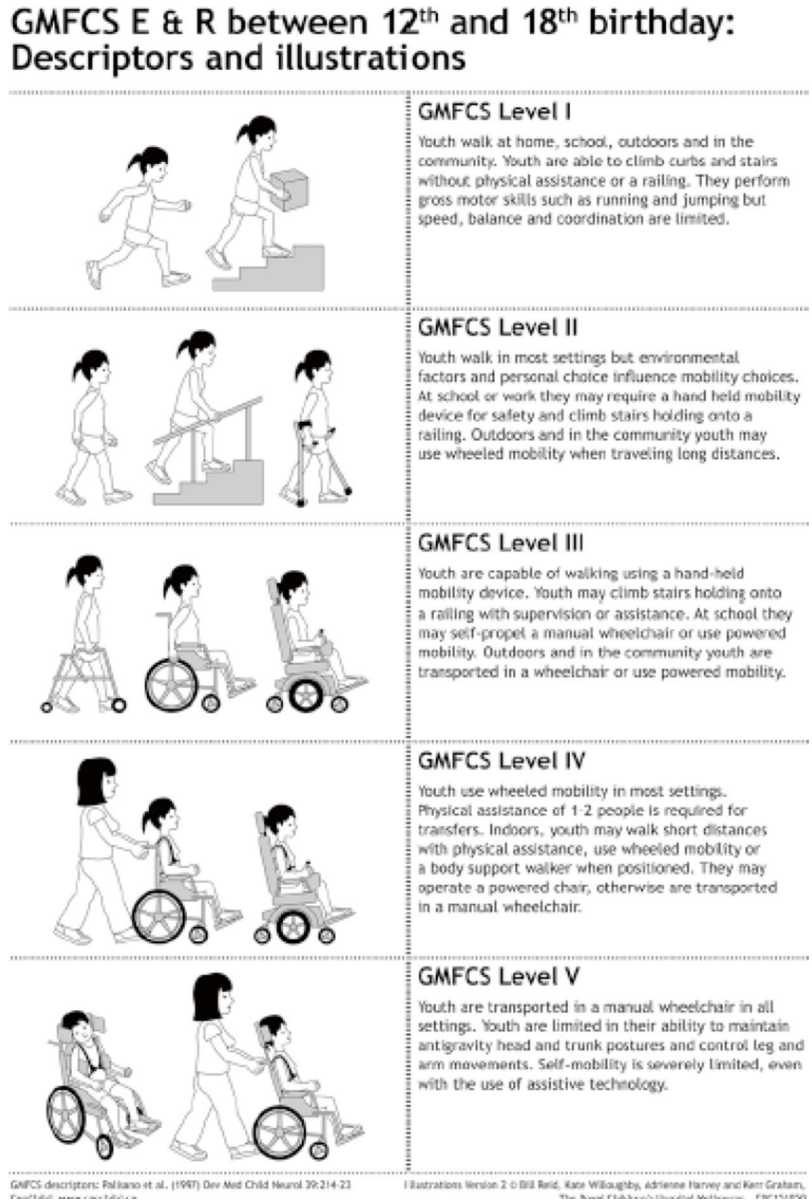


Fig. 25.4 GMFCS age 12–18 years: GMFCS E&R descriptors and illustrations between 12th and 18th birthdays. (© Reid, Willoughby, Harvey and Graham, The Royal Children's Hospital, Melbourne)

standing 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 [9, 10]. 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. 25.2). 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. 25.3). 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 [11].

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 [12, 13] and the risk of developing scoliosis [14]. 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 [15–18].

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 multilevel surgery *(MLS),* a small number of children move up a level. This is uncommon and should not be expected in more than 5–10% of children [19].

Deterioration in GMFCS level is more common. For example, isolated lengthening of the *Achilles* tendons for toe walking in children functioning 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 [20].

25.3 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 [21]. Rodda and Graham extended the Winters, Gage and Hicks classification to include the coronal and transverse planes ([22], Fig. 25.5). 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) and to guide surgery when children develop fixed deformities (see Figs. 25.1 and 25.5).

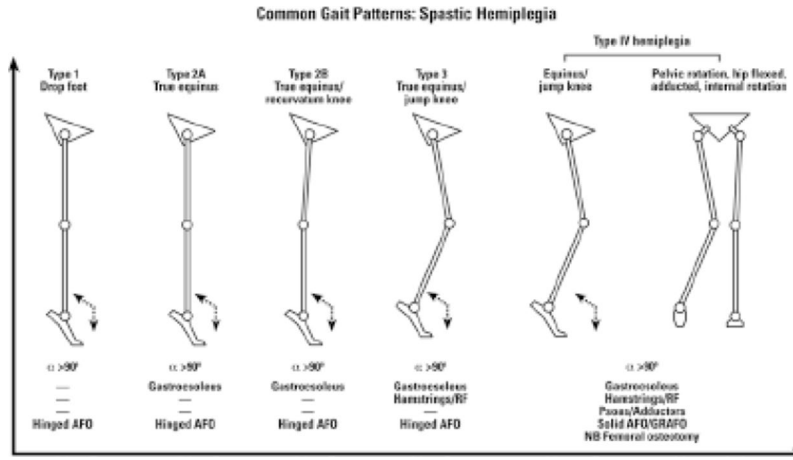


Fig. 25.5 Common gait patterns: spastic hemiplegia (unilateral spastic cerebral palsy (USCP)). Gait patterns and management algorithm spastic hemiplegia. ©Rodda and Graham, Royal Children's Hospital, Melbourne, Australia (2001). Modified from Winters, Gage and Hicks (1987)

25.3.1 Type 1 Hemiplegia

In type 1 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.

25.3.2 Type 2 Hemiplegia

In type 2 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.

25.3.3 Type 3 Hemiplegia

In type 3 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.

25.3.4 Type 4 Hemiplegia

In type 4 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 [23]; see Fig. 25.5.

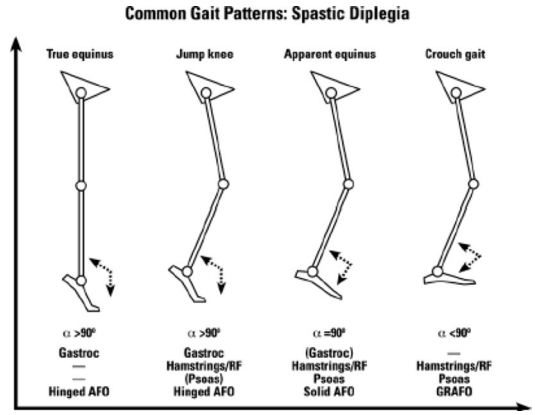


Fig. 25.6 Common gait patterns: spastic diplegia (bilateral spastic cerebral palsy). Gait patterns and management algorithm spastic diplegia (©Rodda and Graham, Royal Children's Hospital, Melbourne, Australia (2001))

25.4 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 multilevel surgery ([22], Fig. 25.6).

25.4.1 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.

25.4.2 Jump Gait

Jump gait is characterised by equinus associated with incomplete extension at the knee and hip in late stance (see Chap. 12). 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.

25.4.3 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, many children will develop crouch gait [22] (see Chap. 12).

25.4.4 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 (see Chap. 12). 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) [20, 24–26]. A key feature of crouch gait is that most muscle-tendon units (MTUs) are excessively long. This is true for all the single-joint muscles such as the soleus, vasti and gluteus maximus and often for the two-joint muscles such as the hamstrings. The only consistent *contractures* are of the iliopsoas. In crouch gait, the hamstrings are short only in children 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 [20].

25.5 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 (see Chap. 22) 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 [27].

The World Health Organization (WHO) describes health conditions in several domains, including body structure and function, activities and participation [28] (International Classification of Functioning, ICF). 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), Modified *Tardieu* and the Hypertonia Assessment Tool (HAT) [29]. 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 [30, 31] (for more, see Chap. 41). Some CP-specific scales have been designed for ambulant children (GOAL™) and others for non-ambulant children (Caregiver Priorities and Child Health Index of Life with Disabilities, CPCHILD©) [32]. Serial radiographic monitoring of hip displacement (hip surveillance) using

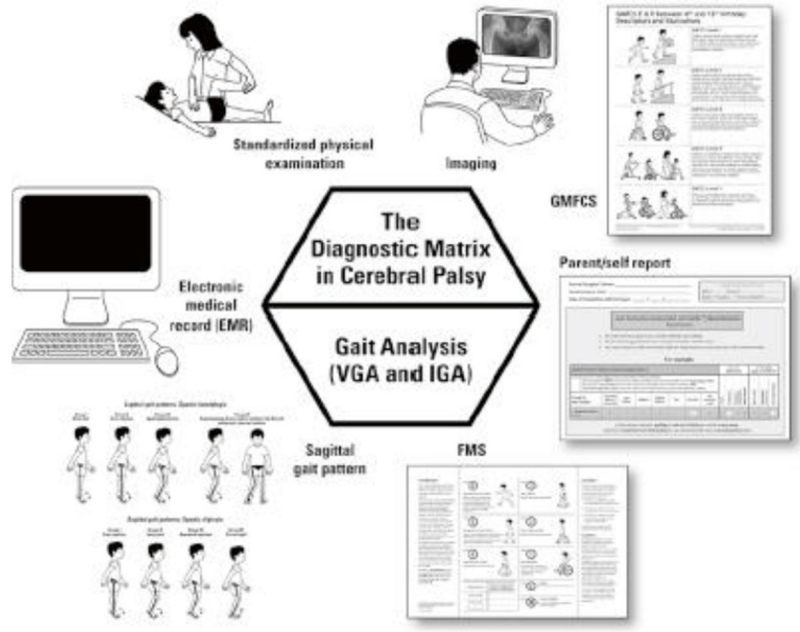


Fig. 25.7 Diagnostic matrix: The diagnostic matrix consists of a standardised approach to clinical history, physical examination, radiology, functional scales (FMS and FAQ) and sagittal gait pattern identification. These components can be used in conjunction with either video gait analysis (VGA) or instrumented gait analysis (IGA)

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 [33] (Fig. 25.7), is utilised. These include instrumented gait analysis (IGA) including kinematics, kinetics, dynamic EMG and energy cost of walking.

25.6 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, many 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 with neurolytic blocks, botulinum neurotoxin A (BoNT-A) and phenol used to manage spasticity (see Fig. 25.1). During this phase, under the age of 6 years, the only surgery may be for early management of hip displacement, when indicated. *Equally*, it is not logical or effective to continue with injections of BoNT-A throughout childhood once the musculoskeletal pathology becomes fixed. 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. A programme of care utilising BoNT-A should be viewed as complementary to orthopaedic surgery and not as an alternative. Information about dosing, dilution, muscle targeting and safety have been published elsewhere [9, 10, 34]. Age 6–12 years is the optimal period for multilevel surgery for correction of fixed deformities and contractures to stabilise or improve gait and functioning for the second decade and beyond [30, 31].

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. 27, 28 and 29). These interventions are used for carefully selected groups of children, and this has been discussed in detail elsewhere [7, 27].

25.6.1 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 [35]. 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, many 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 [26].

A nonoperative *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 [36]. 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 [36–38]. Given that parents and therapists can reliably recognise the effects of BoNT-A injection, randomised clinical trials *(RCTs)* of BoNT-A cannot be double-blinded and are therefore confounded by placebo effects [39].

25.6.2 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 [10]. 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, 34]. 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.

25.6.3 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].

25.6.4 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 IGA before surgery. In cases with deterioration (20.9% out of 110 children), the lengthening was not performed.

25.7 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 [24] caricatured this approach as the "birthday syndrome" (Fig. 25.8). 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) [30]. The 5-year results of this clinical trial show that these improvements were largely maintained at 5 years post-SEMLS [31].

Recently, following long-term follow-up studies, the term SEMLS has been refined to just "*multilevel surgery*" in acknowledgement of the need for "*fine-tuning*" surgery in the years following SEMLS and prior to skeletal maturity. An *example* of this would be growth plate surgery to correct mild deformity [48]. In the MLS 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 [33].

For *example*, muscle weakness is an impairment which is easily overlooked and 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, 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

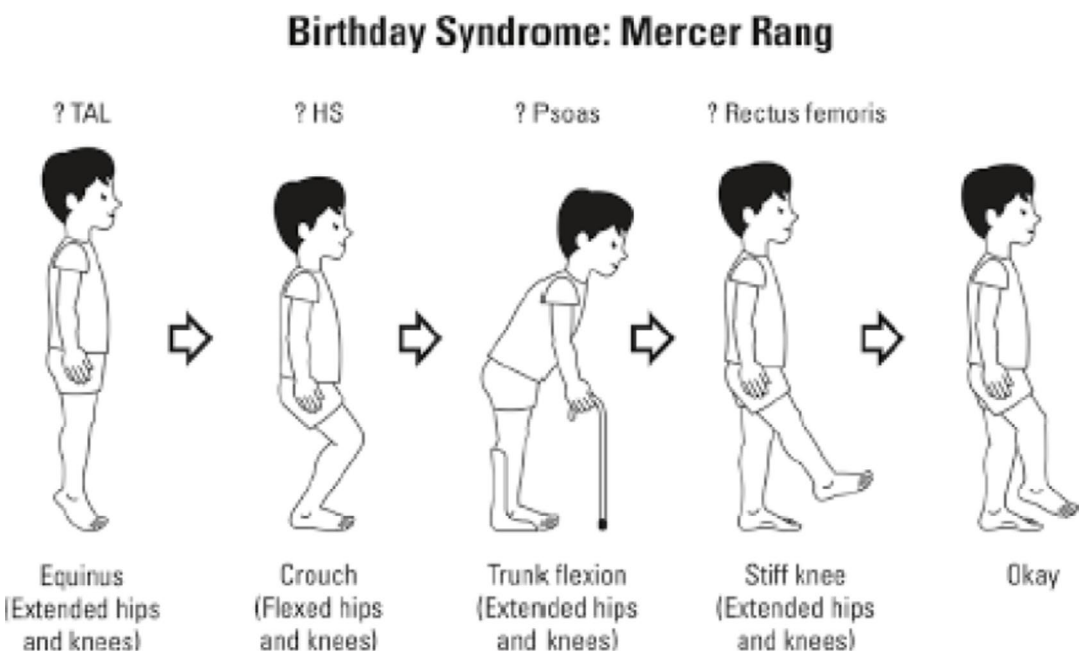


Fig. 25.8 Birthday syndrome: Mercer Rang. The birthday syndrome as described by Mercer Rang. In the younger child walking on tiptoe, surgery starts with bilateral lengthening of the Achilles tendons. This results in a combination of *foot flat* and crouch (increased knee flexion); lengthening of the hamstrings followed by the hip flexors is required. *Finally*, rectus femoris transfer is performed for stiff knee gait

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 [49, 50], may be useful.

It is crucial to distinguish between the needs of children and adolescents. The decision to proceed with MLS 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 MLS 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 the goals of child, their parents and surgeon are consistent and achievable [27]. The Gait Outcomes Assessment List (GOAL™) can be invaluable at this stage of surgical planning [51].

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 post-operatively [27, 31].

The principal components of a successful MLS 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 MLS.
8. Removal of fixation plates and other implants.
9. Follow-up until skeletal maturity, for new or recurrent deformities [27, 52].

The surgical team should consist of two experienced surgeons and two experienced assistants. Expert anaesthesia and pain management are essential. *Post-operative* 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. 25.9 and 25.10). 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 [31]. Only a carefully tailored and carefully monitored rehabilitation programme can ensure that the child will reach a higher level of function [30, 31].

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 ([53]; [54]) 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 or rectus surgery. The goal is to achieve full extension of the knee, combined with regaining full flexion.

New ankle-foot orthoses (AFOs) must be prepared for immediate fitting after cast removal, usually 6 weeks after surgery. The initial post-operative 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 MLS rehabilitation has been described in more detail elsewhere [27].

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 [55]. This



Fig. 25.9 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 multilevel surgery (MLS), which included lengthening of the iliopsoas, lengthening of the medial hamstrings and gastrocnemius recession femoris that does not become *scarred and adherent in its new site*



Fig. 25.10 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

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) [25, 56]. Improved correction of pes valgus by osteotomies and fusions, which permit early mobilisation, is also critical to the long-term success of MLS in BSCP [57].

25.8 Management of Lower Limb in Unilateral Spastic CP (USCP) by Sagittal Gait Pattern

25.8.1 USCP Type 1 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 using an AFO, usually a leaf spring or a hinged AFO. *Most* 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 [58]. 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 [59].

25.8.2 USCP Type 2 Hemiplegia

In type 2 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 use of a hinged ankle-foot orthoses. 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 [10]. *Contractures* develop

insidiously in both gastrocnemius and soleus, and many 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. [55] 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, 61]. In younger children, pes valgus can be managed with an orthosis. In older children, os calcis lengthening may be required [57]. Surgical decision-making should be guided by three-dimensional gait analysis.

25.8.3 USCP Type 3 Hemiplegia

In type 3 *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 [10]. 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.

25.8.4 USCP Type 4 Hemiplegia

In type 4 *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 more common than for other children with hemiplegia and often presents late ([13, 16, 62]; see Fig. 25.5). 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 4 hemiplegia requires unilateral MLS. 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 [21, 63].

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 [60]. 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 [60]. Early *identification* of hip displacement affords the best opportunity for correction during unilateral MLS [62]. However, a few teenagers with type 4 hemiplegia present with symptomatic hip dysplasia during the second or third decade and require a pelvic osteotomy such as the Bernese periacetabular osteotomy.

25.9 Management of Bilateral Spastic CP (BSCP) According to Sagittal Gait Patterns (Fig. 25.6)

25.9.1 True Equinus

25.9.1.1 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 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 IGA [33, 64].

25.9.2 Jump Gait

25.9.2.1 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. 28) is a better option when the spasticity is severe, generalised and adversely affecting gait and function [7, 65].

Older child: This is the ideal time (6–12 years) for MLS. MLS 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 MLS and rehabilitation [27]. *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. 25.8 and 25.9). 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.

25.9.3 Apparent Equinus

25.9.3.1 Sagittal Plane: Ankle

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 [22]. 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 MLS at proximal levels, and IGA is essential for planning the appropriate surgical interventions.

25.9.4 Crouch Gait

25.9.4.1 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 children 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 [66]. *Consequently*, most 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) [20].

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 [25, 26]. There is often a delay between lengthening of the gastrocsoleus and 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 [26]. *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 [25, 67].

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 [50].

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 [56]. 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. 25.10).

25.10 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. 27). Many children functioning 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, 24]. 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 [34]. 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. Where children can *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 [57]. 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 [68].

25.11 Hip Problems in Children with CP (See Chap. 22)

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. 22). Thereafter, displacement proceeds more rapidly, many hips become painful [68–70] and 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, are associated with measurable decreases in health-related quality of life [71]. Hip displacement may be managed by muscle lengthening or bony reconstructive surgery or, for many children, a combination of both (see Fig. 25.11) [72, 73]. When performed in isolation, muscle lengthening aims to facilitate proximal femoral and acetabular development by correcting adduction and flexion contractures; however, its effectiveness is very limited [17]. For the majority of children, it acts, at best, as a temporising measure to delay bony reconstruction for very young, small children in whom bony reconstruction may be challenging or for medically fragile children for whom more invasive surgery may pose unacceptable risk.

Post-operatively, *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. Many of these children will need bony reconstructive surgery, 2–10 years after muscle-lengthening 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]. Many

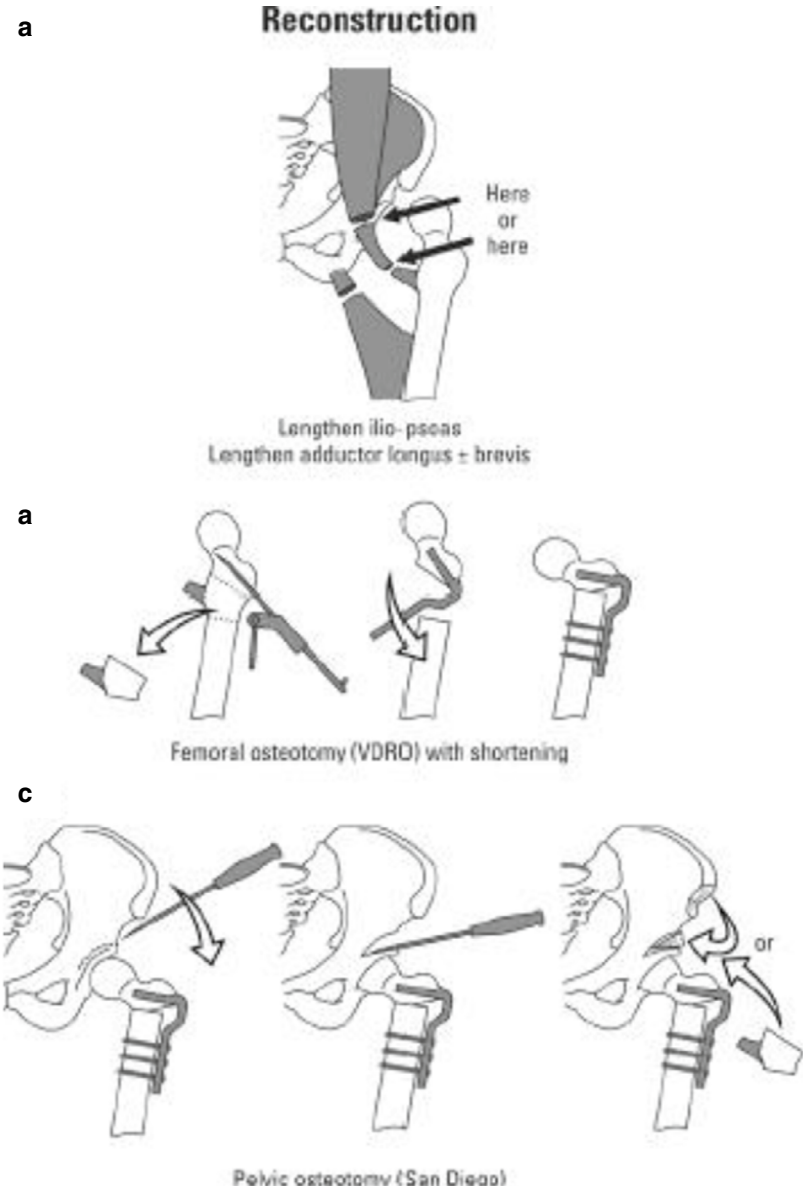


Fig. 25.11 Hip displacement may be managed by preventive or reconstructive surgery or, for many children, a combination of both. In this figure, the three classic stages are illustrated which include (**a**) lengthening of the hip flexors and adductors, (**b**) proximal femoral varus derotation osteotomy with shortening and (**c**) peri-ileal acetabuloplasty (San Diego or Dega)

children have significant hip displacement *without* adductor contracture, and reconstructive surgery should also be considered when MP is persistently >40, or in the presence of deteriorating, secondary *acetabular dysplasia*. Nutrition and respiratory (see Chaps. 34 and 36) status should be optimised before embarking on any major surgery, especially bilateral hip surgery. It is also important to optimise tone management prior to surgery as the surgery is much easier to perform when global tone is reduced.

Reconstructive surgery consists of three main components: adductor release (where indicated), femoral osteotomy and pelvic osteotomy [70] (see Fig. 25.11). Firstly, *abduction* range is restored by an 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 [70, 74]. 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. Pain is prevented or relieved, and sitting tolerance is usually dramatically improved. Blade plates are usually removed about 12 months after surgery. *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 [71]. Fixed deformity, especially the windswept deformity, is also a major impediment to comfortable sitting and care [75]. Excision of the *proximal* femur is widely used but has unreliable outcomes and a high complication rate [76]. 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.

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26 Finding Consensus for Lower Limb Orthopaedic Surgical Interventions in Cerebral Palsy

Erich Rutz and James McCarthy

Abstract

The decision-making process for *surgical* indications in lower limb orthopaedic surgery, for children with cerebral palsy (CP), is complex. There is currently wide variation in surgical practice in this demanding field, which may contribute to unsatisfactory and unpredictable outcomes. To *address* the need for standardisation of surgical indications for lower limb surgery in children with CP, an expert *international* panel with more than 300 years of experience in *3-dimensional* gait analysis and paediatric orthopaedic surgery was established. The most common procedures were identified, and consensus indications established using a Delphi process. Substantial *agreement* has been established and published for the most common lower limb surgical indications.

Keywords

Cerebral palsy · Surgical treatment · Delphi method · Consensus

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26.1 Introduction

We established a 17-member panel of *fellowship trained* paediatric orthopaedic *surgeons* each with at least 9 years (mean of 20.8 years' experience) of experience in the surgical management of children with cerebral palsy (CP) [1–3]. The panel was *international* in composition, with members from Europe, the United States, Canada and Australia. The *goal* of this project was to define surgical indications for common paediatric lower limb orthopaedic surgery in the treatment of children with CP. We *identified* common clinical problem, for example equinus gait, for which many surgical options are available with little established consensus in the literature [4]. *Significant* variation exists in the choice of surgical procedures even for common indications [4]. Practice variation has been shown to lead to poor outcomes [5].

A list of *common* orthopaedic procedures, which are in widespread use to address gait impairments and functional problems, experienced by ambulant children with CP was created.

The list *consists* of 23 commonly performed orthopaedic procedures, for lower limb deformities in ambulant children with CP. From this list, we *initially* agreed to focus on the two commonly performed procedures, medial hamstring lengthening (MHL) and femoral derotation osteotomy (FDO), as our initial attempt to gain consensus and to gain experience with the Delphi process [3, 6, 7].

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The project was given the title '*Mission Impossible*'. The *goal* of Mission Impossible was to understand current practice variation in the surgical management of children with CP and to establish new consensus, from the international panel of experts. This *data* can be used as a foundation from which to identify areas that require further investigations through more traditional research methods.

The overall goals were to:

1. Create a reservoir of expertise: the international expert panel
2. Shorten the learning curve for complex indications
3. Reduce practice variation and unnecessary or outmoded procedures
4. Decrease harms and maximise functional benefits for the target population

26.2 Research Design and Methods

It was decided to use a modified Delphi methodology [3, 6, 7]. The *Delphi* method is usually recommended for use in the healthcare setting as a reliable means of determining consensus for a defined clinical problem. In this setting, it comprised four steps:

26.2.1 Step 1: Expert Panel Formation

The requirement for *membership* of the expert panel was >10 years' experience in using 3-dimensional gait analysis and in orthopaedic management of children with CP. The *combined* paediatric orthopaedic surgeons' years of experience was calculated to be over 300 years, and they included experts from around the world, from different centres [6, 7]. Commitment and continuity of involvement in the Mission Impossible project were critical factors to achieving high-quality research and publications [6–12].

26.2.2 Step 2: Collate and Establish Agreement

For *each* clinical problem, the following domains were identified and studied: definition of the clinical problem; clinical *history* and associated symptoms; and physical examination imaging, where applicable, and 3-dimensional gait analysis, including kinematics and kinetics.

The intraoperative examination should be done under anaesthesia aka "examination under anaesthesia" (EUA).

Outcome measures include technical (gait outcomes) and patient-reported outcome measures (PROMs).

26.2.3 Step 3: Consensus Process on more Common Procedures

In total, we used three to four different rounds (see Fig. 26.1).

26.2.4 Consensus and Criteria

Consensus for an indicated *criteria* was awarded when at least 80% of experts agreed to the top two Likert scales (strongly indicated or indicated) or to a non-indicated procedure if at least 80% of experts agreed to the bottom two Likert scales (not indicated or strongly not indicated).

General agreement was awarded for questions with at least 60%, but less than 80% of experts agreed to the top two Likert scales, or general disagreement for questions with at least 60%, but less than 80% of experts agreed to the bottom two Likert scales.

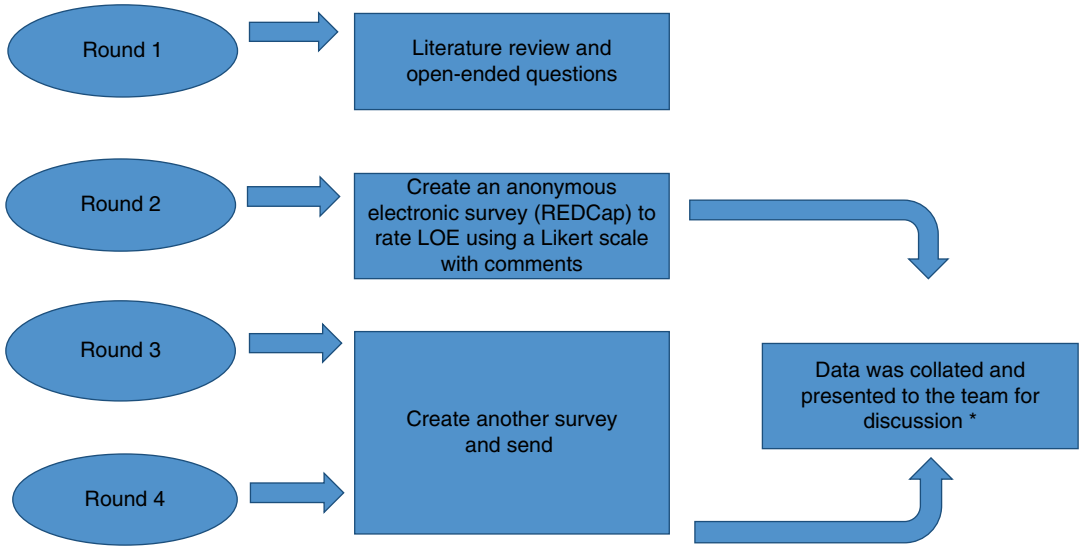


Fig. 26.1 Consensus process on the most common procedures. *In person pre-Covid 19, online post-Covid 19

26.3 Results

At this stage, *seven papers* using this technique have been published in the Journal of Children's Orthopaedics. As outlined in Table 26.1, we focussed on different clinical problems and different anatomical levels. *Surgery* for equinus gait and surgery to improve knee extension are performed (medial hamstring lengthening, hamstring transfer).

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4. Kay RM, McCarthy J, Narayanan U, et al. Finding consensus for hamstring surgery in ambulatory children with cerebral palsy using the Delphi method. J Child Orthop. 2022;16 55–64.
5. Shore BJ, McCarthy J, Shrader MW, et al. Anterior distal femoral hemiepiphysiodesis in children with cerebral palsy: establishing surgical indications and techniques using the modified Delphi method and literature review. J Child Orthop. 2022;16:65–74.
6. Davids JR, Shilt J, Kay R, et al. Assessment of foot alignment and function for ambulatory children with cerebral palsy: results of a modified Delphi technique consensus study. J Child Orthop. 2022;16:111–20.
7. Rutz E, Novacheck TF, Dreher T, et al. Distal femoral extension osteotomy and patellar tendon advancement or shortening in ambulatory children with cerebral palsy: a modified Delphi consensus study and literature review. J Child Orthop. 2022;16:442–53.

Table 26.1 A list of 23 commonly performed orthopaedic interventions

Procedures	
Bony	
1.	Acetabular/pelvic osteotomy
2.	Varus derotational osteotomy
3.	Proximal femoral derotational osteotomy
4.	Distal femoral derotational osteotomy
5.	Tibial derotational osteotomy
6.	Distal femoral extension osteotomy
7.	Patellar tendon/tibial tubercle advancement (shortening)
8.	Hindfoot arthrodesis
9.	Calcaneal sliding osteotomy (medial/lateral)
10.	Mid/forefoot arthrodesis
11.	Calcaneal opening wedge osteotomy
12.	Midfoot osteotomy
13.	Guided growth of the anterior distal femur
14.	Guided growth of the proximal femur
Soft tissue	
15.	Hip adductor lengthening
16.	Psoas lengthening
17.	Hamstring lengthening
18.	Rectus femoris transfer/lengthening
19.	Gastrocnemius recession
20.	Gastrocsoleus lengthening/heel cord lengthening
21.	Posterior tibialis lengthening
22.	Split posterior tibialis transfer
23.	Split anterior tibialis transfer

26.4 Summary and Conclusion of Mission Impossible Project

We were able to *formulate* an expert panel with overall more than 300 years of experience. Furthermore, we were able to collate and agree upon the most common procedures. Therefore, we were able to create and agree on the *most* common surgical indications. Our publications have been cited many times and set a new standard for surgical care of children with cerebral palsy. *Future* projects will focus on new important research questions. Such topics include minimally invasive and percutaneous techniques, indication for botulinum toxin use and ethical questions.

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8. Jason Rhodes, MD, Children's Hospital Colorado, Aurora, Colorado
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14. Matthew Veerkamp, BA, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio
15. Laura Brower, MD, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

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Oral Medication Use in Cerebral Palsy

27

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. The chapter is in all fields up to this day revised.

Keywords

Medication · Cerebral palsy · Spasticity · Dystonia

27.1 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, 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 Organization's [2] International

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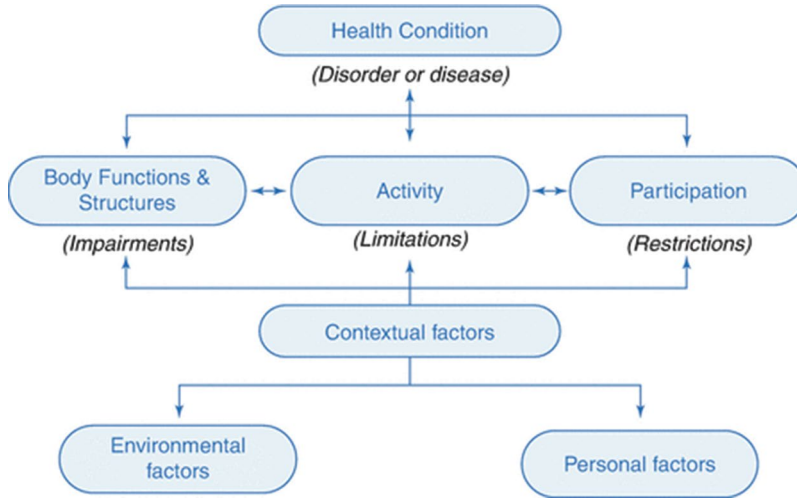


Fig. 27.1 International Classification of Function model

Classification of Function (Fig. 27.1). 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 allow 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].

27.2 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. 12 and 21). 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 coexists.

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 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].

27.3 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 or 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. 27.2). 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* (see Chap. 35). Evaluation of pain itself should be made at the outset, with consideration of appropriate measurement tools for use with both children and young people, and their caregivers. Alternate treatments, such as botulinum toxin type A intramuscular injections or orthopaedic surgery, generally offer benefit for focal or segmental problems (see Chap. 25). Another treatment for generalised hypertonia, intrathecal baclofen, is described in the chapter on intrathecal baclofen therapy (see Chap. 28).

27.4 Treatment of Spasticity

27.4.1 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 such as substance P which play a role in producing spasms (see Chaps. 12, 21 and 28) (Table 27.1).

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

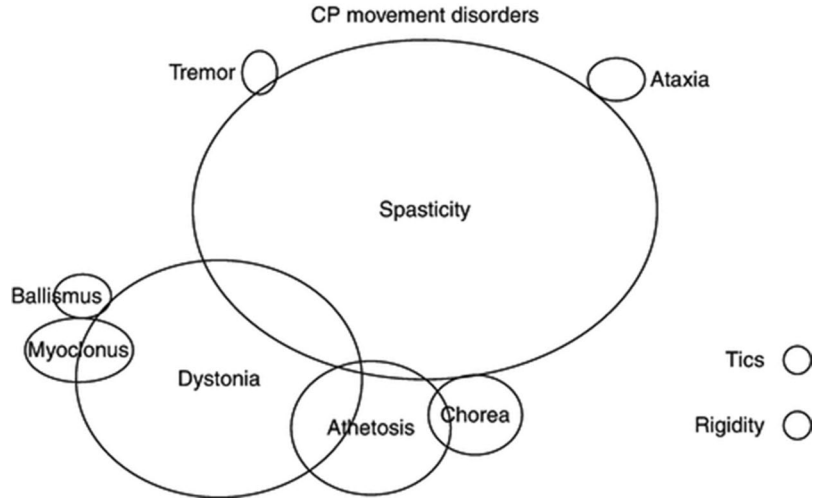


Fig. 27.2 Overlap of movement disorders seen in CP

Table 27.1 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

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 (see Chap. 26). 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. 28). 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.

27.4.2 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.

27.4.3 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.

27.4.4 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. 21). 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 ten 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. 28). 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.

27.4.5 Clonidine

Clonidine is an α2-adrenergic agonist. There is also limited evaluation 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. Sayer and colleagues [27] undertook a retrospective review of children and young people with secondary dystonia prescribed clonidine in an outpatient setting and analysed a subset of 24 patients, of whom 83% described improvement in at least one symptom area of pain, seating, sleep, muscle tone and/or involuntary movements. *Side effects* were reported in 50% of participants including drowsiness and increased movements.

27.4.6 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 [28]. An observational study assessed the effect of gabapentin on severe *dystonia* in 69 children, 25 of whom had CP [29]. 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. A recent open-label pilot study of children with dystonic cerebral palsy who were prescribed gabapentin for 12 weeks found that dystonia was not significantly changed; however, improvements were seen in pain behaviour, comfort and related goals [30]. 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.

27.5 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 [31]. 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 [32]. This forms the basis for use of both anticholinergics and dopaminergic medication in the treatment of dystonia.

27.5.1 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 [33]. 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

proportion of children, an increase in movements was noted [34].

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 [34]. 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 in one-third for upper extremity function and verbal expressive language and in a smaller proportion for drooling [35]. 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 [36].

27.5.2 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 [37]. 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 [38]. 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 [39]. 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.

27.6 Treatment of Chorea and Athetosis

27.6.1 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. [40] 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 [41].

27.6.2 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 [42]. There is limited description on the use of tetra-

benazine 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 to 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 [43]. 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 [44, 45].

27.7 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. 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

28

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, 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 thin catheter tracking to the spinal subarachnoid space for the release of baclofen into the cerebrospinal fluid. There can be surgical complications as well as complications related to the patient's medical condition, the hardware implanted, and the medication. Despite this, the overall perceptions of *ITB* therapy have been found to be positive with most parents or caregivers satisfied and willing to go through the process again if needed for their child.

Keywords

Baclofen · Intrathecal

28.1 Introduction

Baclofen is a gamma-aminobutyric acid (*GABA*) agonist whose therapeutic effects are attributed to impeding 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. 27). 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 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 [1, 3]. The efficacy of *ITB* has also been reported in a randomized controlled trial [4].

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28.2 Patient Selection

Children considered for *ITB* are usually those affected with more severe cerebral palsy [5]. This would correspond to the *NYUMC* classification (see Chap. 29) Group IV (commando or belly crawlers, wheelchair bound) and Group V who are nonambulatory and fully dependent. These children may have upper extremity spasticity as severe as in their lower extremities. The spasticity is usually chronic and a result of cerebral palsy, spinal cord lesions, or central nervous system trauma. The gross motor functional classification system (*GMFCS*) is commonly used to classify the severity of impairment. 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 (wheelchair bound with lack of 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 was no longer as effective. As a non-ablative and potentially reversible therapy, *ITB* has been increasingly used for children with spastic diplegia and sometimes 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 orthopedic procedures. This is in comparison with the ideal candidates for *DRR* who are young, ambulatory children with spastic diplegia and had no prior orthopedic 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. [1] 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 seventh 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* [8]. Intraventricular baclofen was found to be as safe as intrathecal baclofen in a large series of patients (Table 28.1) [18].

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. 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 can be videotaped. Tone is graded using the Ashworth scale, in addition to the 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. [19] 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.

Table 28.1 Intrathecal baclofen

Candidate selection in a comprehensive spasticity program with a team of experts	Selection process is important but does not necessarily require a comprehensive spasticity program Usually performed in GMFCS groups IV and V Can be used in children with dystonia
Improvements	Improvements in tone and gross motor function Procedure usually performed in nonambulatory children Improves daily care and comfort Can improve upper extremity spasticity and function [9] Musculoskeletal pain decreases [10] Quality of life improves [11]
Permanence	Non-ablative Long-term maintenance requirements
Intrathecal baclofen (ITB)	Pump refill errors can lead to medication-related complications, including withdrawal, tolerance, and overdose [12]
Cost	Higher cost than dorsal root rhizotomy surgery (at least three times more), especially because of the implanted material More cost saving compared with conventional therapy for children with cerebral palsy [13]
Need for postoperative specialized center	Proximity to specialized hospital services is very important, especially for pump refills and reprogramming. As well, not favorable in low-resource regions/countries
Potential neurological complications	Potential mild to life-threatening neurological and cardiovascular symptoms from baclofen withdrawal or toxicity
Respiratory	Upper respiratory tract infections
Orthopedic issues	Future orthopedic procedures for hip dislocations and scoliosis [14]
Postoperative pain	Temporary local wound pain
Surgical complications	Device-related issues are the most common *ITB* complications [15] that may result in baclofen under- or overdosing Meningitis, CSF leakage, seromas and hematomas, wound dehiscence, and infections [16] Infection (mean of 10% in literature) decreased to 4.4% with protocol [17]
Hardware	Possible programming errors, implant (pump, catheter tubing, connectors) related issues (end of pump battery life, catheter kinking/disconnections), including infections and potential unplanned reoperations to explant/re-implant hardware
Degree of patient and family satisfaction	High

28.3 Surgical Implantation

The *SynchroMed* programmable pumps that are implanted are manufactured by Medtronic (Fig. 28.1). They are usually positioned *subcutaneously* or *subfascially* [20] in the right or left subcostal space, as far away as possible from any gastrostomy feeding tube. A silicone catheter (Fig. 28.1) attaches the pump and tracks subcutaneously to the low mid-lumbar region where the catheter is inserted into the intrathecal space via a lumbar puncture and tracked rostrally. In children with severe scoliosis, a small lumbar laminectomy may be required to insert the intrathecal catheter, which 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 [21], through the foramen magnum or through a small one-level laminotomy to the right of the midline between *C6* and *T2* [22]. 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. 28.2) to deliver a baclofen bolus and to start functioning. The whole surgery takes about 2–3 h. After a short stay in hospital, the patients are followed up in clinic to assess the degree of spasticity relief and to refill the pumps under sterile conditions.



Fig. 28.1 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, © Medtronic, Inc. 2022)



Fig. 28.2 Medtronic N'Vision® handheld wireless portable programmer device (model 8840) for the SynchroMed II programmable baclofen infusion system. (Photo used with permission, © Medtronic, Inc. 2022)

Catheter tip position has been studied as a means of providing greater upper extremity spasticity relief if positioned more rostrally in the spinal canal. By positioning the catheter tip in the midthoracic region at the *T6–T7* level, compared with *T11–T12*, lower *ITB* doses are required to achieve better upper extremity spasticity relief without any changes in the lower extremity spasticity relief in children with spastic quadriparesis. Albright et al. [1] suggested that for spastic diplegia, the catheter tip be positioned at *T10–T12*, at *C5–T2* for children with spastic quadriparesis, and even more rostral at *C1–C4* for generalized secondary dystonia. Saenz et al. [23] have described a pre-brainstem catheter tip placement.

28.4 Complications and Side Effects

Complications can be related to the medical condition of the patient, drug overdose drug withdrawal, refills, or implantation [16]. The latter includes catheter-related problems such as disconnections, kinks, fractures, or migration [12]. 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 [15]. In a multivariate analysis, Spader et al. [24] identified that 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. Hagemann et al. [25] reported that *ITB* therapy in infants and small children is as safe and effective as in older children. In a large series review over 15 years, Imerci et al. [15] reported a 44% complication rate; in the literature, the overall complication rate varies between 4% and 31% depending on how complications were defined [26, 27]. Institutional infection rates have been reported to range between 3 and 40%, with a mean of about 10% [17]. Motta and Antonello [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, Bollo et al. [17] developed an infection pre- and postoperative protocol that decreased the infection rate to 4.4%. Long-term follow-up of the subfascial technique showed decreases in CSF leakage and complications from erosion, infection, and catheter malfunction [20]. Ward et al. [28] found the complication rate 2.8 times higher in children with dystonia, compared with children with spasticity alone, with a greater than five-time infection rate and four times more catheter-related problems. Turner et al. [8] surmised that the increased catheter occlusion problem may be related to intrathecal *arachnoiditis* that may occur in children with dystonia because of previous infections and spinal interventions.

Infection of the actual pump is uncommon and usually requires explanation [29]. 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. [30] reported on the possibility of long-term intravenous antibiotic treatment without removal of the baclofen pump in selected cases. Motta and Antonella [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.

In a systematic review [9], there were no increased complications when the catheter tip was placed in the cervical region as opposed to the thoracolumbar region. A *Chiari I* malformation may occur after a lumbar puncture, with chronic leakage of cerebrospinal fluid around the catheter or even through an unrecognized catheter fracture. In children who have ventriculoperitoneal shunts, it is essential that the shunt is confirmed to be functioning prior to baclofen pump implantation; a shunt malfunction, and its subsequent revision, may alter the effects of the *ITB*. An association of scoliosis progression with *ITB* therapy has been identified compared with the natural history in children with cerebral palsy in a meta-analysis [14], and early bracing and spinal fusion are recommended to prevent progression of the spinal deformity [31].

28.5 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. Speech is improved as well as dressing, transferring, sitting time, and toileting. 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 [32]. In more severely affected patients, musculoskeletal pain is significantly reduced [10] and decubitus ulcers get a chance to heal. With *ITB* therapy, physiotherapy and occupational therapy become easier to implement. With time, the range of baclofen concentration that offers reduction in spasticity without causing a global decrease in tone and weakness may narrow. *Vles* et al. [3] 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 did not respond to less invasive treatments [13, 33, 34]. Compared with the patients in the selective dorsal root rhizotomy management plan, *ITB* therapy is at least three times more expensive [35]. 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 categorization is no longer well followed, 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* [1].

The overall perceptions of *ITB* therapy have been studied by Gooch et al. [36] and found to be positive; 81% of care providers strongly agreed and 14% slightly agreed that they would have the procedure performed again [11]. Similarly, Campbell et al. [37] had 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 [3, 26, 36].

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Dorsal Root Rhizotomy for the Treatment of Spasticity

29

Michael Vassilyadi

Abstract

Dorsal root rhizotomy (*DRR*) surgery is an effective and long-term treatment in young children with spastic diplegia. It has maximal effectiveness when combined with intensive physical and occupational therapies. In carefully selected children evaluated in a multidisciplinary spasticity clinic, *DRR* provides benefit when spasticity is the main factor compromising their gait and motor function. The risk of surgical complications is generally low. Selective dorsal root rhizotomy (*SDRR*), which includes intraoperative electrophysiology and physical muscle monitoring, is strongly recommended as an evidence-based procedure for reducing spasticity and improving both gross motor functioning and gait kinematics. Overall, the levels of satisfaction in adults who have undergone *SDRR* 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.

Keywords

Rhizotomy · Dorsal · Trents

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29.1 Introduction

Dorsal root rhizotomy (*DRR*) is an evidence-based ablative neurosurgical procedure that has been proven to offer a reduction in spasticity and an improvement in movement and posture in selected children afflicted with spastic diplegia and less frequently in those with spastic quadriparesis, in both the short and long terms [1–5]. As the proper selection of children is paramount to the success of this irreversible surgery, it is crucial to have a multidisciplinary team of experts 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 perinatal difficulties such as prolonged intubation, low *APGARS*, intraventricular haemorrhage, seizures (see Chaps. 5 and 9) 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. Some centres have widened the age criteria for surgery to include children between 2 and 14 years of age [6]. On physical examination, there is velocity-dependent increase in tone, increased deep tendon reflexes, clonus with Babinski sign and scissoring gait with exaggerated lordosis; there

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should be adequate underlying strength, good protective responses, good balance and absence of multiple orthopaedic procedures, fixed severe contractures or dystonic features.

29.2 Patient Selection

In spastic diplegia, spasticity interferes primarily with the function of the lower extremities (see Chap. 12). 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 can also be candidates for *DRR* [7]. 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. [8] 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 *SDRR*.

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 where the best surgical outcome is found in *Groups* I, II and III [9]. 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 are 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. 28); however, there are recent reports of improvements in these groups with *DRR* surgery [10–12].

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. 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.

Grunt et al. [13] 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.

29.3 Surgical Treatment

DRR surgery is usually performed selectively and termed selective dorsal root rhizotomy (*SDRR*). During the surgery, a physiotherapist is present in the operating room to accurately document the lower extremity muscle contractions by palpation. The involved paediatric neurologist or pae-

diatric physiatrist is also present, along 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 have reported similar results to *SDRR* without the added intraoperative time and cost of all the additional personnel [14].

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–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 [15]. Zhan et al. [16] developed a modified rhizotomy protocol for the treatment of children *with spastic diplegia* and *quadriparesis* cutting either 50 or 75% of the dorsal rootlets. Surgical approaches have included limited laminectomies at either the level of the conus medullaris or more caudal at *L5/S1* and various forms of laminoplasty [17, 18]. An absolute requirement for *SDRR* surgery is intraoperative monitoring with at least an eight-channel muscle response monitor [19, 20]. Intraoperative stimulation of nerve roots and rootlets differentiates less abnormal from more abnormal responses recorded from the biceps, quadriceps, hamstrings and gastrocnemius muscles on each side. More lower extremity muscles can be monitored, and even the external anal sphincter via stimulation of the pudendal dorsal root (*S1*, *S2*, *S3*), which is especially valuable in the single-level conus medullaris approach [21].

Electrophysiologic abnormalities in dorsal nerve rootlets include spread to ipsilateral but abnormal myotomes, spread to contralateral myotomes, suprasegmental spread (upper extremities, neck and face), sustained responses with incremental patterns throughout the stimulus duration, firing after stimulation cessation and crescendo/decrescendo responses [22]. Many of the original criteria have been revised several times to limit the rootlets sectioned without changing the best possible outcome [15].

Variability exists in the way *SDRR* surgery is performed, and electrophysiology responses obtained may differ substantially with only a slight alteration in technique. 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 and from the root exit foramen; the interelectrode distance; the tension applied; the placement of the cathode/node; the type of stimulator (*constant current* or *constant voltage*); the definition and determination of threshold; the tetanic stimulation parameters (how much above the threshold intensity, frequency, duration); 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. Other factors that may influence outcome include the disease process itself, which is primarily in the brain, corticospinal tracts and disorganised spinal interneuron pools. As such, *DRR* surgery attempts to reduce the disinhibition by sectioning dorsal nerve rootlets that are quite peripheral from the regions of pathology.

29.4 Effectiveness

DRR provides benefit to carefully selected cerebral palsy children with spasticity, as spasticity is the main factor compromising gait and motor function in these children (Table 29.1). The randomised trial by Steinbok et al. [30] demonstrated that the surgery is responsible for the improvements seen rather than the maturation of the child or the physiotherapy alone. Intensive physiotherapy alone does not improve long-term motor outcome [24]. However, postoperative physiotherapy and occupational therapy are required, usually after a 5-day convalescent period, of which there are three components: muscle stretching to gain mobility and range of motion, muscle strengthening to increase endurance and re-education to impart a better pattern of muscle use (see Chap. 20). The benefits of intensive physiotherapy (gains in strength, gait speed and overall gross motor function) are improved with the addition of *SDRR* surgery [23].

Table 29.1 Dorsal root rhizotomy

Candidate selection in a comprehensive spasticity program with a team of experts	Selection process is very important in children with spastic cerebral palsy GMFCS groups I, II and III are the best candidates
Improvements	Larger magnitude of improvement in lower extremity tone, range of motion and gross motor function compared with ITB [12]. More effective than ITB in reducing spasticity and improving function and gait [23] Beneficial effect on the quality of life, including reduced pain [24] and activities of daily living [25]
Permanence	Ablative
Intrathecal baclofen (ITB)	If ITB was used in ambulatory patients and there is no improvement, subsequent selective dorsal root rhizotomy surgery can reduce spasticity and improve mobility [26]
Cost	Cost-effective [27]. Longer surgical time required with the need of surgical experience and electrophysiology expertise
Need for post-operative specialised Centre	Proximity to a specialised hospital services is not an issue in the long term. Immediate post-operative intense physiotherapy is very important
Potential neurological complications	Low, but higher than ITB Persistent, but not functionally important sensory loss (3.8%) and urinary bladder deterioration (1.3%) [28]
Respiratory	Low risk (1.3%) of aspiration pneumonia [28]
Orthopaedic issues	Fewer spinal and orthopaedic surgeries compared with ITB [12]
Post-operative pain	Temporary neuropathic pain and dysesthesia (11.7%) [29] Possible chronic back pain. In most cases, it does not interfere with daily activities and can be managed medically when necessary [7]
Surgical complications	Low risk of CSF leakage and wound complications (5.8%) [29]
Hardware	None
Degree of patient and family satisfaction	High

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 are particularly important in these cases. *Gait velocity* is improved with an increased stride length. Assistive devices are reduced, and orthotic needs may change. Sitting posture improves, scissoring ceases and movements become more isolated with less energy expenditure. Other improvements include speech, personality, seizure control, upper extremity function and bladder control [31]. Improvement in cognitive performance not only may be due to improved mood and reduced physical discomfort but also possibly secondarily due to "suprasegmental effects" induced by the *DRR* surgery. There are improvements in self-care, mobility and social functioning with less caregiver assistance. Mittal et al. [32] identified improvements in activities of daily living using a validated evaluation measure with the functional improvements persisting 3 and 5 years after surgery; they also showed a sustained upper extremity functional improvement in children in *NYUMC* Groups I, II and III. Bolster et al. [33] reported greater than expected gross motor function improvement in some children 5 and 10 years after *DRR* surgery. Assessments during adolescence and early adulthood have shown lasting benefits [1, 34]. *SDR* has been found to be cost-effective in a large observational study on children who did and did not have *SDR* surgery [27]. As well, *DRR* surgery can reduce spasticity and improve mobility after long-term intrathecal baclofen (*ITB*) therapy in ambulatory children with spastic diplegia who continued to have persistent spasticity despite the *ITB* [26].

29.5 Complications and Side Effects

Complications of *DRR* surgery are low [29, 35] and related to the medical status of the patients, the surgical exposure and the potential neurological consequences of cauda equina manipulation and sectioning. Santos et al. [29] reported a 5.8% overall complication rate related to *DRR* surgery performed between 2012 and 2018. In 150 consecutive children who underwent *DRR* surgery between 2011 and 2016, Jeffery et al. [35] reported no cerebrospinal fluid leaks and no new motor or sphincter deficits. Post-operatively, complications included neuropathic pain (5.3%), sensory symptoms (8.7%), nausea and vomiting (19.3%), superficial wound infection (3.3%), urinary retention (1.3%), headache (6.7%) and urine or chest infection (4.7%). Higher complication rates were reported by Steinbok and Schrag [28] in 158 children, but these were patients who were operated much earlier between 1987 and 1996.

Spondylolysis and spondylolisthesis, which are more common in children with cerebral palsy, can develop or progress after *DRR* surgery [7]; children with more severe cerebral palsy are more likely to develop scoliosis after surgery. Older age at the time of surgery and female gender were associated with greater post-operative lumbar lordosis. Patients have reported some degree of chronic back pain [34].

O'Brien et al. [6] found that children in the 2–5-year 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 *SDRR* surgery can be attributed to the surgery itself.

In a systematic review, *SDRR* was *strongly* recommended for reducing spasticity (moderate quality of evidence in the literature) and improving gait kinematics (low quality of evidence). There is evidence for *SDRR* to improve gross motor function, but it is weakly recommended for improving function and participation (very low quality of evidence) [36]. Overall, the levels of satisfaction in adults who have undergone *SDRR* as children have been reported to be generally high, with no negative influence on life satisfaction [34]. Overall, the high functional benefit of *SDRR* over the longitudinal cerebral palsy history in carefully selected patients has been well documented [3] with a beneficial effect on quality of life [25].

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Hyperbaric Oxygen Therapy in Cerebral Palsy

30

Shelley S. Selph, Tracy Dana, and 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, and 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 after chronic injury. The *evidence* on HBO in CP is limited by imprecision and control groups with methodological flaws. 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. In all these fields, the hyperbaric oxygen therapy is reviewed.

Keywords

Hyperbaric · Oxygen therapy · FDE

30.1 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.

The US Food and Drug Administration (FDA) has approved HBO treatment for a number of injuries and illnesses [1]. The uses that are currently recognized by the FDA are listed in Box 30.1. 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 last updated by the UHMS

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in 2018 [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 30.1 US Food and Drug Administration-Approved Uses for Hyperbaric Oxygen Therapy

1. Air and gas bubbles in blood vessels
2. Anemia (severe anemia when blood transfusions cannot be used)
3. Burns (severe and large burns treated at a specialized burn center)
4. Carbon monoxide poisoning
5. Crush injury
6. Decompression sickness (diving risk)
7. Gas gangrene
8. Hearing loss (complete hearing loss that occurs suddenly and without any known cause)
9. Infection of the skin and bone (severe)
10. Radiation injury
11. Skin graft flap at risk of tissue death
12. Vision loss (when sudden and painless in one eye due to blockage of blood flow)
13. Wounds (nonhealing, diabetic foot ulcers)

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 13 indications 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) [3]. Manufacturers cannot advertise or promote uses that are not approved by the FDA. While provision of HBO treatment for the indications in Box 30.1 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 out-of-pocket costs can range from less than $100 to several hundred dollars per session depending on the location and whether the chamber is associated with a medical facility. The *total* cost of treatment will depend on the duration and total number of sessions.

30.2 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 [4, 5]. 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 [6, 7]; 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; for example, 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 [4]. 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 face mask, 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 face masks or hoods that do not fit snugly may result in dilution of 100% oxygen with room air.

30.3 Why HBO?

In chronic infected or nonhealing soft tissue wounds, local tissue hypoxia predisposes to infection and prevents effective healing [5]. 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 [4, 5, 7]. 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 [8].

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 [9], 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.

30.4 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 [10].

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 [11–14] (see Chap. 14).

In some experimental models of acute cerebral *ischemia* and acute carbon monoxide poisoning, HBO prevents cell death [9], 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 [9]. 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 [15]. 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 [16]. 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 [17, 18].

30.5 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 [9, 19]. 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 [20]. According to this theory, recovery occurs as surviving neurons establish new synaptic connections that can help reactivate cells that are temporarily inactive. 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 [20]. 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. For example, 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 [21]. 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 [9]. 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).

30.6 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 study of HBO for acute carbon monoxide poisoning raise concerns over worse cognitive outcomes in patients receiving HBO compared with normobaric oxygen [22].

30.7 HBO and Cerebral Palsy

The published evidence on the effects of HBO in patients with CP is limited to five randomized controlled trials (total of 422 patients enrolled) and five observational before-after studies (total of 455 patients) that measured patient-oriented outcomes such as the Gross Motor Function Measure (GMFM), which evaluates a person's motor ability, e.g., ability to sit, stand, walk, and run (see Chap. 24).

The best evidence on the benefits and harms of HBO therapy in CP is provided by two similar, fair-quality randomized controlled trials (Table 30.1) [24, 28]. Both trials 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. 25). A GMFM scale score increase of greater than 2.73 points from baseline is considered the minimal clinically important difference (MCID) [30]. 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. At the end of the 2 months and 40 treatments, motor function scores improved in both groups in the earlier, larger trial (111 total children) conducted by Collet et al. [24]. 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 smaller trial (49 children) conducted by Lacey et al. [28], the changes from baseline were small and not statistically significant (1.5 and 0.6 points in HBO and control, respectively). This trial was stopped

Table 30.1 Characteristics of randomized controlled trials of hyperbaric oxygen therapy for CP

Study Country (quality)	Population	*N* Age range	HBO protocol Control protocol (type of chamber
Azhar, 2017 [23] Pakistan (poor)	Clinical diagnosis of CP	90 HBO 103 control	HBO: 100% oxygen at 1.5 atm × 60 min × 40 sessions × 5 cycles (total 200 sessions); sessions 5 days/week × 8 weeks Control: No treatment
Collet, 2001 [24]; Hardy, 2002 [25]; Muller-Bolla, 2006 [26] Canada (fair)	Children with CP with a 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 Control: Room air at 1.3 atm × 60 min × 40 sessions; sessions 5 days/week × 8 weeks (monoplace or multiplace chamber, depending on facility)
Khalil, 2023 [27] Saudi Arabia (fair)	Spastic, hemiplegic CP able to swallow or blow through a straw, 1 to 1+ on modified Ashworth scale, level I or II on Gross Motor Function Classification System	19 HBO 20 control 5–10 years	HBO: 100% oxygen at 1.7 atm × 60 min × 40 sessions; sessions 5 times/week × 8 weeks Control: No treatment Both groups received physical therapy 3 times/week × 6 months (multiplace chamber)
Lacey, 2012 [28] USA (fair)	Children with spastic CP able to 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)
Sethi, 2003 [29] India (poor)	All types of CP, mild-to-moderate IQ, SPECT scan showing recoverable penumbra	15 HBO 15 control 2–5 years	HBO: 100% oxygen at 1.75 atm × 40 sessions; sessions 6 days/week Control: No treatment All patients received 1 h of occupational therapy × 6 days/week × 6 months (multispacer chamber)

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 the score of −0.11 (95% confidence interval −1.25 to 1.03, not statistically significant) (Fig. 30.1). Both studies evaluated the children at longer follow-up 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. trial [24], secondary outcome measures, including neuropsychological tests, also did not show a difference between the groups [25]. When the caregivers' viewpoint was measured with the Pediatric 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 [24]. Similarly, in the trial by Lacey et al. [28], 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. There was not a statistically or clinically significant differ-

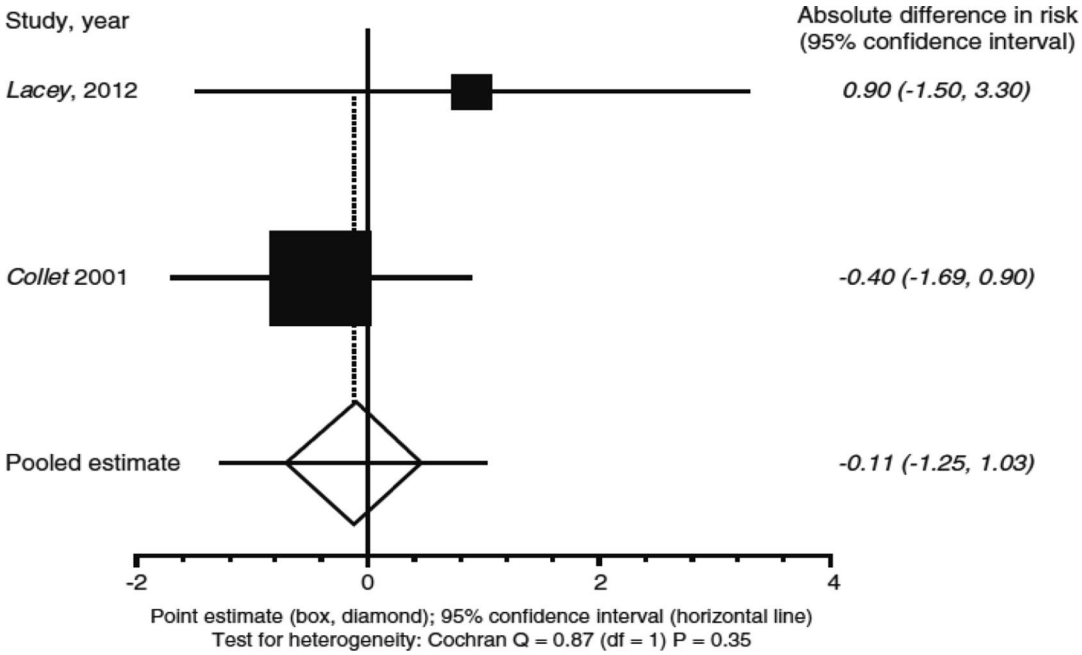


Fig. 30.1 Meta-analysis: difference in change in GMFM-88 scale scores after 40 HBO sessions versus sham treatment

ence [30] between groups based on individual studies or based on the results of meta-analysis. While the study findings are generally consistent, the studies have a few methodological limitations, and the resulting estimate is not precise due to small sample sizes. 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. [24] 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. [24]; 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. [28] 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, it was unclear whether the children included in the trials were representative of children with CP. In Collet et al.'s study [24], 196 children were screened, with 111 being enrolled, and in Lacey et al.'s study [28], 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 randomized trials, one other, fair-quality randomized trial (39 children) compared HBO with no treatment [27]. In this study, 100% oxygen was given at 1.7 atmospheres for 40 sessions; all patients also received physical therapy three times per week for 6 months. Children with CP aged 5–10 years with a Modified *Ashworth* Scale score of 1 to 1+ and Gross Motor Function Classification System (GMFCS) level I or II were enrolled (see Chap. 24). This trial used the GAITRite System (CIR Industries, Clifton, NJ) to measure gait parameters, e.g., walking velocity, steps/minute, stride

length, and the Pediatric *Balance* Scale (PBS) to assess balance, and found improvement at the 6-month follow-up in all walking measures and a balance for both the children who received HBO and physical therapy and the children who received only physical therapy. However, improvements were greater in the children who received HBO at both 6 months and immediately posttreatment. While this study suggests that exposure to HBO may improve gait and balance in school-aged children (mean age 7.3 years in study group and 8.5 years in control group), it has methodological limitations. Firstly, the differences in age between the two groups, although not statistically significant, may have played a role in the magnitude of benefit each group experienced, if physical therapy, for example, made a greater difference in younger children. Secondly, all parties involved, including outcome assessors, knew whether or not the child received HBO, which is a major limitation. Thirdly, the method of randomization was not provided, nor were the methods to keep the randomization concealed from researchers stated. While the study results are promising, evidence is limited and insufficient to draw firm conclusions, with future research needed to confirm these findings. In *addition* to these three fair-quality studies, two poor-quality randomized trials examined the effect of HBO in CP [23, 29].

One small, poor-quality randomized trial (30 children, mean age 3.6) used Norton's Basic Motor Evaluation Scale (scale not provided, not cited, and not locatable) and reported improved scores with HBO plus occupational therapy compared with occupational therapy alone (both groups improved over baseline) [29]. However, the study has serious scientific flaws. Based on the highly unlikely symmetry in the HBO group and control group concerning type of CP, i.e., *ataxia*, *athetoid*, *diplegia*, and *quadriparesis*, it seems questionable whether this was a true randomized study. Further, it is unclear if the two groups of children were similar at baseline characteristics other than age and gender. Finally, the study was not blinded, individuals who assessed the motor skills knew which group the child was assigned to.

The *second*, poor-quality randomized trial enrolled 193 children aged 1–14 and found greater improvement in gross motor function and activities of daily living measures with HBO than control children who received no treatment, while control children demonstrated more improvement in hearing than children who received HBO [23]. This trial also has serious scientific flaws including study enrollment occurring after randomization (which could lead to bias in selecting which children to enroll), and it was unclear if the two groups of children had similar abilities at baseline, e.g., similar baseline GMFM scores, *Barthel* index scores, and hearing ability. An additional concern is that all seven children who were dropped from the study due to having excluded neurological disorders were randomized to receive HBO, which is another concern for bias in the selection of children to include, in the event that some children randomized to no treatment also had excluded neurological disorders but were not dropped from the study: if only seven children had excluded neurological disorders identified after randomization and enrollment, the probability due to chance that all seven were randomly assigned HBO therapy is less than 1% (Table 30.1). Although children with CP did better with HBO in the poor-quality studies, the scientific flaws in these studies are so great that the results are highly questionable and need to be confirmed in better quality randomized trials.

In addition to randomized trials, five published observational studies (total number of children 305) assessed outcomes after exposure to HBO therapy (Table 30.2). 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 the study conducted 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) [34]. This study is sometimes referred to as the McGill study and

Table 30.2 Characteristics of nonrandomized studies of hyperbaric oxygen therapy for CP

Study Country (quality)	Population	*N* Age range	HBO protocol Control protocol (type of chamber
Jovanovich, 2017 [31] Serbia (fair)	Children with spastic CP	52 3–7 years	HBO: 100% oxygen at 1.55 atm × 60 min × 120 sessions with 60 sessions over 30 days, then a 6-week pause, then treatment protocol was repeated; all children received standard physical and speech therapy a mean of 4 × week (chamber type not specified)
Long, 2017 [32] China (fair)	Children with CP and hypoxia in the perinatal period and a motor development delay of more than 3 months and abnormal signs on imaging studies	71 2–6 years	HBO: 100% oxygen at 1.6 atm × 50 min (oxygen for 60 min) for 15–20 sessions at 1 session/day × 5 days/week (multiplace chamber)
Mukherjee, 1999 [33] Canada (fair)	Children with CP	150 1–17 years	HBO (plus intensive rehabilitation): (a) Room air at 1.3 atm × 60 min × 40 sessions at 6 days/week × 7 weeks (b) 100% oxygen at 1.5 atm × 60 min × 40 sessions at 6 days/week × 7 weeks (c) 100% oxygen at 1.75 atm × 60 min × 40 sessions at 6 days/week × 7 weeks (d) (Multiple chamber for 100% oxygen, "soft chamber" for air) Control: Intensive rehabilitation only
Montgomery, 1999 [34] 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 (a) 10 patients received 1 treatment/day × 20 sessions (5 days/week × 4 weeks in a monoplace chamber) (b) 15 patients received 2 treatments/day × 20 sessions (5 days/week × 2 weeks in a multiplace chamber)
Waalkes, 2002 [35] USA (fair)	Children with varying diagnoses of CP	7 1–16.6 years	HBO: 100% oxygen at 1.7 atm × 60 min × 80 sessions (1 treatment/day × 5 days/week × 4 months in multiplace chamber)

was conducted by the group of investigators that later conducted the largest randomized controlled trial (above) [24, 34]. The researchers found an average improvement of 5.3% in the GMFM score after HBO. The assessment of gross motor function indicated that 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 (see Chaps. 27 and 29). 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 fair-quality, before-after study enrolled 52 children with spastic CP aged 3–7 years [31]. Children differed in their motor scores on the GMFCS with 30 children categorized as GMFCS level II and 22 children as GMFCS level V. *Standing* and *walking* were improved after HBO therapy in children with GMFCS level II and lying with rotation and sitting were improved in children with GMFCS level V. Average scores on the Sleep Disturbance Scale were improved for children with both GMFCS levels, as was speech production. While this study did examine the effects of gender, age, and previous physical therapy on results, and reported no significant interactions, this study also has limitations. Although the study report's outcome evaluations were conducted by a physician and speech/language pathologist who were not providing care to the child, because the evaluations were performed in the Center for Hyperbaric Medicine in Belgrade, it is assumed that the individuals assessing the children's progress knew that the children were exposed to hyperbaric oxygen, which can bias the results. *Additionally*, the assessment of vocalization was made using an individualized, potentially unvalidated instrument.

Another fair-quality, before-after study [32] enrolled 71 children aged 2–6 years and focused on improvement in sleep with HBO. While most children were at GMFCS Level I (23%) or GMFCS Level II (31%), several children were at GMFCS Level V (23%). Most children had spastic CP (58%) followed by mixed type (11%). Twenty-three children had difficulty falling asleep (32%), 21 children (30%) slept 7 h or less at night, and 31 children (44%) were awakened easily. After ten HBO sessions, average time to fall asleep, average hours of sleep duration, and average number of night awakenings significantly improved for both younger (*aged 2–4 years*) and older (*aged 4–6 years*) children. This study also has scientific limitations such as excluding the results from seven children who completed fewer than eight HBO sessions and exclusion of five children whose parents failed to complete three total sleep scores. If a lack of response to HBO therapy is the reason why parents stopped bringing their child to therapy and stopped recording sleep scores, the above results may show an inflated benefit when no benefit or lesser benefit of HBO therapy on sleep is actually the case. Another limitation is the lack of blinding of outcome assessors.

Another 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 [33]. The study combined the HBO groups with the pressurized air group and found that 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-year period, the control subjects were identified. The analyses controlled for age, but did not control for 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. The other observational study was too small (seven patients) to provide meaningful data [35].

30.8 Evidence on Harms of HBO for CP

None of the studies explicitly defined an a priori plan to monitor potential harms from HBO; however, ear problems were reported and, less frequently, seizure (Table 30.3). The most comprehensive description of harms comes from a follow-up publication [26] of the trial by Collet et al. [24], which reported that significantly more children experienced middle-ear *barotrauma* with HBO treatment compared with the control

Table 30.3 Harms reported in studies of hyperbaric oxygen therapy for CP

Study	Seizures	Ear problems	Other significant harms
Randomized controlled trials			
Collet 2001 [24] and Muller-Bolla 2006 [26]	Not reported	Middle-ear barotrauma RR 1.5; 95% CI 1.1–2.2; $p = 0.02$	Pressure/volume-related events[a] RR 1.0; 95% CI 0.9–2.1; $p = 0.07$
Lacey 2012 [28]	One case reported in the control group (4.5%; 1/22)	29% vs. 36%; $p = 0.76$	Withdrawals due to adverse events (1/24) vs. (1/22)
Nonrandomized studies			
Azhar 2017 [23]	Not reported	3.5% (7/200) described as having minor side effects such as ear pain and/or confinement anxiety; not reported by treatment group	None in either group
Long 2017 [32]	3.4% (2/59) during decompression	Ear pain 20.3% (12/59) No cases of middle-ear barotrauma on blinded ENT examination	Not reported
Mukherjee 2014 [33]	Not reported	Study exclusion due to ear pain 2.0% (3/150)	Not reported

Abbreviations: *RR* relative risk

[a] Includes middle-ear barotrauma, sinus barotrauma, tooth barotrauma, and ear pain

group (50% at 1.75 atm vs. 27.8% at 1.3 atm; relative risk 1.5, 96% CI 1.1–2.2, $p = 0.02$). 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. Regression analysis did not identify factors that would predict middle-ear barotrauma, although both baseline global GMFM and gender were positively associated with this adverse event [26]. Changes in motor function were similar in children with and without barotrauma: 3.3 ± 3.9 versus 2.7 ± 3.0 ($p = 0.22$). The risk of any pressure- or volume-related event was similar between HBO and control groups (relative risk 1.0; 95% CI 0.9–2.1; $p = 0.07$).

Reporting of *adverse events* in the second trial [28] was more limited. There was no statistically significant difference in the incidence of ear pain, 29% (7 of 24) in the HBO group and 36% (8 of 22) in the control group ($p = 0.76$), but incidence was only reported for children who had completed all treatments. 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). Evidence from observational studies was consistent with that from the trials in reporting ear pain/barotrauma [23, 32, 33].

30.9 Conclusion

Current evidence is inadequate either to establish a significant benefit or to precisely 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. One trial *reported* benefit in walking measures with HBO, but it was a small study. Two studies reported benefit in sleep outcomes with HBO, but they were not randomized and had no control group. Some proportion of children undergoing HBO will experience adverse events including seizures and the need for ear pressure equalization tube placement, but due to inadequate methods of assessment, esti-

mates of the prevalence of these are uncertain. *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 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. *Additionally*, while it is unknown how the effectiveness 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.

Evidence from the controlled trials is preferred over evidence from the observational studies because bias and confounding are serious concerns. Overall, there is Grade A evidence that HBO is not different from pressurized room air in improving gross motor function for the treatment of CP, with only Grade C evidence supporting improvements in various other measures after HBO. There is also only Grade C evidence for harms of HBO in children with CP.

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Comorbidities in Children and Adults with Cerebral Palsy

31

Monica Cooper and Giuliana Antolovich

Abstract

In this chapter, we explore the range of *comorbidities* and complications of cerebral palsy (CP). Understanding the child in the context of their family and building relationships is of utmost importance. Together with good medical and mental health care, a child's participation and quality of life can be enhanced. *Managing* the comorbidities of CP requires a systematic approach, with recognition that the bodily systems are interconnected. A *systems-based* approach during childhood will also aid in preparing the young person for their healthy adult years. This *chapter* includes the example of health systems and the complex care program, which encompasses a team-based approach to medical care, with a medical lead. This systems- and team-based methodology can improve communication between different teams and sectors, as well as the overall inpatient and outpatient experience. The *process* of transition to adult services requires planning, care and clear communication. The *overall* goal is to enhance the dignity and autonomy of the young person with CP as they transition to adult services.

Keywords

Multi-system disorder · Pain · Irritability · Transition

31.1 Introduction

Cerebral palsy (CP) should be considered a *multi-system* disorder, and, as such, a systems-based model of care should be utilised to manage the comorbidities [1, 2]. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour; by epilepsy; and by secondary musculoskeletal problems [3]. The associated *complications* should be screened for in all patients with CP. High-*quality*, population-based registry studies provide details of the complications and co-occurring comorbidities [4]. The complications of CP increase in prevalence with increasing level of physical disability [1]. In this *chapter*, we will focus mostly on the child with a severe physical disability, for example, functioning within Gross Motor Function Classification System (GMFCS) Levels IV and V (see Chap. 25).

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The *musculoskeletal*, respiratory and gastrointestinal complications in CP can be progressive. The distinction between the static brain lesion and the progressive consequences should be clearly explained to families, caregivers and patients, so that they do not assign blame to themselves when there is a progression or changes in abilities. *Adults* with CP also have complex multi-system complications, for *example*, cardiac impairment, chronic kidney disease and increased risk of stroke, highlighting that monitoring must be considered for pre-emptive care in childhood to optimise health during the adult years [1].

The term "*severe neurological impairment*" is a broad term encompassing children with CP and other severe neurological conditions [5]. Medical *comorbidities*, based on systematic reviews and narratives on children with severe neurological impairment, are applicable to children with CP [1, 2, 6]. The role of the paediatrician is to help support the *family* to optimise healthcare outcomes and prioritise quality of life, by provision of unbiased, evidence-based medicine and clinical experience (see Chap. 38). The *paediatrician* should work with the family to synthesise the complex management plans from the other specialists involved in their child's care. Population-based studies and single-site studies show that half of the children with CP have at least one comorbidity, with general medical complications, neurological sequelae and mental health disorders occurring more frequently in children with CP than in the general population (Table 31.1) [4]. These *comorbidities* and *complications* can be wide-ranging and include problems with mobility and pain, respiratory health and sleep problems, gastrointestinal issues and malnutrition, hearing and vision impairment, epilepsy, cognitive impairment and mental health disorders [4, 7].

Goal-directed care is ideal to maximise *functional* outcomes and *rehabilitation* plans. With increasing fragility and a more severe motor disability, often the primary paediatricians require input from many specialists to provide best care. We *recommend* early discussion about values and priorities and involvement of palliative care specialists for those with cerebral palsy considered

Table 31.1 Common physical complications in children with cerebral palsy

System	Comorbidities
Respiratory	Respiratory infection—acute and chronic Bronchiectasis Upper airway obstruction Central and obstructive sleep apnoea Sleep issues
Gastroenterology	Oropharyngeal dysphagia—drooling and nutritional consequences Gastro-oesophageal reflux disease Constipation Vomiting, acute feed intolerance, dysmotility Progressive feeding failure Visceral hyperalgesia Pancreatitis Gallstones and biliary sludge
Neurological	Aetiology of cerebral palsy Epilepsy Paroxysmal non-epileptic events Hypertonia, spasticity and dystonia Pain Irritability Dysautonomia Cognition Speech Mental health Vision and hearing
Kidneys and urinary tract	Incontinence of urine—daytime and night-time Urinary retention Urinary tract infection Chronic damage from injury during the neonatal period Renal stones Overactive bladder
Endocrine system	Osteopenia Puberty—premature adrenarche, halted puberty Sexual health
Cardiology	Autonomic dysfunction—reduced heart rate variability Cardiometabolic disease
Dental	Poor oral hygiene Malocclusion Bruxism
Dermatology	Pressure sores Perineal hygiene
Haematology and immunology	Coagulation profiles Vaccination
Musculoskeletal	Upper and lower limb spasticity and contractures Bony deformities—hips, neuromuscular scoliosis Degenerative arthritis

to be life-limiting. Whilst some children demonstrate a clear decline, for many, there is a fluctuating state, with a period of stability.

31.2 Comorbidities

31.2.1 Oropharyngeal Dysphagia

Oropharyngeal dysphagia (*difficulty swallowing*) can lead to drooling, a consequence of infrequent swallowing and an open-mouth posture [8]. A problem with drooling occurs in more than half of the children with cerebral palsy [9]. *Drooling* can be subdivided into anterior or posterior drooling, whereby anterior drooling causes saliva to spill out forward, whereas posterior drooling is difficulty managing saliva, such that it causes pharyngeal pooling [9]. *Posterior* drooling contributes to aspiration and respiratory disease [10]. *Medications* or uncontrolled seizures may reduce swallowing frequency and worsen drooling. It is important to provide individualised care to assess for any reversible contributors of drooling, such as an obstructed upper airway. Enlarged tonsils and adenoids, sleep-disordered breathing and hay fever and allergy should be considered [11]. Similarly, *gastro-oesophageal* reflux should be treated (see Chaps. 35 and 36).

Speech therapy and *behavioural* interventions are an option for children who have adequate cognition and motivation to reduce anterior drooling. However, the evidence for these interventions is low [12]. Medications, such as glycopyrrolate to thicken saliva, could be considered [13, 14]. Other medications, including trihexyphenidyl or scopolamine transdermal patches, are second-line options [13].

The *side effects* of these medications should be counselled for, especially constipation, urinary retention, blurred vision or behavioural changes. There are options for botulinum toxin injections into the submandibular and parotid glands, which should be ultrasound guided [15]. Various *surgical* procedures to treat anterior drooling, posterior drooling or a combination of both are offered in multiple centres [15, 16]. Surgical procedures are associated with more adverse effects than botulinum toxin injections, but overall are a more effective treatment [17].

Oropharyngeal *dysphagia* can occur across all GMFCS levels, but increases in keeping with more severe GMFCS [18]. Children functioning within GMFCS Levels IV and V are more likely to have less ability to chew and swallow, have more oral and *pharyngeal* spillage or require consistency modification [19]. *Swallowing* safety can be screened utilising the *Dysphagia* Outcome Severity Scale [20] in children younger than 3 years of age or the Eating and Drinking Ability Classification System [21] in children aged 3 years and above.

Symptoms and signs of feeding issues *include* prolonged mealtimes; stressful mealtimes for the caregiver, child or both; static or poor weight gain over a period of a few months; and respiratory symptoms with meals [22]. Choking and coughing with meals are also a concern.

Given the high *incidence* of oropharyngeal dysphagia and aspiration (including silent aspiration) in children with CP functioning within GMFCS Level V, a low threshold to discuss, consider and investigate whether the swallow is unsafe is warranted. In the *first* instance, there should be a clear discussion with the family about the ease and pleasure of feeding for their child, and whether the family would make any changes to their child's feeding based on *recommendations* from a speech pathologist. A speech pathologist can take a thorough history, conduct a clinical assessment and complete a videofluoroscopy swallow study (VFSS). A VFSS can *provide* information about the quality and efficiency of the swallow and effectiveness of a cough as well as whether there is laryngeal penetration and aspiration when food goes beyond the vocal cords (see Chaps. 35 and 36). Different food consistencies can be tested. The speech *pathologist* can assess the parent-child interactions and the parent's responsiveness to the child's cues. Mealtime management plans with caregiver training for cues, ideal positioning and texture modification can be effective. Small feeds can be an option if there are signs of pharyngeal dysfunction, and oesophageal dysmotility may be improved with fluids post a meal or fluids

mixed with food. Oral *feeding* is an emotive and complex interaction between the child and caregiver. Some parents feel very strongly about continuing oral feeding, even in the face of an unsafe swallow, despite their child experiencing recurrent episodes of aspiration pneumonia or failing to grow adequately.

Oropharyngeal *dysphagia* may impact nutritional status. *Ideally*, a feeding regime that is initiated prior to loss of weight or negative consequences for nutrition should be introduced. If oral feeding is safe and nutrition is adequate, this mode of feeding should be encouraged. A *dietician* can help provide multiple solutions to optimise the feed or supplementation. Children with high *energy* requirements and intolerance of large-volume feeds may benefit from high-energy fibre or addition of long-chain triglycerides or glucose polymers [23]. For *example*, feeds that are more hydrolysed or have a higher content of medium-chain triglycerides may improve symptoms of delayed gastric emptying [24]. If oral feeding is inadequate for growth, a *nasogastric* tube is recommended, leading to the need for a more permanent percutaneous gastrostomy tube. Gastric feeding is the preferred method, as this allows for bolus feeding, freeing up time the child is disconnected from the feeding pump (see Chap. 35) [25].

31.2.2 Pain

Pain is a *sensory* and/or *emotional* experience that is unpleasant and associated with actual or potential tissue damage. Pain in cerebral palsy remains under-recognised, underappreciated and difficult to assess. Pain contributes to poor quality of life (see Chap. 38) [26]. Effective pain *management* requires removal of the stimulus as well as non-pharmacological and pharmacological measures to manage pain. The *prevalence* of pain may occur in three-quarters of individuals with CP and increases with age and severity of the motor disability [27].

Given the multiple potential sources of *pain* and *irritability*, and even in the absence of localising features, a complete system review may be required. A thorough history, followed by a "top-to-toe examination", is required, *including* examination of the mouth for dental caries, gingivitis, gums, eyes, ears, nose, throat, chest and abdomen; examination of external genitalia; search for pressure sores; hair tourniquets, etc. *Acute pain* may be caused by fractures (consider pathological fractures, with a low threshold for imaging) as well as childhood illnesses and infections such as pharyngitis, otitis media and urinary tract infections.

Children with CP experience pain *commonly* from the musculoskeletal complications of cerebral palsy. The paucity of movement means that an individual with CP may be stuck in a position and not be able to right themselves. *Similarly*, spasticity and joint destruction occur in an insidious and progressive nature. Fixed flexion deformities and joint destruction mean that nerve fibres may inadvertently be on stretch or compressed. This may trigger neuropathic pain with a burning sensation or sudden shooting pain.

Pain may also be due to *gastrointestinal* conditions as discussed earlier, such as GORD or visceral hyperalgesia. Interventions such as stretching, motion manipulation, wearing splints and orthotics could be contributors to pain. *Chronic* pain may fluctuate. It may be recurrent, episodic or continuous. Clinical manifestations in non-verbal children may be irritability, crying, grimacing, drooling, sleep disturbance, anxiety or anticipatory pain, e.g. crying before being hoisted or during cares (see Chap. 38).

Assessing *pain* in a non-verbal child has its challenges, but often parents and caregivers will be clear about a change from baseline in their child. There are multiple pain assessment scales, and whilst the *majority* are for children who are able to communicate, there are others for children who are unable to reliably communicate. Pain medication should be considered an adjunct to management, even when the source of the pain is being investigated. There are sometimes concerns from parents that certain medication may cause their child to become "*addicted*".

31.2.3 Irritability

Irritability in children with severe CP is seen. First and foremost, any reversible biological cause should be investigated and treated. An *understanding* of the temporal association of the irritability should be sought, as to whether this is a form of communication. If so, consider what *strategies* can be implemented to respond to a certain need, such as *optimising* communication or removing the irritating stimulus for the child. Sometimes, irritability is a manifestation of a comorbid psychological disorder, for example, anxiety which warrants an approach to reducing anxiety.

Occasionally, irritability is a *communication* of a challenging behaviour, which warrants behavioural strategies, prescribed only by a behavioural specialist (for example, a psychologist) to provide positive behaviour support therapy. The *therapy* involves observing the child and their family in the home setting and can prescribe an intervention which is in keeping with the individual's cognitive and sensory needs. The *therapy* can set up expectations, dialogue, rules and limits. Often, when the rules of engagement are clear to both parties, over time, less challenging behaviours are exhibited.

31.2.4 Cognition

Intellectual disability is an important *comorbidity* for individuals with CP, whereby 50% have an intellectual disability (as measured by full-scale intelligent quotient below 70%). *Overall*, the prevalence of cognitive impairment increases with severity of motor impairment [28]. A carefully conducted neuropsychological assessment by a clinician who can adjust for motor disability and communication impairments is required. An *individual* with CP, functioning within GMFCS Level V, may be non-verbal and communicate via an assistive and augmentative communication device but have no cognitive impairment (see Chap. 20).

31.2.5 Mental Health

Mental health issues and *psychological* disorders are increasingly being sought and recognised in children with CP. High-quality evidence is emerging, demonstrating the high incidence of mental health disorders in *neurodisabilities*, such as CP, which were previously under-reported and under-recognised. In children with CP, studies have shown an increased incidence in children with anxiety, depression, attention deficit hyperactivity disorder (ADHD) and conduct disorders [29]. More *depression* was seen in children with more severe motor disability and pain [29]. In one study, at least 46% of children with cerebral CP had self-reported anxiety, and, similarly, almost 38% of parents noted anxiety in their child [30].

The co-occurrence of autism spectrum disorder (*ASD*) in children with CP is rising with more recent studies reporting ASD in up to 45% of children with cerebral palsy [31]. There is often comorbid ADHD and intellectual disability [31]. The motor disability may impact the usual way that children with mental health conditions present. It can be difficult to separate features of an *intellectual* disability and the motor disability with usual testing. Psychological rigidity, obsessiveness and altered pain thresholds can be seen.

31.2.6 Vision and Hearing

Screening for hearing and vision should be *conducted* early, in order to maximise function, learning and participation. Hearing impairment occurs in up to 30% of children with CP. The majority (50%) have 50% conductive hearing impairment, only 5% have sensorineural hearing loss, 25% have mixed hearing loss and the rest are unspecified [32]. Aetiology plays a role in incidence, with sensorineural hearing loss seen more frequently in children with severe neonatal encephalopathy, secondary to hyperbilirubinemia, or children with CP secondary to cytomegalovirus [32]. Sensorineural hearing impairment merits further genetic investigation.

Understanding a child's hearing abilities will directly impact the learning and communication strategies they will use. Up to 70% of children with CP have ocular complications, which warrant early assessment [33]. The most common ophthalmological complications are cortical vision impairment, acquired optic atrophy, refractive errors, amblyopia, strabismus and nystagmus. Lens opacities, such as cataracts, also require treatment (see Chaps. 9 and 33).

31.2.7 Puberty

Early pubarche is seen in some children with CP but in isolation is not indicative of central precocious puberty. *Pubertal* induction is recommended for children with CP who have delayed or halted puberty, with topical or enteral oestrogen and testosterone. Over time, secondary *hypogonadism* can develop in the adult years, which should also prompt consideration of hormonal therapy. A history of *menorrhagia*, menstrual pain and whether mood or seizures are connected to the menstrual cycle should be actively sought. There is increasing prescription of hormonal therapies, such as the oral contraceptive pill and intrauterine devices, which *can* be inserted under a general anaesthetic, to improve symptoms.

31.2.8 Cardiac

Cardiac dysfunction is not classically considered a *common comorbidity* in children with CP. However, autonomic dysfunction occurs in children with CP with orthostatic tachycardia, postural hypotension and absent sympathetic skin responses [34]. Children with CP with a history of neonatal encephalopathy with concurrent cardiac dysfunction do have evidence of myocardial ischaemia [35]. How this directly translates to cardiac function is hard to assess. *Individuals* with severe CP have abnormalities in the function of the autonomic nervous system (which controls the sinus node). When the *head* is moved from supine to sitting up to 90°, there is an increased mean heart rate compared to typically developing children, suggesting that children with CP have difficulty in adjusting their *sympathovagal* balance to certain stimuli [34]. Children with CP have reduced heart rate variability, which is more apparent the more severe the motor disability [36]. Reduced heart rate variability is thought to lead to cardiac impairment.

31.2.9 Dental

Periodontal disease is common in individuals with CP. The reasons are *multifactorial*, with the primary reason being poor motor control, which leads to poor oral hygiene. An *oropharyngeal* dysphagia contributes to an open-mouth posture leading to malocclusion and mouth breathing. *Independent*, twice-daily or daily brushing or oral hygiene methods are recommended. If independent brushing is not possible, parents and caregivers may need education about equipment, positioning and methods that are individualised to their child. *Teeth* cleaning should be approached using gentle, consistent methods which become routine. Starting at a different place in the mouth each time will provide better overall dental hygiene, rather than the same order of brushing, which may mean that certain teeth are rarely cleaned. *Parents* and *caregivers* should be as gentle as possible and respond to verbal and nonverbal gestures. A mouth prop can help with accessing teeth.

31.3 Health Systems

Health systems aim to *provide safe*, effective and timely treatment. Future paediatric health system priorities include focusing on the well-being and values of the "*whole child*", not just their diagnosis, aiming to support both the child and their family and to focus on the quality of life (see Chap. 38) [37]. There has been a major shift to include consumers for planning and implementing new goals and changes within the hospital system [38]. Studies show that inadequate age-specific supports during childhood lead to *reduced opportunities* to develop independence [39]. Children with disabilities miss more school than typically developing children, have difficul-

ties making friends and participate less in organised activities [38]. Health frameworks must aim to meet priorities which cover the health and disability sectors, to ensure optimisation of function, independence and participation, as well as dignity and autonomy [40].

Measuring the *effectiveness* of complex care services for children with medical complexity is not straightforward. Measuring the cost-effectiveness of *treatments* and complex care programs may not be the appropriate focus to measure their helpfulness [38]. For example, in one study, authors reported reduced utilisation of unplanned presentations to the emergency department [41]. In another study assessing implementation of a complex-care program, a nurse specialist-paediatrician dyad was assigned to a child and their family to provide care coordination and pre-emptive planning [42]. However, this *service* did not reduce healthcare utilisation. Yet, with time, other important outcomes such as parental health, sleep and fatigue were improved [42].

31.4 Transition to Adult Services

The process of *transitioning* from paediatric care to an adult hospital for an individual with CP brings with it new challenges. Our current generation of patients with severe CP and severe neurological impairment are facing *social* and *ethical* challenges, with some adult doctors not familiar with this complex phenotype and patient, with dependence on technology and interventions. For some, there is a degree of emerging autonomy, self-advocacy and moral agency [43]. For others, for *example*, those with severe CP and intellectual disabilities, the parents remain the medical decision-makers. This surviving cohort's transition to the *adult services* is different to the usual practice in adult services; usually, an adult can make their own decisions or, in the setting of an acquired injury or dementia, their loved ones help guide decisions for them. For *children* and then *adults* with severe neurological impairment, often their parents, acting as a proxy, make decisions for their adult child.

The *adult model* of care, particularly for an admission to the intensive care unit, is often about reversibility of illness and chance of survival. Older adults, who have age-related disease, such as dementia or pneumonia, may not be the ideal candidate, given the gain of quality of life and the likelihood of inevitable death in the near future. However, there are *many* differences between an adult with dementia and young adult with severe neurological impairment.

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Bone Status in Cerebral Palsy

32

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, low body weight, sex steroid deficiency, and medication use (e.g., antiepileptic drugs). Dual-energy X-ray absorptiometry is most commonly used as a diagnostic method for assessing bone quality. *Supplementation* 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. The chapter reviews all these fields.

Keywords

Bone · Documents · Treatment

32.1 Introduction

Health problems concerning the musculoskeletal system are common in cerebral palsy (CP). Next to spasticity, paresis, and contractures, there is a higher incidence of osteoarthritis as well as osteoporosis in adults with CP [1–3]. Compromised bone health and low bone mass appear to be common from a young age in this group [1, 4]. Fracture risk is therefore increased in people with CP, and fractures may even occur after minimal trauma [2, 5–12] (Fig. 32.1).

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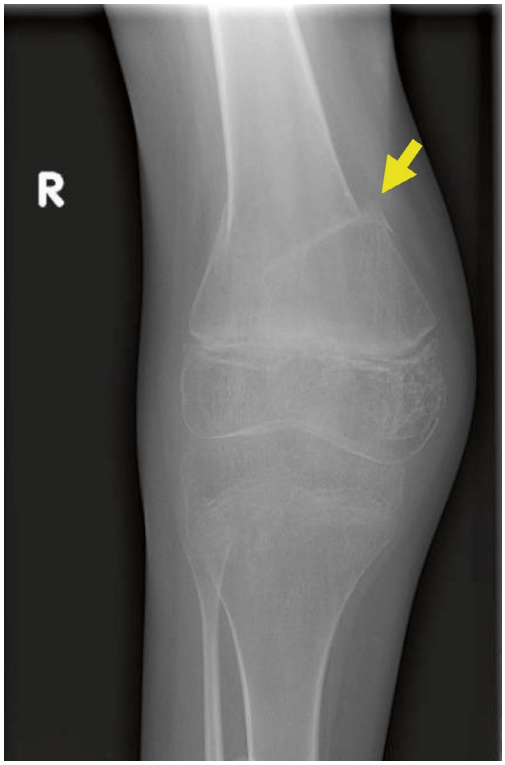


Fig. 32.1 Radiograph of right knee of a 16-year-old boy with severe osteopenia. The yellow arrow indicates a fracture of the femur

32.2 Pathophysiology

There are many factors known to influence bone mass (Fig. 32.2). Risk factors for compromised bone health in people with CP *include* malnutrition and low body weight, immobility, sex steroid deficiency, and medication use, e.g., anti-epileptic drugs [13]. Children with moderate-to-severe CP are also known to have poor growth compared with healthy children [14]. Low body mass index (*BMI*) and need for transfer assistance have a negative impact on bone mineral density (*BMD*) in people with CP [15, 16]. Increasing evidence is present showing that deficits in BMD are not restricted to nonambulatory people with CP but concern ambulatory persons with CP as well [17].

To adapt to stress and to maintain calcium homeostasis, the bone undergoes a constant process of remodeling. Bones will adjust their strength in proportion to the amount of stress placed upon them. *Normal* bones can detect and repair small amounts of microdamage. In this process, remodeling "units" remove and replace bone in a coordinated manner. *Osteoclasts* are responsible for 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 [18].

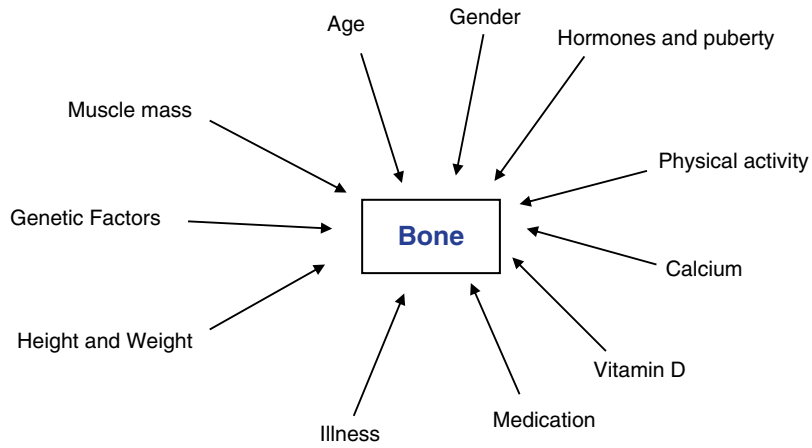


Fig. 32.2 Determinants for bone health

Foundation for skeletal health is established early in life. In healthy children, in spite of constant remodeling 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 [14, 19]. While with increasing age bone mass further declines [16, 20], lower borders of fracture risk and bone density are reached at an earlier age in people with CP and can even occur in childhood [8, 21].

32.3 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 numbers in children without disabilities [22]. *Fracture* prevalence in adults with CP is higher (6.3%) compared to adults without CP (2.7%) [12]. Most fractures occur at the lower extremities (*femur and tibia*) [23].

In children with moderate-to-severe CP, the *prevalence* of low bone density varies from 23 to 97% depending on the diagnostic method and measurement site [24, 25]. 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 [26]. In *adults* with CP, both incidence and prevalence of osteoporosis are higher than those in the general population [1, 2, 27]. Prevalence of low bone density is around 45% in the lumbar spine and 30% in the hip region [15].

32.4 Diagnostic Measures

32.4.1 Radiological Imaging

Different methods are used to assess bone status. Advantages and disadvantages of these methods are described in Table 32.1 [28–33]. To determine *bone* mass and to diagnose osteo-

Table 32.1 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	• Susceptibility to motion artifacts
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 X-ray absorptiometry; *QUS* quantitative ultrasound; *QCT* quantitative computed tomography; *MRI* magnetic resonance imaging; *DXR* digital X-ray radiogrammetry

porosis, 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 [34–36].

Additionally, disrupting factors like movement during measurement, scoliosis, contractures, and metallic implants are frequently present in people with CP [37]. The distal femur has been shown to have more reliable BMD outcome in children and adolescents with impaired mobility in comparison to lumbar spine BMD [38]. The distal femur site in adults has not been extensively investigated, and in adults, total hip BMD and femoral neck are frequently used regions of interest [28].

32.4.2 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. The blood level of bone-specific alkaline phosphatase (BALP) is a good indicator of bone formation [21]. Other frequently used *bone markers* in assessing bone metabolism are osteocalcin, procollagen 1 N terminal extension peptide (P1NP), and carboxy-terminal telopeptide of type 1 collagen (CTX) [39].

32.5 Treatment and Prevention

Interventions aimed at increasing bone density in children with CP during childhood and adolescence may improve BMD and decrease the risk of fracture later in life [11, 40].

32.5.1 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 [40, 41].

32.5.2 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 [28].

There is very limited evidence that passive standing devices and low-amplitude mechanical loading may be effective in the treatment and prevention of low bone density [40, 42, 43].

32.6 Bisphosphonates

Bisphosphonates inhibit osteoclast activity [28]. Although generally used in women with postmenopausal osteoporosis, only small studies are present concerning children with CP and low bone density. There is limited evidence that intravenous bisphosphonate therapy increases bone density in people with CP [44–47] and reduces fracture occurrence [48]. A restrictive policy on oral bisphosphonates seems appropriate because of the side effects (e.g., gastritis, esophagitis). The duration of treatment is at present unclear.

32.7 Growth Hormone

In a small study, growth hormone has been shown to improve linear growth and bone density in children with CP [49].

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Visual Impairment in Children with Cerebral Palsy

33

Nikolaos Kozeis and Saurabh Jain

Abstract

Cerebral palsy (CP) is a disorder of movement and posture due to damage to immature brain. Early brain malformations and congenital or postnatal lesions affect not only the motor areas of the brain but also many levels of the visual pathways, leading to various visual disorders. Ocular and visual abnormalities are very frequent in cerebral palsy (50–90%). The severity of those abnormalities is related to the location, the timing, and the extent of the brain damage. Most CP children show impaired visual acuity; visual fields; contrast sensitivity; eye coordination; binocular vision; ocular motility affecting the fixation, saccades, and smooth pursuits; visual perception; and visuomotor skills. Since visual impairment affects the psychomotor development of a child globally, as well as the quality of life in adulthood, an early neuro-visual intervention program planning is necessary. Ocular, visual abnormalities, visual problems related to all types of CP, and recommendations are reviewed in this chapter.

Keywords

Cerebral palsy · Visual disorders · Cerebral visual impairment · Early intervention · Visual deficits

33.1 Introduction

Cerebral palsy (CP) is a disorder of movement and posture due to damage to immature brain. It is a common developmental disability, with a prevalence of around 2 per 1000 live births (see Chaps. 2 and 3). Half of CP children have also a form of epilepsy, and 30–50% have cognitive dysfunction, such as short attention and learning and memory problems [1].

According to brain MRI findings, classified by the Classification System proposed by the Surveillance of Cerebral Palsy in Europe, CP children could be divided into five main categories: (A) those with brain maldevelopments, (B) those with predominant white matter injury, (C) those with predominant gray matter injury, (D) those with miscellaneous issues, and (E) those with normal findings [2].

Causative factors include early brain malformations, premature birth, hypoxic ischemic encephalopathy, hydrocephalous, metabolic disorders, congenital or postnatal infections, and lesions (see Chap. 5). These factors could affect many areas of the developing brain, including the visual pathways, mainly the retro-geniculate

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visual system, associated visual cortical areas, and subcortical visual areas, leading to various visual disorders and to a misinterpretation of the visual world [3].

33.2 Ocular and Visual Abnormalities in CP Children

Visual deficits are common findings in cerebral palsy (CP) (50–90%), being 10–70 times more common than in general pediatric population of equivalent age, and they are now considered an integral part of the clinical presentation of CP. This is mainly due to co-involvement of optic radiations and corticospinal tracts. The most common etiologies are hypoxic-ischemic encephalopathy, seizures, and structural brain malformations [4, 5].

The clinical spectrum of these visual deficits is extremely broad, ranging from mild to severe, related to the area, time, and extent of the brain damage. It includes ocular, visual, oculomotor, visuo-reflective, visual perceptual, and visuomotor disorders [6–10].

Up to 11% of children with CP have severe visual impairment (SVI), which 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 [11]. However, CP children with very severe attentional problems are at risk of being misdiagnosed as "SVI."

It was found that the severity of the visual disorders correlates with the severity of the motor deficits. Children with tetraplegia show severe visual disorders, children with diplegia show moderate visual disorders, while children with hemiplegia show mild visual disorders [4, 11].

A study showed that only 4–9% of children with mild CP (Gross Motor Function Classification Scale—GMFCS Level I) have visual deficits, compared to 58–60% of children with severe CP (GMFCS Level V). Seventy percent of the children with severe CP (GMFCS Level V) have more than one visual deficit, including high refractive error, strabismus, severe gaze dysfunction, absence of fusion, optic nerve deformity, and cerebral visual impairment (CVI) [12, 13].

In another study, it was found that visual acuity, visual field, stereopsis, and color perception are commonly compromised in cortical damage, while oculomotor functions are compromised in subcortical damage [14].

So, the visual disorders in CP children show a great heterogeneity, depending not only on the type of CP but also the etiology, location, timing, and extent of brain lesions [10, 14].

Most CP children show impaired visual acuity; visual fields; contrast sensitivity; eye coordination; binocular vision; ocular motility affecting the fixation, saccades, and smooth pursuits; visual perception; and visuomotor skills [6].

Fundus abnormalities are not uncommon (30%). A pseudoglaucomatic cupped optic disc (due to subcortical insult of the immature visual system in premature babies), a temporally pale optic disc (due to cortical insult to the mature visual system in full-term babies), and optic nerve hypoplasia are common findings in CP and may be associated with some visual dysfunction. It has been hypothesized that it is related to axonal loss due to brain damage (retrograde transsynaptic degeneration). Findings due to retinopathy of prematurity are also common since many CP children are born premature [6].

33.3 Abnormalities in Basic Visual Skills

33.3.1 Visual Acuity

Although the best corrected visual acuity (BCVA) is reduced in many CP children (35–75%), total blindness is rare (Fig. 33.1). The reduction of BCVA (amblyopia) is more severe when strabismus coexists, and it is probably due to a disruption to the process of emmetropization. Although BCVA represents neither the whole visual function nor the visual functioning of CP children, it is important to be measured in various distances,



Fig. 33.1 Testing the visual resolution (acuity)

because it is involved in many everyday activities. Although visual acuity improves slowly over the years, 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 the environmental distractions [5, 6, 14, 15].

33.3.2 Refractive Errors

Refractive errors are very common in CP children, especially astigmatism associated with hypermetropia or less frequently with myopia, 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. It is not clear why myopia is more frequent in children with severe levels of CP. It is hypothesized that the cytokines implicated as the cause of cerebral damage may also interfere with the emmetropization by mechanisms that are currently unknown [4, 16, 17].

Correction of the refractive errors is important, since uncorrected refractive errors can limit activities of daily living, impair the development of cognitive functions, and increase the risk of reading and near work [16, 18, 19].

33.3.3 Peripheral Vision (Visual Fields)

The visual fields are usually impaired in CP children (20–50%) with the types of visual field defect depending on the area of the brain affected (Fig. 33.2). 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 towards the hemianopic field; however, children with visual inattention compensate by rotation of the body towards 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



Fig. 33.2 Testing the peripheral vision



Fig. 33.3 Testing the color vision

targets simultaneously and impaired guidance of motion (optic ataxia) [15, 19, 20].

33.3.4 Color Vision

The color vision appears to be grossly normal (Fig. 33.3). However, acquired damage to the temporal lobes in older children can lead to abnormalities of color perception and interpretation [4].

33.3.5 Contrast Sensitivity

Contrast sensitivity is a very important component of visual function. The contrast sensitivity threshold can be significantly reduced in CP children (25–30%). That creates difficulties in their activities of daily living. These children require toys and educational material to be bright and clear, and distinct color boundaries [13, 21]. A progressive improvement in visual acuity, contrast sensitivity, and visual fields was found as the children became older [19].

33.3.6 Stereopsis and Binocular Vision

Stereopsis and binocular vision are very commonly affected in CP children (50–85%), due to either retro-geniculate damage, amblyopia, or oculomotor dysfunction. Due to that, these children have no good stereovision, grossly affecting their visuomotor skills [21, 22].

33.4 Abnormalities in Bi-ocular Coordination and Ocular Motility

Marked abnormalities of bi-ocular coordination and ocular motility have been found in all types of CP children (Fig. 33.4). Fixation and gaze disorders, disturbed saccades, smooth pursuits, OKR asymmetry, and nystagmus are evident in severe CP children.

33.4.1 Fixation-Strabismus-Nystagmus

A significant proportion of CP children display 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." 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 [23].

Strabismus shows a markedly increased incidence (40–80%) in CP children due to defects of afferent pathways caused by axonal interruption in the optic radiation, abnormality of vergence neurons, and maldevelopment/dysfunction of visual cortex [23].



Fig. 33.4 Testing the bi-ocular coordination



Fig. 33.5 A child with spastic quadriplegia and left-eye exotropia

Although in most studies nonparalytic esotropia is commoner than exotropia, accompanied by vertical incomitant deviations and A/V patterns (65–85%), there is contrasting data on which type of misalignment is the most common in CP children [18, 24, 25] (Fig. 33.5).

It seems that various factors are related to the expression of type of misalignment, as the type and the severity of CP, the brain injury, or the ethnicity [24, 25].

Dyskinetic *strabismus* is a distinct type of strabismus characterized by variability of the direction and magnitude of the strabismus. It is seen exclusively in severe CP children 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 [26].

These children are poor candidates for surgical correction, while children with stable deviations respond favorably to cautious strabismus surgery. Otherwise, the success rate of surgery is low, and this is probably due to loss of input to binocular cells in visual cortex, which may disrupt the fusional mechanisms, potentially resulting in decreased ability to maintain ocular alignment after strabismus surgery [5].

Nystagmus is also common in CP children (30–50%), in continuous and transient forms. It is mostly jerk nystagmus, accompanied by extrinsic ocular motility disorders, like abduction deficit. Nystagmus seems to be stable with age [11, 14, 19, 27].

33.5 Conjugate and Disconjugate Eye Movements

The most frequent oculomotor function anomalies are discontinuous smooth pursuit and impaired saccadic movements, leading to environmental scanning strategies and learning difficulties.

Smooth pursuits are tracking eye movements to follow a slowly moving target and to keep on the maculae of both eyes. They are significantly impaired in CP children (22–85%). The affected children show difficulties in seeing multiple targets at once, in following moving targets, and in watching cartoons on the TV.

Saccades are fast eye movements to alter fixation quickly. These movements are often affected in CP children (18–89%), being mainly dysmetric with increased latency. Due to this, these children adopt compensatory strategies, such as brusque head movements, frequent blinking, or both. It was also found that school-aged CP children and older CP persons show severe micro-saccadic disturbances when they are reading [4, 22].

Convergence and divergence are disconjugate movements, used to maintain fixation on a target as it moves towards or away from the face. These movements are impaired in many CP children (30–50%) interfering with the focusing mechanism.

CP children show an improvement of oculomotor functions with age comparable to that of healthy subjects. It starts with the improvement of the fixation pattern and being followed by an improvement to the smooth pursuits and saccades. This seems logical, since the eye movements depend not only on target-related signals from the peripheral visual field but also on the ability to fixate a target at the fovea. Also, fixation is controlled by neuronal mechanisms that include many of the same brain regions involved in the generation of voluntary eye movements (superior colliculi and medio-posterior cerebellum) [27, 28].

A possible explanation of this amelioration may be that the participation in daily life activities spontaneously improves oculomotor functions during childhood.

33.6 Abnormalities in Visual Reflexes

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 as objects/people tend to move rapidly in the periphery, which requires a rapid ocular response, while maintaining primary fixation stable. A high percentage of CP children appear to have altered OKR (55–87%).

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. In that way, it maintains the balance of the body by keeping the world steady when the head moves. VOR is impaired in CP children (50–80%).

Accommodation is a reflex, which is elicited in response to focusing on a near target. It comprises coordinated changes in vergence, lens shape, and pupil size. Accommodation is impaired in CP children (55–65%) (Fig. 33.6). These children find it difficult to see near targets, and they could be misdiagnosed as inattentive. Near-vision glasses are a simple and very effective solution [4, 29].



Fig. 33.6 Testing the accommodation

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 [14].

33.7 Abnormalities in Retrogeniculate Cortical and Subcortical Structures (CVI)

Cerebral visual impairment (CVI) is defined as "a verifiable visual dysfunction, which cannot be attributed to disorders of the anterior visual pathways or any potentially co-occurring ocular impairment, involving mainly visual perceptual/visuo-cognitive and visuomotor disorders" [30, 31]. It is also the major non-ocular cause of pediatric visual impairment worldwide [14, 31–34].

It is widely known that CVI is very frequently observed in CP. About two-thirds of CP children may present with CVI. This is more common in children with periventricular leukomalacia (PVL) [4].

According to a recent classification, there are three different clinical profiles of CVI: (A1) selective visual perception/visual cognitive and visuomotor deficits; (A2) more severe and broader visual perception/visual cognitive and visuomotor deficits, and variable visual acuity; and (B) very severe visual perceptual/visual cognitive and visuomotor deficits, accompanied with reduced visual acuity, high refractive errors, strabismus, nystagmus, and more [34].

Visual 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.

Visuomotor skills are related to visually guided activities and **visuo-cognitive** skills are related to problem-solving activities. Both the visuomotor and visual perceptual abilities are involved in different levels of visual word processing and other visuo-cognitive activities, like in academic skills [35–37].

Many CP children (>60%) appear to have *visuo-perceptual/visuo-cognitive and visuomotor*

problems due to damage to the associated visual cortical areas (inferior temporal and posterior parietal), to the streams (ventral and dorsal) connecting the primary visual cortex with these areas, or to the superior longitudinal fasciculus, connecting the occipital cortex with the parietal-frontal cortices. These children may show delay in the learning process, as well as the development of perceptual experiences [22, 38–40].

The **ventral stream** connects the occipital (visual) cortex to the inferotemporal cortex ("storage" of prior visual experiences). Damage to ventral stream and/or to the inferotemporal cortex can lead to impaired visual recognition of faces, interpretation of facial expressions (*prosopagnosia*), and impaired recognition of objects, shapes, letters, and route finding, particularly in new places (topographic agnosia) [41, 42].

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/scanning 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 [43–45].

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 [46].

As in healthy newborns, the perceptual visual abilities improve with age, especially during the first years of life due to visual system maturation (development of foveal cones, refinement of retinal and cortical architecture, and environmental factors). It seems that the same happens in brain-damaged children [47, 48].

Due to that, although it is not easy to diagnose visuo-perceptual and visuo-cognitive problems, a detailed history taking and careful observation of the child's visual behavior help to identify CP children with visual perceptual, visuomotor, and visuo-cognitive problems. Based on that, it is easier to plan special intervention programs to empower visual system through neuroplastic changes involving local and global functional connectivity networks by activating, modulating, and strengthening residual visual signals [3, 45, 48, 49].

33.8 Ocular and Visual Abnormalities in Types of CP

33.8.1 Spastic CP

Visual disorders are more common *in spastic bilateral CP* than in any type. More than 65% of these children have hypermetropia, more than 70% have no binocular vision and stereopsis, more than 60% show reduced best corrected visual acuity, 30% show optic disc abnormalities, 7% show visual field defects, and 15% have CVI. Esotropia and vertical deviations are the most common types of strabismus (50–15% of them have dyskinetic strabismus) in this group. Ocular motility and gaze disorders are also common (saccadic and pursuit asymmetry 51%, nystagmus 15%, gaze apraxia 17%, and fixation instability 12%) [17].

More specifically: Bilateral spastic quadriplegic CP (Q-CP) children are the most severe visually impaired (see Chap. 12). 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). Seventy-seven percent 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 (30%) are also very common. Most of the children (80%) have no binocular vision and stereopsis, gaze and movement disorders (40%), CVI (30%), and visual field defects (11%) [22].

33.8.2 Spastic Diplegia

There is a strong correlation between *spastic diplegia-CP (D-CP)* and prematurity, due to the high possibility of hemodynamic and respiratory instability of the premature newborn resulting in periventricular leukomalacia (PVL).

A review study has helped establish a correlation between visuo-perceptive, visuospatial, and visuoconstructive deficits and neuroimaging findings in individuals with D-CP and PVL. The visual profile of diplegic CP (D-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. Visuo-cognitive dysfunction is a typical finding in individuals with diplegic CP (50%) (see Chap. 12).

33.8.3 Spastic Hemiplegia

The visual profile of *spastic hemiplegic* CP (H-CP) 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%), oculomotor impairment (35%) particularly in smooth pursuit and saccades, and CVI (12%). Fundoscopy reveals optic disc abnormalities in 12% of the cases (see Chap. 12) [12, 14, 18].

33.8.4 Dyskinetic CP

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), 22% of them present optic disc abnormalities, 22% present with CVI, and 11% are 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 (see Chap. 12) [22].

33.8.5 Athetoid CP

Athetoid 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 (see Chap. 12) [22].

33.8.6 Ataxic CP

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 target what they are looking at lead to problems with depth perception (see Chap. 12) [22].

33.8.7 Hypotonic CP

Hypotonic CP is caused by severe brain malformations or brain damage, usually during the early stages of brain development while the infant is still in utero. Hypotonic CP children appear with no head control, floppy muscles (including ocular muscles), and poor reflexes, affecting their visual performance [55].

33.8.8 Mixed CP

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 [55]. It was found that children with cortical damage showed visual improvement much more frequently (78%), suggesting that children with PVL are less likely to show visual improvement. It was also found that the incidence of strabismus, nystagmus, and optic atrophy in the PVL group is significantly higher (see Chap. 12).

33.9 The Importance of Early Intervention Programs

Visual disorders in CP children are considered a core symptom, with a great impact on their daily life [11, 50, 51]. However, visual disorders caused by early brain damage could be influenced by adaptive neuroplasticity, especially during the first years of life, since gross anatomical structures continue to develop, together with the maturation of neural circuits of the visual cortex [52, 53].

Synaptogenesis in human visual cortex reaches a peak between 8 months and 2 years and is followed by a long period of synaptic pruning to reach adult levels later in childhood [66]. Something similar is seen in dendritic refinement, with a peak at 5 months and adult levels by 2 years [53].

Anatomical features like cortical thickness, synaptogenesis, and horizontal and interlaminar connections are already adult-like at this stage, but vision continues to mature well beyond the first years of life [65]. Basic visual functions, like visual acuity, reach adult level between about the sixth year of life, while higher visual functions, like visual perceptual/visuo-cognitive and visuo-motor, develop in adolescence [32, 54].

Younger CP children present with more signs of CVI compared to older children. Then, an early neuro-visual evaluation is necessary to define the weak functions that can still improve. Intervening as early as possible is crucial, since the neuroplasticity is maximal within the first 2 years of life [55].

An early intervention program empowers the visual functions and the developmental process, especially during the first years of life and quality of life, at the school age and later [31, 48]. Thus, a neuro-visual assessment is important to CP children, as early as possible.

33.10 Conclusion

Visual disorders due to cerebral palsy can present in many ways. Visual impairment plays a key role in psychokinetic development of CP children and affects the quality of life for the rest of their lives. An early ocular, visual, oculomotor, visuo-perceptual, and visuomotor assessment is very important. The accurate detection of visual disorders leads not only to a complete clinical diagnosis but also to appropriate intervention planning. *Visual assessment* requires a multidisciplinary step-by-step approach, including visual function globally, as well as visual functioning.

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Pulmonary Management of the Patient with Cerebral Palsy

34

Rachael Marpole and Garey Noritz

Abstract

Pulmonary problems are a major source of morbidity and mortality, especially among patients with severe cerebral palsy. The pulmonary 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 pulmonary 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. Pulmonary problems, physiology, assessment, importance of immunizations, and therapies are reviewed in this chapter.

Keywords

Pulmonary disease · Tracheostomy · Ventilation · Immunization · Sleep-disordered breathing

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34.1 The Burden of Pulmonary Disease for Patients with Cerebral Palsy

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 pulmonary system are of particular importance and are the leading cause of death among children and adults with CP, ranging from 37 to 74% in different population-based series [1–3]. Pulmonary issues are also the leading cause of hospitalization for patients with CP [4, 5].

Risk factors associated with hospitalizations in children and young people with CP are Gross Motor Function Classification System Level V (unable to lift their heads off a bed or drive an electric wheelchair independently), hospital admissions for pulmonary disease in the last 12 months, oropharyngeal dysphagia, seizures, frequent pulmonary symptoms, pulmonary symptoms during meals, gastroesophageal reflux, nightly snoring, and at least two courses of antibiotics for pulmonary symptoms in the previous year [6, 7] (Fig. 34.1).

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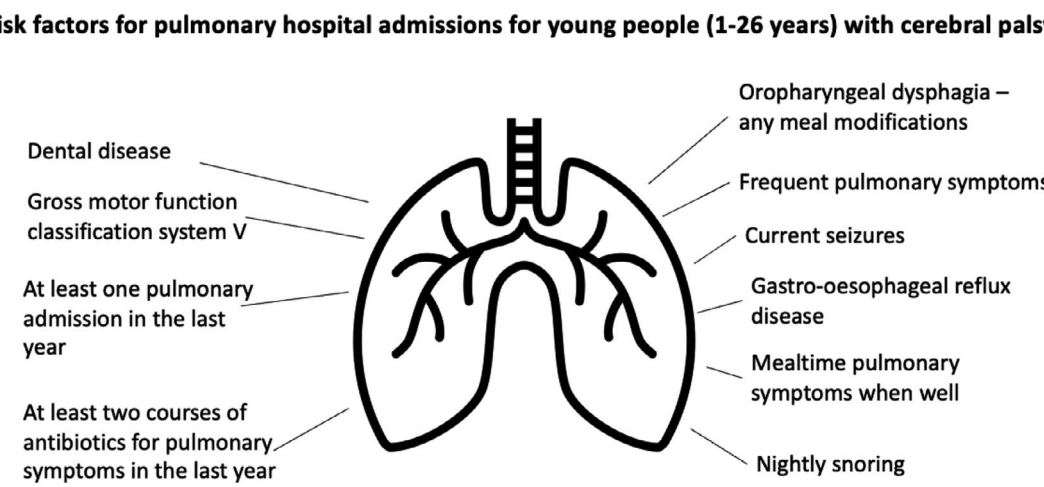


Fig. 34.1 Risk factors for pulmonary hospital admissions for young people with cerebral palsy

34.2 Review of Pulmonary Physiology, with Special Attention to Issues Common in Cerebral Palsy

Simply put, the pulmonary system includes the conduits between the nose and mouth, and alveolus where gas exchange occurs; 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 pulmonary problems.

The nose and oropharynx provide an important filtering and humidification 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 pulmonary 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 CP, particularly among more severely impaired patients [8]. Dysphagia can lead to chronic lung inflammation and infections, often with organisms heavily resistant to antibiotics [9]. The lungs are also vulnerable to aspiration from gastroesophageal reflux, which is highly prevalent in CP, particularly among patients requiring tube feeding [10]. The presence of reflux is an independent predictor of an increased risk of pulmonary illness requiring hospital admission [11].

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 [12].

More severely impaired individuals with CP are prone to hypoventilation because 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 pulmonary system [13–15].

At the level of the alveolus, there may be abnormal gas exchange because of chronic lung infections, scoliosis, 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 the 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 [16]. 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 might be expected to have a high rate of DVT/PE because of immobility, this has only been reported rarely [17] or as a result of screening for asymptomatic DVT [18]. The true risk of PE in this population is unknown, though a higher rate of PE has been reported in adults with CP than adults without CP, and this seems particularly true for adults with CP and more severe motor disability [19, 20].

34.3 Assessment of the Pulmonary System in Patients with CP

The pulmonary assessment in patients with CP is multifaceted and often 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 pulmonary 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 acidemia with increased bicarbonate production.

Formal *pulmonary* function tests (PFTs) 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 [21, 22]. There are emerging techniques of pulmonary function measurement that do not require the cooperation of the patient [23], 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 cardiac catheterization is warranted.

34.4 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 CP, particularly those who are severely affected or have epilepsy [24]. 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 towards management. Patients may pres-

ent with obvious signs, such as observed apneas or choking while sleeping and/or awake, 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.

34.5 The Importance of Immunizations

Immunization against preventable pulmonary diseases is of paramount importance to maintaining optimal pulmonary health. Immunization recommendations are frequently updated; in the United States, 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, annual influenza vaccine, and COVID vaccine. Close contacts of the patient with CP should also be immunized to "cocoon" the individual [25]. People with intellectual disability and developmental disabilities are at higher risk of morbidity and mortality from COVID [26]. Current treatment recommendations should be followed with low threshold for treatments with antivirals or monoclonal antibodies.

34.6 Orthopedic Interventions and the Pulmonary System

The role of orthopedic interventions in maintaining pulmonary function is controversial. Even though *kyphoscoliosis* and chest wall deformities are major causes of pulmonary problems in patients with CP, surgical correction has not been definitively shown to improve pulmonary function or reduce pulmonary morbidity [27]. As discussed above, the assessment of pulmonary function in people with CP can be very difficult, which interferes with ascertainment of the effect. Proxies for pulmonary function, such as the number of pneumonias [28] or the need for pulmonary medications [29], have not supported a positive effect for scoliosis repair. This may be because the disease is too advanced by the time the deformities are repaired. 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 [30].

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 pulmonary status following surgery, and that they were satisfied with their decision to have their child undergo surgery [31]. Further study is clearly needed in this area.

34.7 Therapies for Pulmonary 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 pulmonary 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 the size of the oral bolus. Reduction of salivary volume using anticholinergic medications or salivary procedures can also decrease the risk of aspiration [32]. Regular dental care has been shown to reduce subsequent admissions in children with neurological impairment [33]. The risk of aspiration from gastroesophageal reflux can be reduced

using medications or surgical options such as fundoplication or post-pyloric feeding [34].

Patients with *tracheostomy* are prone to chronic pulmonary infections, especially with highly resistant organisms. Efforts to keep the tracheostomy and tube clean are important, but all will eventually be colonized [35]. In a small series, prophylactic inhaled antibiotics targeted to resistant organisms was shown to reduce the frequency of pneumonia in children with CP and tracheostomy [36].

Chronic *infection* and inflammation of the airways can lead to bronchiectasis, characterized by chronic productive cough with intermittent exacerbations. When frequent, exacerbations can be prevented using macrolide prophylaxis. This has also been used in children with CP and frequent pulmonary infections, even in the absence of bronchiectasis.

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, are effective and easily taught and do not require specialized equipment, unless suctioning is also needed to clear the airway [37]. High-frequency chest wall oscillation therapy by means of a vibrating vest is commonly used and usually well tolerated [37, 38]. Newer devices, which insufflate and exsufflate the lungs through a mask, are frequently used in patients with neuromuscular disorders [39] and can be applied to patients with CP with impaired cough. In patients that can cooperate, incentive *spirometry* exercises have been shown to improve parameters of pulmonary function [40], as has pulmonary muscle feedback training [41].

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 pulmonary insufficiency or failure because 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, and 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 healthcare system. The involvement of a palliative care team to help the family and primary care team sort through these issues is desirable [42].

34.8 Summary

The care of patients with CP is incomplete without careful attention to the pulmonary system. *Pulmonary* problems are a major source of morbidity and mortality, especially among patients with severe CP. The pulmonary 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 pulmonary 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

35

David I. Campbell and Morag J. Andrew

Abstract

Feeding and gastrointestinal symptoms are common in children with cerebral palsy (CP) 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, gastro-oesophageal dysmotility, retching, delayed gastric emptying and chronic constipation can occur. The *assessment* and management of children with CP and comorbid gastrointestinal problems require a multidisciplinary team experienced in the management of children with CP and gastrointestinal problems. This *chapter* considers the gastrointestinal problems experienced by children with CP and outlines current management strategies.

Keywords

Cerebral palsy · Gastrointestinal problems · Oropharyngeal dysfunction · Gastro-oesophageal reflux · Constipation

35.1 Introduction

Gastrointestinal problems are encountered in at least one-third of children with cerebral palsy (*CP*). Common problems include eating, drinking and swallowing difficulties (with *associated* aspiration of food or fluid into the lungs); 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 that newborn infants undertake. Weak suck and poor feeding in infants may indicate neurological impairment [1].

Children with the most severe motor deficits (bilateral CP) have the highest risk of oropharyngeal dysfunction [2]. The possibility of oropharyngeal dysfunction should be considered in all children with CP. Where concerns about oropharyngeal function are identified, further evaluation should *include* a detailed feeding history, *including* from early infancy, and direct observation of eating and drinking carried out by an appropriately trained professional, usually a speech and language therapist with expertise in dysphagia. *Videofluoroscopy* is indicated when there is clini-

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cal evidence of a poorly coordinated swallow and/or symptoms suggestive of possible aspiration, e.g. recurrent chest infection. The *management* of oropharyngeal dysfunction requires input from a multidisciplinary team experienced in the management of eating, drinking and swallowing difficulties, including a paediatrician, speech and language therapist, dietitian, and occupational therapist or physiotherapist. A number of evidence-based interventions for eating, drinking and swallowing difficulties exist [3]. An individualised eating and drinking plan is a helpful way to share information about a child's eating and drinking needs with parents and carers and those who support mealtimes out-with the home, e.g. staff in school (see Chap. 36).

Oral-motor dysfunction may lead to limited food and/or fluid intake and subsequent undernutrition [4] and impaired growth [2]. Nutritional impairment from limited calorie intake may be compounded by factors such as comorbid health conditions, medications, foregut dysmotility leading to increased loses from vomiting, and constipation causing reduced appetite. *Gastrostomy* insertion should be considered for children who are unable to safely maintain their nutritional and/or fluid requirements by mouth.

35.2 Indication for Gastrostomy

Gastrostomy tube insertion may be recommended for children who:

- Have a clinically unsafe swallow
- Are unable to achieve their nutritional and fluid requirements orally
- Have an excessively long (>3 h/day) oral feeding time
- Are dependent on nasogastric tube feeding for more than 6 months

35.2.1 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. *Undernourished* children with severe CP may show significant increases in body fat and muscle following gastrostomy tube feeding. Catch-up growth is demonstrated irrespective of the age at which gastrostomy tube feeding commences.

Anecdotal reports have suggested improved neurodevelopmental progress, pubertal development and reduced irritability following gastrostomy feeding.

For some *families*, gastrostomy tube feeding reduces mealtime stress and improves quality of life. Less time is required for feeding, making more time available for other family activities.

35.2.2 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/transfixion and complex peritoneal-gastrocolic fistulae. Many of these complications are now avoided or reduced in likelihood by refinements to the technique of insertion, i.e. single stage or pull through/laparoscopic assisted. Later *complications* include stoma leakage, cellulitis, granulation tissue formation around the gastrostomy site and displacement.

Buried *bumper* is a complication of a single device which is in common usage, but the complication is rare and easily dealt with, supporting the ongoing use of this device.

Gastrostomy site *infection* is the commonest problem occurring in up to 20% of cases but is eas-

ily treatable. Less common and significantly more difficult to deal with are contact dermatitis/plasticiser sensitivity to the silicone and plastic material in the PEG tubing. More serious *later complications* such as bowel obstructions, gastrointestinal bleeds (peristomal ulceration), 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 for all gastrostomy-related complications range from 14 (after 1 year) to 26% (after 5 years). Death rates are most likely related to the underlying neurological impairment and associated comorbidities, e.g. recurrent chest infection, rather than the gastrostomy itself [6].

35.2.3 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, which is 16–50% less than the recommended daily allowance [7]. Such low *energy* intakes may 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 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]. *Conversely*, low energy but nutritionally complete enteral feeds can produce weight gain without excess fat deposition.

35.3 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 important in the nutritional assessment of children with CP. There is 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. Taken together, sequential assessment with adjustments of nutrient intake is essential.

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.

35.3.1 Drooling

The pooling of excessive saliva in the anterior part of the mouth and its subsequent escape through poor lip closure lead 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) levels IV–V are most likely to experience problematic drooling [10] (see Chap. 5). 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 symptoms such as recurrent coughing, choking with feeds and recurrent chest infections requiring antibiotic therapy (see Chap. 34).

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 patches 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 show that these medications are similarly efficacious, but that hyoscine hydrobromide patches produced more problematic side effects leading to a greater chance of treatment cessation [15]. Botulinum toxin injection of the salivary glands can also be beneficial but must be repeated at intervals and is only available in a small number of specialist centres. *Salivary* gland excision or rerouting is invasive and can lead to permanent excessive saliva reduction, leading to problems with mastication and dental decay (see Chaps. 20 and 25).

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* are 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].

35.3.2 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 typically affected because of the primary innervation of the foregut by *vagal* routes. The *vagus* has *three* dominant brain stem nuclei (dorsal motor nucleus, nucleus ambiguous and nucleus tractus solitarius). These nuclei are richly innervated from the circumventricular apparatus, which in turn are frequently damaged by ischaemic insults, e.g. perinatal hypoxia-ischaemia. Mid-gut and hind gut are innervated by *thoracolumbar* and *lumbosacral* nerve routes, which are less frequently involved in hypoxic-ischaemic perinatal events. The *majority* of nerve innervations of the foregut are sensory (up to 80%). The form of foregut *dysmotility* typically seen in children with CP is feed-induced pain, which then shows signs of disordered motility later (but very variably). *Dysmotile* bowel due to defective efferent motor nerves rarely occurs in transplanted bowel, which is totally separated from the central nervous system. Intestinal grafts have an *intrinsic* nervous system but no extrinsic connection to the spinal cord or brain. In *situations* where patients that have small bowel grafts get infection or graft rejection, they get diarrhoea, but feeding is rarely painful. This *compares* to the situation in CP where foregut dysmotility can be extremely painful.

Modulation of the neural activity in the enteric nervous system by *extrinsic* innervation is abnormal in children with central nervous system disorders; more *recently*, the view that this is secondary to disordered afferent signals or the disordered central processing of afferent, sensory signals has been considered. *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 *distension* of the fundus of the stomach, which leads to transient relaxation of the *lower* oesophageal sphincter and gastro-oesophageal reflux. Typical symptoms of foregut dysmotility include vomiting, retching, gagging and bloating and noxious somatic symptoms such as sweating, pallor and pain [16]. Gastro-oesophageal reflux (GER) is the commonest manifestation of foregut dysmotility. The *most* severe form of feed intolerance presenting as gastrointestinal dystonia (enteral feed-associated dystonia) is *status dystonicus*. Status dystonicus is life threatening with rhabdomyolysis, malignant hyperpyrexia and renal failure. Withholding *enteral* feeds is an essential part of managing this condition.

35.3.3 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 peptic oesophageal 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.

Sandifer syndrome may occur irrespective of vomiting if silent episodes of reflux onto an inflamed oesophagus produce significant pain. 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, e.g. 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.

35.4 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]. More recently, blended feeds (using a wide range of varied foods) via a *gastrostomy* have been adopted into practice and can significantly reduce reflux symptoms [33].

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 [34]. *Retching* is a key symptom of activation of the emetic reflex.

35.4.1 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 [35]. In *these* situations, alimemazine may be a very helpful adjunct to reduce retching.

35.4.2 Delayed Gastric Emptying

Delayed gastric emptying (*DGE*) accompanies many (28–50%) cases of GER [36, 37]. 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 [38]. This *association*, however, may to some extent depend upon the type of food given [39]. 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, 40, 41].

35.5 Constipation

Children with CP regularly suffer from constipation; the reported prevalence ranges from 24 to 74% of all children with cerebral palsy [38, 42]. *Contributory* factors include prolonged immobility, skeletal abnormalities, extensor spasm or generalised hypotonia as well as abnormal bowel motility associated with certain neurological lesions [43]. Dietary *factors* such as low fibre and fluid intake (often due to associated eating, drinking and swallowing difficulties) are important contributors. The *use* of anticonvulsant, opioid, antispasmodic, antihistamine 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 and recurrent urinary tract infection; as well as gastrointestinal manifestations such as recurrent vomiting, chronic nausea, chronic or recurrent abdominal pain and early satiety.

Abdominal *pain* may also worsen dystonia in children with this condition. *Constipation* is diagnosed through *careful* history and abdominal, perineal and if necessary rectal digital examination. Although constipation is a *clinical* diagnosis, abdominal X-ray may be helpful in the identification of faecal impaction and rectal distension. *Constipation* in the child with CP represents a significant therapeutic challenge, and standard *treatment* regimens may prove to be insufficient.

35.5.1 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 that *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 *health* professionals in assessing the response to treatment.

35.5.2 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 distension 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 gastro-oesophageal reflux due to the *significantly* increased risk of aspiration [44].

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.

35.5.3 Second-Line Treatment

In children with rectal impaction and megarectum, disimpaction should *first* be attempted. Disimpaction with oral medication should be attempted in the first instance. The use of rectal medications (e.g. sodium citrate enemas) for disimpaction should be reserved for situations where oral medications have failed and only if the child or young person and their family consent [45].

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. In patients with an *anal fissure*, treatment should firstly address their constipation with the use of stool softeners. Topical *glyceryl* trinitrate (*GTN*) is most likely to heal anal fissure compared to placebo [46]. The use of GTN is limited by the side effect of headache.

Botulinum toxin A injection and neuromodulation are relatively novel treatments for refractory constipation in children. *Large* prospective trials with long-term follow-up are required to determine the true effectiveness of these interventions [47].

35.5.4 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 defaecation. 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 [48].

35.6 Hind Gut Dysmotility

Children that have late *onset* of feed-associated pain (*around* an hour after feeds are commenced), with gut *dystonia*-type symptoms (pain, pallor, swelling, sweating), may be suffering from hind gut dysmotility. These children are *constipated* but have huge colonic distension with or without pneumatosis coli. *Pneumatosis* is often a benign finding, but may be a clue to a significantly compromised colon. There are case series of *significantly* neurodisabled children with gut dystonia developing complete and long-term feed tolerance when the colon is defunctioned or a colectomy performed [49].

35.7 Conclusion

Gastrointestinal symptoms are *common* in children with CP. 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, paediatric gastroenterologist, paediatric surgeon, occupational therapist, dietitian and speech and language therapist as a minimum. *Gastrointestinal* problems in children with CP should always be considered within the broader family and social context.

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Nutritional Management of the Patient with Cerebral Palsy

36

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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, reduced gastrointestinal motility, 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.

Keywords

Nutrition · Body composition · Feeding tubes · Undernutrition

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36.1 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*). Such patients often have difficulties with oromotor function, dysphagia, gastroesophageal reflux (*GER*), poor gastrointestinal motility, intestinal malabsorption, or constipation, all of which can interfere with oral feeding [1].

When oral feeding is inadequate for growth, supplemental feeding is often recommended, usually by nasogastric (NG), gastrostomy (G), or jejunostomy (J) tube (see Chap. 35). While these measures are usually 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 status and mortality, underscoring the importance of careful and proactive nutritional management in this population.

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36.2 Challenges in Measuring Nutritional Status

Determining the nutritional status among patients with CP is challenging. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition published *guidelines* in 2017 [5] for the evaluation and treatment of gastrointestinal and nutritional complications in children with neurologic impairment. As part of the guideline, the work group suggested "red flag warning signs" to help identify children who need further assessment. These are:

1. Physical signs of undernutrition such as decubitus ulcers, skin problems, and poor peripheral circulation
2. Weight for age z score <−2
3. Triceps skinfold thickness <10th centile for age and sex
4. Mid-upper arm fat or muscle area <10th percentile
5. Faltering weight and/or failure to thrive

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 the patient in 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 fifth 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. 25). If possible, we recommend that the weight of patients with CP be plotted on these growth charts. Researchers from *Mexico* found that their patients with cerebral palsy were comparable to patients in the USA and proposed to use these charts as a reference [6]. Wright et al. [7] looked to see how children with CP in the UK performed compared to children with CP in the USA using the above growth charts. It was found that children with severe CP from the UK fit well using these growth charts. This provides further support for the use of these growth curves.

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 [8]. 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 [9]. 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 a gold standard for measuring body composition [10]. However, it is not available everywhere, may be cost prohibitive, and 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 [11].

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, amount of typical daily activity, efficiency of movement, fat mass, and underlying medical illnesses. A rough rule of thumb is to *estimate* 15 kcal/cm of length for children with CP who are ambulant and 10 kcal/cm for non-ambulant children. Non-ambulant 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 [12]. The important concept here is to recognize that this is only an estimate, and the feeding regimen must be evaluated and adjusted frequently over time to account for growth and changes in medical status.

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 [13] and may lead to poor cardiopulmonary fitness among adults with CP, along with decreased ambulatory ability, which in turn leads to even poorer fitness [14]. Low-calorie diets are often prescribed to children with severe CP to counteract this.

Protein needs do not seem to be different for patients with CP compared to typically developing children [15]. 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, electrolytes, and extra water.

36.3 Etiologies 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. [16] found that severe feeding dysfunction was associated with lower triceps skinfold and weight. Many studies have shown that the likelihood of feeding issues increases as the GMFCS level increases, with GMFCS Level V having the most significant issues [17–19]. This has also been shown in children with CP in low- and middle-income countries (LMIC). From the Global LMIC CP Register, it was found that moderate-to-severe motor impairment (GMFCS III–V) was a significant predictor of undernutrition, as was maternal education [20]. 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 at Levels II–III may be self-feeders, but getting the food into their mouths may take increased time (see Chap. 25). 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 for the child and the amount of time available for them to eat. Henderson et al. [21] found that 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 because 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 estimate 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 per 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 later. 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. 35).

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 prefer 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 the gastrointestinal tract, resulting in retching, gagging, and vomiting during feeding (see Chap. 35). 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 osmolality of the formula and cause gastrointestinal symptoms including vomiting or diarrhea, further limiting calories available for maintenance and growth.

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 may 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 often take medications that affect the nutritional status. These may include anticonvulsants, antipsychotic medications, and antibiotics, which can affect appetite and the tastes of foods (Table 36.1). Chronic benzodiazepine use can result in significant pharyngeal phase dysphagia, especially cricopharyngeal and hypopharyngeal incoordination,

Table 36.1 Medication effects on eating and swallowing. Compiled from Carl and Johnson [22]

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

resulting in aspiration. Phenytoin can result in atrophy of the cerebellum leading to skeletal muscle dysfunction, ataxia, and oropharyngeal dysphagia [22].

36.4 Assessing the Nutritional Status of Patients with CP

To determine if a child with CP is adequately nourished, the provider and the caregiver must recognize that there is a potential concern. Fogarasi et.al [23] collected data from 497 patients from *eight countries* (the Czech Republic, Greece, Hungary, Italy, the Netherlands, Poland, Slovakia, and Turkey) looking at characteristics, management, current objective nutritional status, and perception of nutritional status for healthcare providers and caregivers. What they learned is the following:

1. Poorer nutrition status is associated with higher GMFCS.
2. Perceived and objective nutritional status do not agree.
3. Healthcare providers' and caregivers' perceptions of nutritional status do not agree in that caregiver thought that their child had normal nutritional status and the healthcare provider did not.

The study reinforces that there needs to be a purposeful assessment of the child's nutritional status on a regular basis.

A thorough nutritional history is the cornerstone of assessment. Finding out what happens throughout the course of a typical 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 pneu-

monia (see Chap. 34). 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. Efforts should be taken to assess for food insecurity during the nutrition assessment. Utilizing the Food Insecurity Screen has been shown to be valid in identifying families who need help finding food [24]. These statements are as follows: (1) Within the past 12 months, we worried whether our food would run out before we got money to buy more and (2) Within the past 12 months, the food we bought just did not last and we did not have money to get more. *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 [25]. In a systematic review and meta-analysis, Da Silva et al. [26] found nine studies reporting high rates of deficiencies in calcium, zinc, copper, and vitamin D. *Copper* deficiency has been found in patients who are exclusively fed through the jejunum [27]. Lark et al. [28] found that prealbumin and albumin were rarely below normal and showed little correlation to body composition, so they are not recommended for monitoring nutritional status. It is recommended to measure the complete blood count, blood chemistries, and levels of iron and 25-hydroxylated vitamin D [29].

36.5 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. 35). 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 [30]. 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 [31].

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 [32].

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* [33]. Blenderized tube feeding has been found to be safe and may improve GI symptoms in pediatric patients [34, 35]. 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 [36]. 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 [37]. Today, many food-based formulas are commercially available and are well tolerated. It is recommended that a dietitian be involved to assess nutritional completeness.

36.6 Conclusion

The most important concept in the nutritional *management* of patients with CP is that there must be frequent re-evaluation 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

37

Harald Bode

Abstract

In children with cerebral palsy (CP), prognosis regarding unaided walking, need for walking aids or wheelchair is possible 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 prevalent in adults with CP. Secondary musculoskeletal problems occur frequently. More than 90% of children with CP survive into adulthood. Life expectancy depends on GMFCS level and swallowing problems. *Transition* into those for adulthood remains difficult, 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. This chapter is up to date in all historical fields.

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Keywords

Cerebral palsy · Prognosis · Motor function · Pain · Life expectancy · Transition · Quality of life · Participation

37.1 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 can be attributed to not only counselling of parents but also therapeutics and therapy concepts in infancy. Here, we discuss the long-term prognosis of motility and some pertinent aspects of the essential highly complex concept of cerebral palsy.

Effects of physiotherapeutic treatments and medical and operative procedures on motility have to be evaluated in this context. Various factors explain the significantly higher *mortality* in individuals with severe as compared to those with mild forms of CP. Better transition concepts and adequate structures for medical care are required to impede the reduced service use of adults with CP. Addressing the typical medical problems, comorbidities and social needs in adults with CP should improve their long-term quality of life and participation.

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37.2 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 and children with minor motor deficiency (*Level 1*) at about 5 years (see Chap. 25). 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 (see Chap. 12) [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 ninth 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 a promising sign in this respect is an unaided sitting at 24 months and/or an alternating crawling within 30 months. 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 orthoses and possibly orthopaedic operations (see Chap. 25). 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. Prognosis may be more favourable in individual cases due to intensive therapeutic measures and adequate aids.

Into 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 [3].

Hand function within 18 months in children with spastic diplegia has a prognostic value for the child's future hand function (see Chap. 12) [4]. Function of the paretic hand remains stable for many years if there has been adequate function primarily during early childhood. However, we often observe a decreasing use of the paretic hand during early school age in hemiplegia.

37.3 Motor Functions of Adults with CP

Motor function takes a turn for the worse in many adults with cerebral palsy [1, 5, 6]. Ando and Ueda [6] 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 (see Chaps. 39, 40 and 41).

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 (see Chaps. 39 and 40). 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 [5].

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 [7].

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 [8].

Bates and Wilson [9] 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, such as 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 till 5 months after termination of the intensive therapy [9].

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 [10].

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 (see Chaps. 25 and 26) [11]. 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 (see Chap. 29) [12].

37.4 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 [13].

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 [14].

Adult people with CP suffer, depending on the severity and kind of their motor disturbances on various secondary musculoskeletal problems; 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 (see Chaps. 12, 25, and 26) [15].

As a 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 [16]. As a consequence, about 26% of the above-mentioned 10-year-old patients have already suffered f*ractures*. A systematic review revealed an incidence of fractures in children with moderate-to-severe CP of 4% per year [17]. The prevalence of low bone mineral density, secondary osteoporosis and fractures increases in adolescence and adulthood, preferably in case of mobility limitations. Dual-energy X-ray absorptiometry is feasible to monitor bone density. Vitamin D alone or with bisphosphonate increases bone mineral density and should be considered in CP patients taking antiepileptic drugs.

Dislocations of the hip appear, but rarely in patients with CP capable of walking; however, about 20–47% suffer from hip pains (see Chaps. 25 and 26) [18].

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 tetraparesis, often associated with myelomalacia or radiculopathy [19].

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 [20]. Other common causes are dental problems, constipation or oesophagitis [21].

Fatigue is being reported as a main problem in adults with CP. It is unrelated to the type or severity of cerebral palsy and may be associated with pain. Consequences may be deterioration of functions, activities and quality of life [20].

Other secondary disease characteristics for CP in adults appear especially in badly affected patients, concerning mainly the respiratory system (*bronchitis* and *pneumonia*) and the nutrition (disturbed eating habits, subcaloric nutrition, chronic constipation) (see Chaps. 34, 35, and 36). The comorbidities already known from the children's age (subnormal height and weight, reduced intelligence, disturbed vision, epilepsy, possibly emotional disturbances) remain (see Chap. 31).

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 [17].

37.5 Mortality

The life expectancy of people with CP is dependent on the severity and disturbance of motor function, on the comorbidities, on the socioeconomic status of the patient's family and on the resources of the regional healthcare system (see Chap. 31).

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 (see Chap. 34) [22]. 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 [23]. A causal interrelation with CP appears to be speculative [22].

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 [24].

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. Fifty percent 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 these survival rates was noted over the entire observation period [25].

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) [26].

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, and fewer deaths from injuries and accidents [27]. A Japanese cohort of children with CP born between 1988 and 2005 showed 5- and 18-year survival rates of 98% and 89%, respectively. GMFCS Level V was the only significant predictor variable [28].

37.6 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 programmes exist (see Chaps. 39, 40 and 41) [29]. Main components of such programmes 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. 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 [30]. 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. 41). 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. The expert knowledge of the medical personnel concerning the specific problems and requirements of adult persons with cerebral palsy is also limited [31]. The health and well-being of caregivers are strongly influenced by the patient behaviour, caregiving demands, family function and social support (see Chap. 38). Strategies for optimising caregivers' physical and psychological health should include supports for behavioural management, daily functional activities, stress management and self-efficacy techniques [32].

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 [33]. This underscores the need for effective prevention which so far is difficult.

37.7 Quality of Life and Participation

Children with CP seem to have a fairly similar quality of life as compared to their healthy peers (see Chap. 38) [34]. However, they have fewer reciprocal friendships, exhibit fewer sociable/leadership behaviours and are more isolated and victimised by their peers than classmates without a disability already at an age of 10.

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 variance in quality-of-life scores [35].

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 [36]. 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 (see Chap. 38) [37].

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 [38]. 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%) [29]. 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 [5, 39].

The *Danish* Cerebral Palsy Registry revealed the long-term social prognosis of children born between 1965 and 1978. Thirty-three percent 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* and 22.5 for a developmental quotient 50–85 vs. >85 and 3.7 for those with epilepsy vs. those without epilepsy [40]. 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 (see Chap. 38) [41].

Those adults with CP which have a regular school education and walking abilities have obviously better prospects on the occupational market. For many afflicted with CP, the problems of decreasing motor ability and various morbidities greatly impair their quality of life in adult age (see Chap. 41). Comorbidities, such as epilepsy,

disturbances of cognition, vision, hearing, gastrointestinal function, cardiorespiratory diseases, dysphagia and others, require multidisciplinary management [42, 43].

Improvements of rehabilitation techniques [44], *domestic* assistance and *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. 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.

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Quality of Life in Children and Adults with Cerebral Palsy

38

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 QoL have been deemed *variable* and *individual*, pain is the single most common element throughout all domains to negatively impact QoL. Investigation and treatment of pain appear 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. For the fourth edition, this *chapter* has been reviewed/revised by the book editor.

Keywords

Cerebral palsy · Definition · Childhood disability · Quality of life · Measurement tools · Client-specific goals · Adult QoL

38.1 Introduction

Cerebral palsy (*CP*) is the term applied to a group of children with motor impairment and related service requirements, primarily affecting posture and mobility (see Chaps. 2 and 12). In order to correctly assess the handicap of patients with CP, the accompanying *comorbidities* have to be taken into account. Equally, quality of life (QoL) depends on all limitations that result from and go along with CP. Hence, evaluation of QoL in CP is a *complex* and *difficult* task that calls for specialized institutions (see Chaps. 31, 32, and 37).

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 consideration when providing care. In lifelong conditions with high variability of presentation, as is the case with cerebral palsy,

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assessment of this broad concept with multiple dimensions presents significant challenge.

The WHOQOL-100 and WHOQOL (World Health Organization and Quality of Life) in a last manual describe the development and use of the quality-of-life assessments. The most cited definition by the World Health Organization views QoL as a broad-ranging concept which includes, at a minimum, an "*individual's*" perception of their physical state, their affect, and the interpersonal relationships and social roles in their life [2].

To work toward greater understanding of this concept, the clinician must become knowledgeable about ways to assess and quantify QoL, the 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 can provide a significant positive impact in this area. Essentially, people should feel physically well and 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. The *management* is done by a *multidis ciplinary/multidimensional* team, such as occupational therapist, physical therapist, surgical therapist, orthopedist, and physician.

38.2 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 the quality of life [3]. 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 [4] 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 the 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 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 38.1. The 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

Table 38.1 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 a 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

(continued)

Table 38.1 (continued)

Tool	Age range	Number of domains	Self-report and proxy, Y = both	Condition specific (CS) vs. generic (G)	Focus/differences
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 system 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

CP. A number of tools 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.

38.3 Specific Measurement Tools

The CP QOL-Child questionnaire [5] 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) [6] 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 [7] 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, 27 items with 5 dimensions, and a 10-item index version [8]. 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 [9] 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) [10] 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 [11].

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) [12] 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 [13] 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 [14]. As well, combining a general tool with more specific individualized outcome measures may give added quality to research in this area.

38.4 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 the tools used. There is also variability based on age at the time of assessment. Regardless of clear variability for many reasons, there are a number of determinants of QoL that the evidence supports. It is obvious that the QOL is different and depends on the type of CP *parallel* and *comorbidities*. According to Vitrikas et al. [15], the comorbidities and functional limitations are common and disabling including chronic pain (75%), epilepsy (35%), intellectual disability (49%), musculoskeletal problems, e.g., hip displacement (28%), behavioral disorders (26%), sleep disorders (23%), functional blindness (11%), and hearing impairment (4%).

38.4.1 Focus of Tool

Measures focusing on physical aspects, function, and health have reported lower scores in individuals with CP [16]. 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 [17, 18].

38.4.2 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 (see Sect. 38.4). 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 [16]. *Similar findings* were reported from an American study in youth from 10 to 13 years of age [17]. Although one must remember the focus of the tool and the individual and 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 those of the general population. Scores were

however lower for physical health, psychological well-being, and role of function domains [18]. 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 [19].

No clear association has been found between physical indicators and psychosocial well-being [20]. 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.

38.4.3 Individual Determinants of QoL

Pain has repeatedly been documented as the single most common element throughout all domains to negatively impact the 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 an 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 a 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 a significant impact on important aspects of life. The *domains* of QoL in the literature include physical, psychosocial, health-related, and emotional QoL.

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.

According to Jiang et al. [19], the most identified determinants by children and adolescents in the bibliography are related sequentially to functional activities, body functions and structures, and environmental factors. According to Murphy et al. [20], determinants of QoL are related to participation and personal characteristics of children with cerebral palsy in order to improve their QoL.

38.5 Proxy Data

Communication difficulties and cognitive involvement in cerebral palsy result in increased challenge in assessing the 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. Jiang et al. [19] examined in young adults with CP QOL and the relationships between QOL, level of impairment, function, social participation, and personal factors. According to this study, these persons have good psychosocial well-being regardless of their disability (https://pubmed.ncbi.nlm.nih.gov/?term=%22Disabil+Health+J%22%5Bjour%5D&sort=date&sort_order=desc). Data has suggested that proxy-reported quality of life for children with cerebral palsy is related to parental psychosocial distress [20]. Parental distress has been found to be negatively correlated with the domains of parent proxy-reported QoL. There may also be lower scoring in domains related to social support and higher rating in psychological domains when parent proxy is compared to health professionals.

Whenever *possible* data is collected directly from the individual, they are the persons 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.

38.6 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 holds 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.

38.7 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 that 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. In a systematic review article [30] in children and adolescents with CP, physical QoL is, invariably, more affected in those with cerebral palsy. The *connection* between CP and psychosocial QoL is less clear, and in the QoL assessment of children with CP, they conclude that QoL of children with CP should extend beyond functional abilities and include less obvious, but critical, psychological and social issues. According to Rapp et al. [31], psychological problems and parenting stress in childhood and their worsening from childhood to adolescence predicted a lower QoL. Also, contemporaneous pain predicted lower adolescent QoL. In another article [32], the essential *comorbidities* associ-

ated with cerebral palsy are pain, intellectual problems, gait disorders, speech problems, epilepsy, incontinence, vision impairment, hearing impairment, and cognitive impairment (see Chaps. 12, 15, 16, 31, and 33).

38.8 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 the assessment and provision of care. It is often the most important outcome of treatment for *chronic* conditions [33–35]. A recent review publication [36] highlights the dearth in studies using preference-based outcome measures and the health-related quality of life in children and adolescents with CP. 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 are 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 [37].

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). 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 [35, 36, 38].

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. Alazem et al. [39] developed a *robot* for QoL therapy for patients with CP. A robotic walker with a built-in mechanical lift is available for individuals with cerebral palsy. This study was able to gather *important* information and recommendations to tailor a new robotic walker prototype specifically for individuals with cerebral palsy. In management program in children with bilateral spastic cerebral palsy, the hippotherapy has beneficial effects from intensified physiotherapy programs [40].

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39 Young Adults with Cerebral Palsy and Their Transition 'To and Through' the Healthcare Environments of Young Adulthood

Stacey Cleary, Carlee Holmes, Evelyn Culnane, and Christine Imms

Abstract

Moving into and through *young* adulthood is a significant life stage, encompassing substantial changes to a young person's social world; the environments they live, learn, and work within; and the *roles* and *responsibilities* that they hold. For young people with cerebral palsy (CP), there is added complexity in this life stage. In this chapter, we discuss (1) healthcare management and participation across young adulthood for young people with CP; (2) transition of young people with CP into the adult healthcare system, including key elements for the success of this process; and (3) support for young people and their healthcare participation during young adulthood. The *chapter* concludes with practical recommendations for action to ensure that young people with CP receive the supports they require to participate as they would like, in *healthcare* and *disability* settings, during their transition to and through young adulthood.

Keywords

Cerebral palsy · Adulthood · Transition · Healthcare · Participation

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39.1 Introduction

39.1.1 Why Is the Transition 'To and Through' Young Adulthood Important for Young People with Cerebral Palsy?

Moving into and through *young adulthood* is a significant life stage, encompassing substantial

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changes to a young person's social world; the environments they live, learn, and work within; and the roles and responsibilities that they hold [1]. For *young* people with cerebral palsy (CP), there is added complexity to this life stage, where complexity *refers* to the amassed biological, psychological, social, and environmental factors that influence health and well-being [2]. For *them*, negotiating their learning, vocational and social futures, and supports can occur within a maze of services, often within the less structured and protective environments that schools once held, and perhaps with less space and opportunity for parental and family involvement. Young *adults* with CP must also transfer from paediatric to adult healthcare services and learn to navigate these new and complex systems.

Young adults with CP state that their need for support in young adulthood is broad, is dependent on their interests, and will vary across this life stage and across key life situations. Support required across this life stage may be best considered as that required while young people move 'to and through' young adulthood. '*To* and *through*' incorporates language of a life course approach, encouraging health professionals, educators, and other service providers working with young people with CP to view this period as an opportunity to harness support for young adults in the *context* of their whole life and *understand* that appropriate supports for young adulthood likely look different, and serve a different purpose, to those provided in paediatric systems [3].

The evidence described within this chapter is *based* on the findings of a scoping review synthesising research on the experiences and perceptions of participation of young adults with CP, *across* the key life situations of young adulthood [4]. The *key life* situations of young adulthood were defined as healthcare, home life, education, fitness for life, relationships and friendships, employment, and community participation (Fig. 39.1). Publications included in the scoping review were from 2001 onwards, when the International Classification of Functioning, Disability and Health (ICF) [5] was published. Information for this chapter is therefore drawn from contemporary work that explored the experiences and perceptions of attendance and involvement for young people with CP. The *information* in this chapter has been presented in relation to the family of participation-related constructs (fPRCs) [6], distinguishing elements of the person and environment that contribute to attendance and involvement in activities or situations.

Young people with CP want to participate in all key life situations of young adulthood, alongside their peers. They call for *opportunities* to learn and practice, to grow their autonomy, to explore, to exercise choice, and importantly to be included and belong. While *all key* life situations are important, the focus of this chapter is the participation of young adults with CP in the management of their health (life areas of healthcare and fitness for life) across young adulthood. Healthcare and fitness for life are not, however, separate from the other key

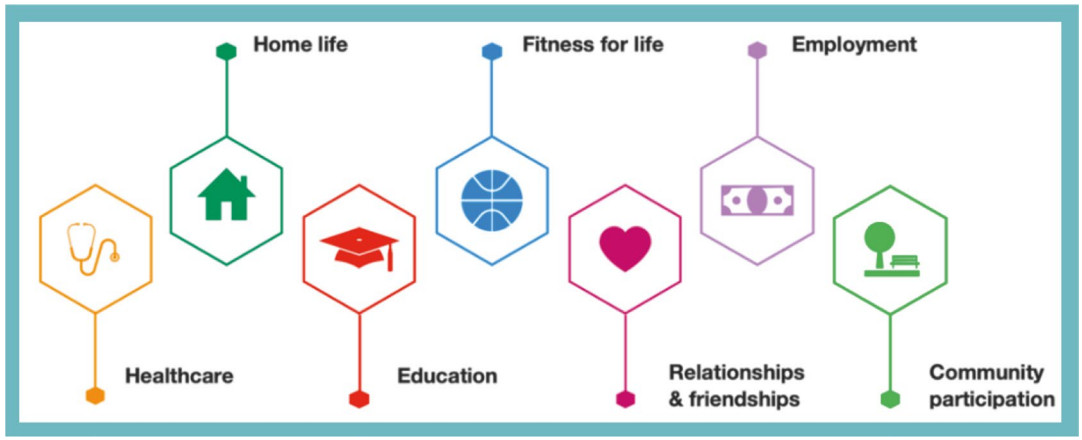


Fig. 39.1 The key life situations of young adulthood for people with cerebral palsy

life situations, but are reciprocally related, with health outcomes and participation experiences influencing other aspects of life.

This *chapter* is framed around (1) healthcare management and participation across young adulthood for young people with CP; (2) transition of young people with CP into the adult healthcare system, including key elements for the success of this process; and (3) support for young people and their healthcare participation during young adulthood. This chapter *concludes* with practical recommendations for action to ensure that young people with CP receive the supports they require to participate as they would like, in healthcare and disability settings, during their transition to and through young adulthood.

Readers should note that the literature available to inform our understanding of young adulthood in people with CP stems predominantly from high-income countries. Therefore, *generalisability* of the knowledge and perspectives to middle- and low-income countries is limited.

39.2 Health Management and Participation in Healthcare Environments During Young Adulthood

Young people with CP want to develop their *health* literacy and *increase* their participation in healthcare decision-making as they age [4] though there is limited evidence or support available on the processes that might assist them to do this [7, 8]. There is, however, an increasing evidence base for understanding the non-communicable health conditions reported as either important to or problematic for young adults with CP (Table 39.1).

Table 39.1 Prevalence of health concerns and health conditions in adults with cerebral palsy and comparisons to normative data

Health concern	Prevalence in adults with cerebral palsy % (95% CI)	Adults with cerebral palsy and normative comparison data % (95% CI)	
		Cerebral palsy	Normative comparison
Pain and mental health concerns			
Anxiety or anxiety disorders	20.7 (17.8–23.9) [9]	23.7 (22.6–24.8) [10]	15.3 [10]
Depression and mood-affective disorders	20.7 (12.1–30.8) [9]	23.4 (22.3–24.5) [10]	11.2 [10]
Pain	70 (62–78) [11]	38.6 (37.3–39.9) [10]	30.4 [10]
General medical concerns			
Asthma	24.0 (11.1–39.9) [9]	27.0 [12]	21.4 [12]
Cardiovascular disease	37.4 (36.1–38.7) [10]	37.4 (36.1–38.7) [10]	25.6 [10]
Constipation	3–28 GMFCS I–III [13] 42–82 GMFCS IV–V [13]		
Dysphagia	8–25 GMFCS I–II [13] 33–82 GMFCS III–V [13]		
Hypercholesterolaemia	14.5 (7.9–22.7) [9]	3.0[a] [12]	1.1[a] [12]
Hypertension	25.9 (22.2–29.8) [9]	11.8 [12]	3.2 [12]
Pressure injury	19–41 GMFCS IV–V [13]		
Musculoskeletal concerns			
Contracture and postural asymmetry			
Windswept hips	96 GMFCS IV–V [14]		
Hip contracture	14–100 GMFCS IV–V [14]		
Knee contracture	32–87 GMFCS IV–V [14]		
Falls (>2 in previous year)	82 [15]		
Fracture (any type)	6.3 (5.7–6.9) [10]	6.3 (5.7–6.9) [10, 16]	2.7 [10]
Spasticity	77 [17]		

[a] These data refer to hyperlipidaemia levels, a sub-category of hypercholesterolaemia

In young people with CP, these *non-communicable* health conditions typically require ongoing surveillance and/or intervention during the years of young adulthood [18]. Lifespan monitoring, using standardised assessment tools, provides a means to gather information, make decisions with young people with CP on the type and timing of interventions, and assess the efficacy of interventions. *Information* on these non-communicable health conditions is also critical to young people with CP as they seek to understand their bodies and the changes that occur as they age with CP [19, 20].

39.3 Musculoskeletal Health During Young Adulthood

As they age, young adults with CP typically experience increasing impact of musculoskeletal issues, such as spasticity, postural asymmetry, and contractures that reduce their quality of life, increase their care needs, and restrict their participation in the key life situations of adulthood [15, 21, 22]. *Musculoskeletal* issues are more prevalent in those with lower motor function (Gross Motor Function Classification System (GMFCS) Levels III–V), typically begin in childhood, are insidiously progressive, and often require the use of assistive technology as a management adjunct (see Chaps. 21 and 25). Assistive *technology* to facilitate posture and function in adults with CP—for example, orthotic devices, lying positioning supports, custom-moulded seating systems, or wheelchairs—plays a significant role in facilitating the function of young adults with CP. The need for *assistive* technology has been shown in one cross-sectional study of 16- to 29-year-olds with CP ($N = 1042$) to be 59% in sitting, 39% in lying, and 33% in standing [23].

39.4 Pain, Fatigue, Sleep, and Mental Health Concerns

Pain, fatigue, sleep issues, and symptoms of depression are highly prevalent in young adults with CP (Table 39.1), are inter-related, and negatively impact global health and participation [4, 24]. These *health concerns* are each complex and multifaceted and are poorly understood in young adults with CP. While many of the *risk factors* for pain, fatigue, sleep, or mental health conditions might be improved through lifestyle changes, intervention is complicated by the age-related musculoskeletal changes experienced by young people with CP [9] (see Chaps. 31, 37, and 38).

The *recently* revised definition for chronic pain centres on personal experience and acknowledges contextual factors as influencers of pain [25] (see Chap. 31). Importantly for young adults with more complex forms of CP, *including* those with impairments of communication and/or cognition, the definition validates the use of behaviourally based or non-verbal methods of reporting pain. Data from the Swedish Cerebral Palsy Follow-up Program reported the presence of pain in 64% of 16- to 29-year olds [17]; despite this *prevalence*, there is a lack of valid pain assessment tools for adults with CP, and even fewer for those with disorders of *communication* and/or cognition [17, 26]. A review of pain measurement tools for children and young adults with CP included recommendations for use of several outcome measures, though it is noted that further psychometric testing and development are required [26].

Similarly, *measurement* of fatigue in young people with CP is complicated by a lack of understanding of the construct itself in those with CP, heterogeneous nature of CP, components of *fatigue* (physical and cognitive), and personal contextual factors.

Qualitatively, fatigue has significant impacts on function [4] and may affect 40% of adults with CP [24]. Dutia et al. [27] reviewed self-reported fatigue measures for adults with CP and developed a decision tree for selecting assessment tools, *based* on the dimension/s of fatigue requiring assessment. At the time of *publication*, there were three options for *assessing* fatigue severity and impact that were valid and reliable. There was no *evidence* available for assessment tools intended to measure cognitive fatigue in adults with CP.

Linked to both *pain* and *fatigue*, poor sleep is also commonly reported by young people with CP [17, 28, 29]. And likewise, mental health concerns and conditions are highly prevalent in young people with CP, with at least 20% of adults with CP likely to have anxiety, depression, or a mood affective disorder [9].

Further research is conducted on these health concerns and their measurement in young people with CP. *Clinicians* working with young adults with CP must be aware of the high likelihood of pain and physical and cognitive fatigue, the experience of poor sleep, presence of mental health concerns, and the impact these will have on function and participation. *Assessments* and *interventions* need to be tailored accordingly, and as suggested by Verschuren et al. [30], the greatest benefits to health and well-being are likely to come from *comprehensively* addressing issues of physical activity, nutrition (see Chap. 36), and sleep (or rest), and, we posit, mood.

39.5 The Impact of Early Ageing and Deconditioning on Activities and Participation

An earlier onset of ageing is seen in *individuals* with CP when compared to nondisabled peers, adversely impacting physical, metabolic, and social outcomes [31, 32]. Participation in *physical* activity may reduce some of this decline, and for those with CP, the physical activity habits established during childhood and adolescence directly translate into adulthood [33]. Children and adolescents with CP, however, have lower levels of participation in physical activity than their peers, and than *guideline* recommendations [34], with barriers attributable to personal, social, environmental, and policy-related factors [35]. These barriers persist into adulthood [36], with the *cumulative* result being that patterns of physical activity that may benefit physical and cardiometabolic health, and reduce early-onset ageing, are not being established.

Part of the *experience* of early-onset ageing in CP is a decline in mobility, often beginning in a person's 20s or 30s. A fear of *falling* and *ongoing* reduction in confidence, due to progressive musculoskeletal changes and postural asymmetries, are self-described causal factors for this decline in mobility [15, 22]. Little is *currently* known about the impact of ageing on the independence of those using wheeled mobility, who may be impacted by age-related changes in their upper and lower limbs, trunk, and pelvis.

Multiple *interacting* elements across domains of the ICF *contribute* to the cycle of deconditioning, functional decline, and decreased physical activity, impacting subsequent participation in the key life situations of adulthood. While there is a small body of evidence to suggest a positive benefit of physical activity participation on fatigue and mental health in adults with CP, *little* is known about the impact on quality of life and participation [37] (Fig. 39.2).

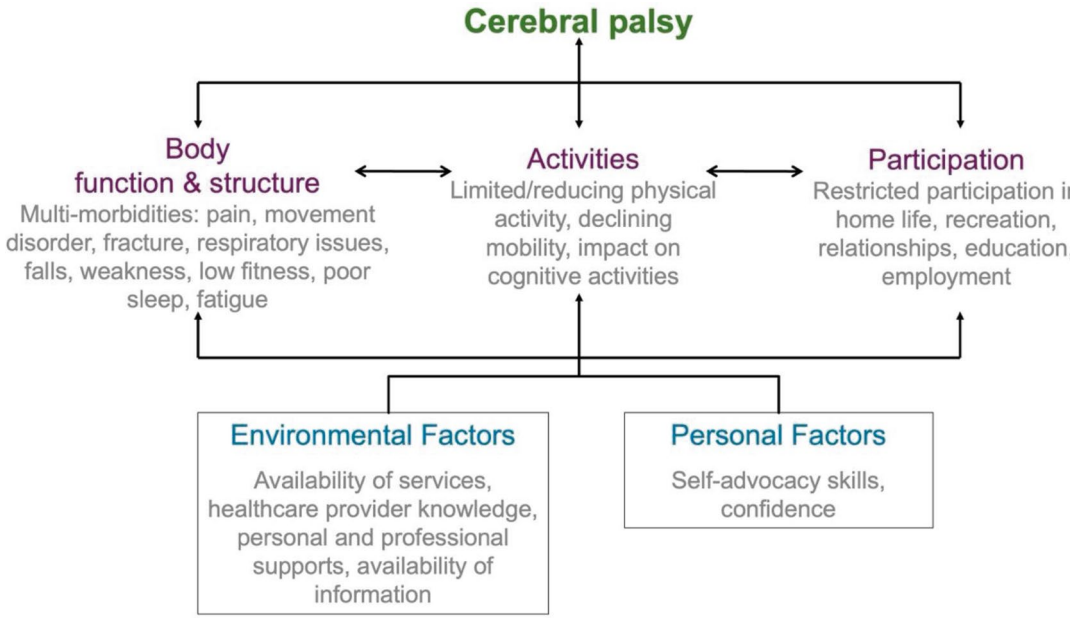


Fig. 39.2 Interacting elements, mapped using the ICF, that can contribute to functional decline

39.6 The Impact of Environment and Context

Environmental elements of healthcare and disability *services* often do not meet the needs of young people with CP and their families. At a *policy* level, health promotion and disease prevention strategies have not been inclusive of those living with a disability [38], and the prevalence of non-communicable health conditions in those with CP compared to normative data is high [18, 31]. Likewise, a *lack of services* and a lack of *screening* protocols for chronic health issues in populations with disability may be factors in high prevalence, and younger age of onset, chronic health issues, and multimorbidity seen in those with CP [39]. The *physical* environment is also often described as a barrier to accessing healthcare, with some facilities not being wheelchair accessible or not having appropriate equipment for safe transfers [40, 41].

Contextually, *healthcare* providers may not have the adult-focused CP-specific knowledge *required* to manage or monitor health conditions; young people with CP describe diagnostic overshadowing and insufficiently detailed answers as examples of this [20, 42, 43]. Young people with CP also describe professionals in the adult health and disability systems as often having negative preconceptions of disability and not providing the time or opportunities required to practice decision-making [19, 40]. These are significant barriers to the involvement of young adults with CP in their health management, and especially for those with complex disability, those who use augmented or alternative communication, and those young adults with additional diagnoses of anxiety or depression [44].

An inaccessible environment or healthcare context results in reduced attendance and involvement of young people with CP and their families. These factors may play a role in inadequate screening, a lack of timely intervention, and higher incidence of non-communicable disease in young people with CP.

39.7 Transitioning to the Adult Healthcare System

A planned and structured *transition* from paediatric to adult health services is a process that may *involve* a general practitioner (family doctor), paediatrician, relevant subspecialists, and other healthcare providers and is intended to result in seamless continued whole-of-life care. *Dedicated* transition programs may be available in some healthcare institutions. Regardless, engaging early *holistic* transition support and advice from a general practitioner and/or relevant subspecialists is recommended to assist with transition planning, coordination, and navigating adult health services.

Ideally, *transition* processes should commence during early adolescence, be well planned, and aim to foster autonomy, decision-making, self-advocacy, and self-care, alongside appropriate supports as needed by the individual. Various *guidelines* on the transition from paediatric to adult services exist, for example, those developed in the United Kingdom [45]. However, as recently *established*, adolescents with CP transitioning to adult services do not always receive support as recommended in guidelines [46]. Much can be *learnt* about the impact of a positive or negative experience from literature capturing the reflections of young people with CP and their families on the transition to adult healthcare services [47–49].

Parents and carers are integral to the transition process as their role evolves from one of '*manager*' to '*guide*', as young adults gain increased autonomy and agency. A *well-managed* healthcare transition ensures that young adults will be fully involved in transition *planning* and experience uninterrupted, supportive care with the right providers, at the right place, and at the right time. *Further*, young adults will be empowered to manage their healthcare to the best of their ability, with a sense of agency over the process, thereby *maximising* their capacity to live well and achieve their goals. For those with ongoing need for alternative decision-makers, or supported decision-making, their needs, and the *approach* best suited

to the individual, will have been collaboratively determined and carefully documented.

A general *practitioner* can play a pivotal role in the transition to adult healthcare and in the life course management of a young person with CP. This practitioner can be a long-term, trusted first contact and may provide *screening* for health concerns and timely referrals to specialists. CP-specific capacity building of general practitioners throughout the transition period will place them in a stronger position to collaborate with young people with CP and their parents or carers and to detect and manage health concerns as they arise in adulthood. *Capacity* building of general practitioners may take the form of detailed correspondence between treating specialists, paediatricians, adult healthcare providers, and the general practitioner, alongside more formal professional development and disability education. Sixteen fact sheets to guide the healthcare of people with CP are also available on the Knowledge Hub of the International Alliance of Academies of Childhood Disability [50].

39.8 Supporting the Participation of Young Adults with CP Through the Adult Healthcare System

Young adults with CP are *typically* experienced with healthcare systems, providers, and multidisciplinary professionals. Their paediatric *experiences*, alongside the situations they experience while entering and learning to navigate adult health and disability systems, form a strong foundation for their preferences for healthcare in adulthood (see Fig. 39.3). While the goal of many young people with CP is increased autonomy for health-related decision-making, this *process*

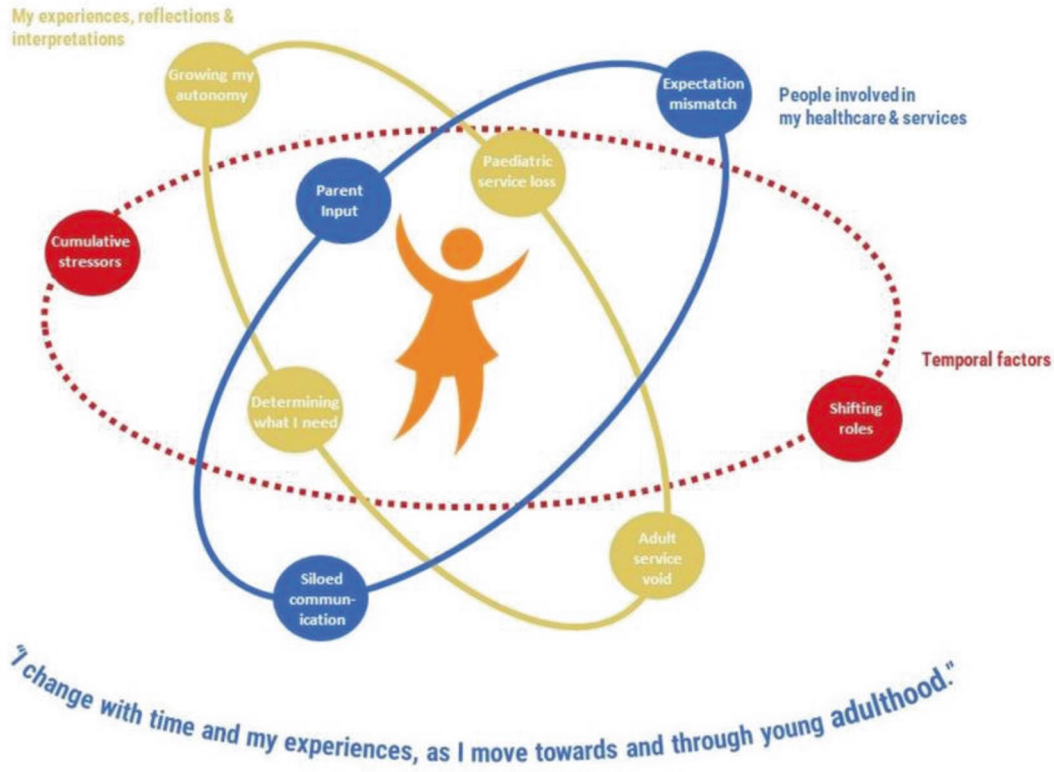


Fig. 39.3 The development of preferences for healthcare and disability service settings for young people with cerebral palsy. (Figure structured according to Green, in Imms & Green, 2020, Chapter 4, p 41–45. From Cleary et al. 2024)

requires time and trust. *Notably*, adults with CP have typically experienced a range of medical procedures, and while these may have increased their familiarity with the healthcare system, an additional outcome may be an increased anxiety of healthcare and disability systems and settings.

Young people with CP report their involvement in adult healthcare and disability service settings as frustrating, disappointing, and, in many cases, insufficient (Fig. 39.4) [4]. As described by one young adult with CP, it is the 'dichotomy of being expected to know everything, but being treated like you know nothing at all'.

Further *research*, lobbying, and policy change are required to address some of the barriers to young people with CP participating as they wish in healthcare settings, for example, insufficient services and burdensome systems. However, in the *shorter term*, there are elements of the healthcare environment and context that can be modified more simply and that may vastly improve the participation experiences for young people with CP and their families.

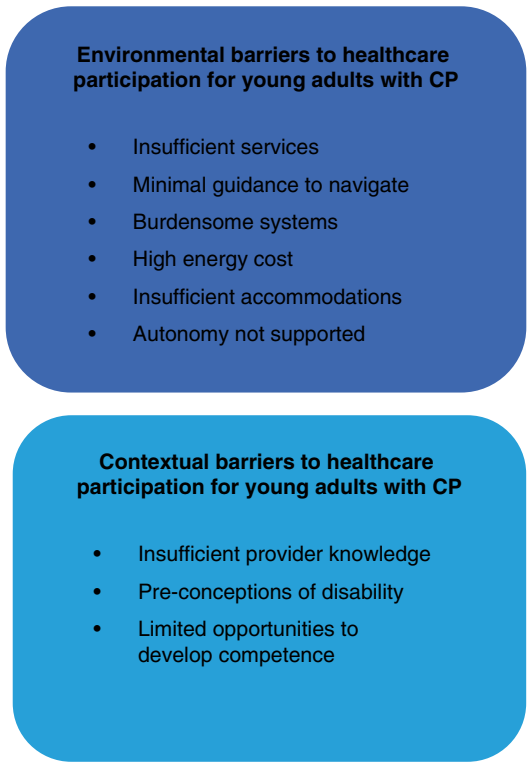


Fig. 39.4 Environmental and contextual barriers to healthcare participation for young adults with cerebral palsy (Cleary et al. 2024)

39.9 Recommendations to Improve the Contexts of Participation

Tailored capacity building of *service* providers, healthcare professionals, and young people with CP and their families is critical to addressing the barriers that impede participation. Young people with CP and their families need to be meaningfully engaged in the development of these processes, including any system assessments or design of resources.

1. **Service providers, ask these questions of your service**
   - What structures (physical, administrative, financial) are needed to make your adult healthcare available, accessible, affordable, and accommodating for young people with CP?
   - Which other services could we share knowledge with, to increase equity more broadly?
2. **Healthcare professionals, ask these questions of yourself**
   - How can I improve my knowledge and understanding of CP in adulthood?
   - How am I challenging my preconceptions and attitudes of disability and working to change them?
   - How can I give opportunities and support young adults with CP to develop their health literacy?
   - Have I checked in with young adults on their pain, fatigue, physical activity, and mood?
3. **Young people with CP and their families**

   Alongside modifications to the environment (service providers) and context (healthcare professionals), young people with CP and their families may also benefit from high-quality, CP-specific resources and training on health literacy and 'ageing with CP' topics.

With this *multi-faced* approach, there is the potential for healthcare participation to be improved and for young people with CP to experience involvement in healthcare environments: and in their health management, in line with their preferences for respect, informed choice, and collaboration.

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Orthopaedic Care in Adults with Cerebral Palsy

40

Christina Herrero and M. Wade Shrader

Abstract

The overall prevalence of cerebral palsy (CP) in society is increasing due to increased survival of preterm infants as well as *increased* survivorship into adulthood. As the number of adults with CP rises, so does the need to address the growing number of problems they face and to improve their quality of care. This *chapter* provides a summary of the *multifactorial* challenges these patients face and the most common lower extremity pathologies seen along with surgical and nonsurgical treatment options.

Keywords

Adult · Transition · Cerebral palsy · Cervical stenosis

40.1 Introduction/Epidemiology

In the developed world, annual incidence of cerebral palsy (CP) is 3–4 per 1000 live births. The *annual* incidence in the USA is estimated to be 8000–10,000 new cases [1]. The overall prevalence in society is *increasing* due to increased survival of preterm infants as well as increased survivorship into adulthood. We also know that the survival of adults is quite good; a 2006 report from the UK followed a cohort of CP patients born between 1940 and 1960 and demonstrated that nearly 90% of those alive at age 20 years survived to age 50 years [2]. The exact number of US patients with CP is unknown, *estimated* between 700,000 and one million. A report from the Canadian Government found that by 2031, the number of CP adults over the age of 65 will triple [3]. As the number of adults with CP rises, so does the need to address the growing number of problems they face. These challenges *include* premature ageing, chronic pain, indirect consequences of the disability itself, and *secondary* health conditions they are at greater risk for [4]. Many patients living with CP report feeling (a) deserted by their health professionals when they are discharged from paediatric services and (b) struggle to access appropriate continuity of care when they begin experiencing declines in health and function as early as young adulthood [4, 5].

The *primary* impairments these patients face include abnormal muscle tone, loss of selective muscle control, impaired coordination and balance, weakness, and loss of sensation. From an orthopaedic perspective, the *interplay* between the consequences of the primary CNS problems and the effects of growth and time along with developmental delays affects one's bones,

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muscles, and joints. Bony *manifestations* include femoral anteversion, external tibial torsion, and hip dysplasia; muscle manifestations include dynamic and fixed contractures and co-contractions; and joint manifestations include contractures, instability, and arthritis. The lack of full weight bearing in activities of daily living may lead to progressive contractures. Furthermore, the increased tone, contractures, and increased *body mass index* (BMI) can then lead to increased loads across joints with subsequent arthritis and pain. What to do once we reach these points is not well documented in the literature. What specific *surgeries* should be performed? Should paediatric or adult orthopaedic surgeons be performing them? Should they occur in paediatric or adult hospitals? These are all *questions* that we need evidence-based research to improve our care.

In *addition* to their disability-specific age-related challenges, it is also important not to ignore the typical problems of ageing. Adults with CP are at greater risk for cervical *spondylosis* due to progressive weakness secondary to athetoid movements of the neck. Their declining mobility may be *primarily* neurologic, arthritic, or multifactorial. This paired with decreased endurance further inhibits their independence. They also experience the typical wear and tear of joints affecting the spine, hip, and feet. The *muscle wasting* of ageing, sarcopenia, may affect them at great rates depending on their baseline muscle anatomy (see Chap. 21). Adding another *complication*, they often have poor soft tissue coverage, which can lead to skin ulcers and shear injuries.

A more intangible *comorbidity*—pain—has more recently been recognized as one of the most important factors negatively affecting the quality of life in patients with CP [6]. Though many patients endorse *pain*, there is a disconnect with the consistency of screening, identifying, and treating it from a physician's perspective (see Chap. 31).

In a study from Fehlings, 55% of children with CP screened had pain in the previous 2 weeks; however, 24% were identified as having moderate-to-severe pain that restricted daily activities [6]. There are a variety of available *interventions* for chronic pain in the CP population, though the follow-up research on the objectiveness is varied. Interventions include spasticity management (Botox, baclofen, valium) (see Chaps. 24, 27, and 28), multimodal pharmaceutical regimens, massage, chiropractic therapy, wheelchair and equipment modifications and enhancements, and improved patient positioning and support. As Fehlings states, *pain screening* is an important first step. But let us ensure that the field moves on to enhance the evidence base around prevention and management of pain in CP [6].

Further compounding on these obstacles are the financial and logistics challenges of transition of care and maintenance of care. Shrader et al. [7] had 85 adult CP patients fill out a variety of patient-*reported* outcomes on their quality of life. They found high rates of unemployment, caretaker need, and Social Security Disability Insurance utilization. This further *emphasizes* the need to better target social resources for adults with disabilities to *allow* equitable access to employment, promote opportunities for independence, and enable full participation in community life [7]. Koop et al. [8] performed a literature review and found the overarching theme that transition to adult care "*lacks*" the informed, collaborative multidisciplinary care they received as children. This can lead to unmet healthcare needs and a shortage of long-term natural history and outcome studies that would inform the care of children today [8]. The number of these patients is not decreasing nor are the medical or socioeconomic problems they face. As *physicians*, as advocates for our patients, it is our duty to improve the care we provide to our adult CP population, improving not just their health, but their quality of life.

40.2 Spine

Spine pathology in the CP population has the *greatest* effect on a patient's longevity. Though scoliosis may be the first spinal pathology that comes to mind, CP patients also experience dys-

tonia, cervical stenosis, and lumbar stenosis, all of which come with their own set of challenges and complications. Willoughby et al. [9] performed a population-based study in 2022 of CP patients who had reached skeletal maturity to ascertain the prevalence of scoliosis in CP. They found a Cobb angle >10 in 41% of patients. Patients at GMFCS V were 23.4 times more likely than those at GMFCS I, and severe curves (>40°) were almost exclusively seen in patients at GMFCS IV and V [9]. We also know that *scoliosis* in CP progresses at a higher rate compared to idiopathic scoliosis and continues to progress past skeletal maturity [10]. In the *nonambulatory* adult population, curves can progress 3–4.4 degrees per year. In *addition*, more severe curves (>50°) progress faster than smaller ones [11].

Initially, you can try *non*operative management including a TLSO, wheelchair modifications, and PT. The pelvic obliquity associated with scoliosis can make seating progressively more difficult. The *indications* when to discuss surgical intervention *include* curves greater than 50°, curves rapidly progressing, patients approaching 25 years of age (after which there are more complications), issues with seating, ischial decubitus, thoracic-pelvic impingement and pain, and progression of restrictive lung disease. The *goals* of posterior spinal fusion for CP patients are as follows: straighten the spine (balance the spine and trunk), lower the risk of progression, allow for easier sitting and positioning, relieve pain, lessen *complications* (decubiti, lung disease, etc.), and improve quality of life. Though families and patients often have been concerned about increased risks of complications from surgeries, there is a wealth of literature confirming the significant benefits of surgery. In 2018, the HARMS group published CPCHILD scores indicating improved personal care, positioning, and comfort domains over 5 years following surgery [12]. Watanabe in 2009 [13] reported 92% satisfaction rate out of 82 patients who underwent PSF, along with better seating in 92% and 71% increase in quality of life. Tsirikos et al. [14] updated their cohort in 2008 to 287 patients and reported that 96% of caretakers were satisfied with surgery. This is not to say that there are no complications; Yaszay et al. [15] reported a 1% perioperative mortality rate. These are important conversations to have with the families before moving forward with surgery but should not deter them from this intervention that can significantly improve the patient's quality of life.

For some CP patients, movement disorders *including* athetosis and dystonia increase the risk of cervical problems (see Chap. 12). Overactive muscles can lead to disc herniations, spondylosis, malalignment, instability, or a combination of these issues requiring operative interventions. For *these* patients, serial neurologic exams and MRIs every other year should occur to maximize early intervention for problems [16] (Fig. 40.1). Any *myelopathic* or *radicular* symptoms should alert physicians to obtain advanced imaging and be aggressive in care as there is a significant amount of instability and stenosis, and diagnosis may be more difficult due to challenges extracting specific complaints from patients [17]. Lastly, there is an increased prevalence of spondylosis,



Fig. 40.1 Cervical spine MRI

20% of patients at GMFCS I–III, whereas it is 6% in the general population [18]. Rates may even be high in those that have undergone selective dorsal rhizotomy [19]. Some may respond to conservative management, but for those advancing towards spondylolisthesis, surgery is often required. When making plans for management of adult CP spinal pathology, it is important to ask: Who is doing these procedures (paediatric or adult surgeons, or operating together)? Where are the surgeries occurring (paediatric or *adult* hospitals)? What are the best critical care teams—adult or paediatric—to manage these patients post-operatively?

40.3 Hips

Although early *intervention* for hip pathology can drastically alter the trajectory of the disease, many CP patients continue to have hip problems that have been missed, undertreated, or progressed despite intervention. Hip *dysplasia* has an overall prevalence of 35%, but increases with GMFCS, ranging from 10 to 90%, and is more common in GMFCS IV and V [20] (see Chap. 22). In our *adult population*, we are considering hip reconstructions (femoral ± pelvic osteotomy, tendon lengthening), hip replacements, and salvage procedures. Young age at the time of intervention and severe displacement are risk factors for recurrence and poorer outcomes.

The natural *progression* of these hips due to the abnormal forces on the femoral head, accelerated cartilage degeneration, and degenerative joint pain ultimately lead to severe arthritis, pain, and sometimes frank dislocation. These untreated hips cause significant morbidity and pain for patients (Fig. 40.2). In 2001, Hodgkinson et al. [21] evaluated 234 nonambulatory CP patients and found that 47.2% reported hip pain. Ramstad et al. interviewed 67 patients in a population-based registry and found 25% hip displacement prevalence that correlated with lower CPCHILD scores [22].

Total hip *replacements* (THRs) in the neuroatypical population have significantly more challenges and pitfalls. A few of these include severe dysplasia that may make acetabular *implantation* technically difficult; some femurs, e.g. particularly in nonambulatory patients, may be too narrow for implants; *osteopenia* increases the risk of loosening and fracture; and muscle tone, such as spasticity and contractures, can increase instability and risk of dislocation. Raphael et al. [23] published the largest series in literature, including 59 hips, and found complete relief in 81%, with a 15% revision rate and 14% dislocation rate. Gabos et al. [24] published a unique type of THA—a shoulder prosthesis interpositional arthroplasty. All had undergone original salvage procedures but had recurrent pain. The *smaller* implant size made implantation easier, and 91% of (10/11) caregivers would recommend the surgery.



Fig. 40.2 Degenerative hip

Salvage *procedures* are less predictable than reconstruction. They are an appropriate mode when there is severe *femoral* head deformity, a high dislocation with severe acetabular dysplasia, or significant medically fragility. The two main *types* of proximal femoral resection (PFR) are a Castle and a McHale. A *Castle* is a proximal fem-

oral resection, interposition arthroplasty. It consists of the proximal femoral resection below the lesser trochanter with interposition of the abductors sewn over the acetabulum and the vastus lateralis over femur. A *McHale* consists of the removal of femoral head, combined with a valgus proximal femoral osteotomy. This *moves* the proximal femur laterally away from impingement. Lastly, hip arthrodesis is mainly a historical procedure. *Complications* for the two salvage procedures are similar, with proximal migration and heterotopic ossification (HO) being the most common problems. Patel et al. reported on outcomes of PFRs with modern perioperative pain and tone management, and 20% at GMFCS IV and V found pain significantly improved, seating improved in all patients, perineal care was easier in 75%, and only 1 required a revision for proximal femoral migration [25]. An even larger PFR series of 79 PFR reported that 90% were either pain free or had mild pain, and seating and hygiene improved in 94%. They did report 20% HO and a 20% complication rate [26].

There have been a few systemic reviews comparing the different surgical options for severe hip pathology in adult CP patients. Boldingh et al. reported on eight studies focusing on palliative hip surgery in patients with severe CP comparing Castle, McHale, THR, and arthrodesis [27]. They *concluded* that there was not much difference between outcomes, and they preferred the Castle procedure. Kolman et al. reported on 28 studies comparing salvage options. They cited high complication rates in arthrodesis and THR. They were unable to recommend a difference between the Castle and McHale, but again the Castle had the fewest complications [28].

Again, when *discussing* how to care for hip pathology in our CP adult patients, we ask: Who is doing these procedures (paediatric orthopaedics or recon specialists)? For THR and salvage surgeries, should they occur in adult or paediatric hospitals? For THR, it is important to think about implant and backup implant/instrument availability (cables, cerclage wires, revision sets, augments, etc.). *Lastly*, should paediatric or adult hospitalists and critical care teams be managing these patients?

40.4 Knees

There are a variety of gait pathologies based on *abnormalities* of the knee *including* jump gait, crouch gait, stiff knee gait, and a recurvatum gait. ***Jump* gait** consists of increased hip and knee flexion and increased ankle plantar flexion. If the focus is just on the increased ankle plantar flexion and the gastrocsoleus complex is overlengthened, crouch gait is iatrogenically created. ***Crouch gait*,** the most common gait, includes increased hip and knee flexion and ankle dorsiflexion. Once it is *iatrogenically* induced, it is very challenging and heavily energy consuming for patients to maintain their ambulatory independence. Stiff knee gait includes knee stiffness during swing phase, which makes foot clearance challenging. Some of the compensatory mechanisms *include* hip circumduction, external rotation of the limb, and contralateral vaulting. When a dynamic cause, this can be addressed with either a rectus transfer or a recession [29]. Recurvatum gait, also often *iatrogenically* created, is quite difficult to treat and due to the deformity and instability at the knee requires long leg bracing, usually a KAFO with the ankle positioned in dorsiflexion.

For paediatric CP patients, knee flexion *contractures* (KFCs) can be treated with therapy, anterior distal femur-guided growth, and hamstring lengthenings. Soft tissue *procedures* around the knee-hamstring lengthenings and rectus procedures are less predictable in the adult population.

In addition, most *deformities* progress past inclusion criteria for these procedures. Once a KFC is greater than 30, KAFOs are not sufficient and patients require distal femoral extension osteotomies, usually with additional procedures to address the patella alta. The *patella alta* can create significant pain, and commonly during DFEOS, significant arthritic changes are seen at the patellofemoral (PF) articulation. In addition to soft tissue realignment, other treatment options include tibial tubercle transfers, PF allograft, and PF joint replacements.

In *addition* to these sagittal abnormalities, there is an axial component of deformity further

complicating things, creating the "lever arm syndrome". This is a culmination of increased femoral anteversion, increased internal or external tibial torsion, "*miserable malalignment*" syndrome, patellar subluxation or dislocation, and foot valgus. These factors make it significantly more taxing for patients to exert energy and walk and usually contribute to a crouch gait pattern. *Treatment* can include proximal or distal femoral osteotomies, tibial derotational osteotomies, and correction of valgus in the foot. These can be grouped together in a single event multi-level surgery (SEMLS).

SEMLS consists of muscle *lengthening* and transfers and correction of all bony deformities in a single surgical session. Benefits include a single rehabilitative period, minimal immobilization, and decreased rate of recurrence of deformities. One of the first reviews in the literature of SEMLS was performed by Saraph et al.in 2002. They reviewed 25 ambulatory patients, who underwent a mean of 8.2 procedures each and found improvements in kinematic, kinetics, power analysis, ROM, and gait [30]. In *addition* to patient satisfaction, parents and caregivers are significantly happier with SEMLS procedures. Lee et al. published a review of 279 patients who underwent SEMLS procedures with high parental satisfaction, specifically that they were happy to leave behind the "birthday syndrome" of surgery every year [31]. With the magnitude of surgery performed, it is critical that the patients and caregivers understand the trajectory of recovery and improvement. Willoughby et al. [9] performed a prospective cohort study of patients with spastic diplegic CP who underwent either SEMLS + PT or standard PT. Though deformity correction was immediate, gross motor function initially deteriorated after surgery, returned to baseline by 12 months, and was better than baseline by 24 months. GMFCS was stable itself after surgery. *Rehabilitation* throughout this postoperative journey is essential to allow these advancements to happen. There are some concerns that SEMLS has fewer clear outcomes for the adult CP population.

Gannotti et al. [32] followed 23 young adults after SEMLS procedures and found that only 1 patient declined ambulatory status, while the rest maintained their status or improved. With this knowledge, it is important to inform patients that outcomes may not be as universally positive as they are for children, rehab may take longer, and if they had SEMLS as a child, they may have worse outcomes [33].

40.5 Foot and Ankle

The most common lower extremity *orthopaedic* manifestations are in the foot and ankle. It is critical to understand the natural progression of foot deformity as children will be at different GMFCS as they age [34]. Equinovarus can progress over time to *planovalgus*, so selecting management (nonoperative or more invasive) at the correct age is important to not iatrogenically accelerate the progression. The *main components* of foot deformities consist of equinus, calcaneus, varus or valgus, and bunions. Like paediatric equinus management, there is a spectrum of surgical dosing including strayer, baker, vulpius, and TAL [35]. A *calcaneus* deformity is usually iatrogenically created. For initial treatment, a floor reaction orthosis helps with *knee stabilization*, maintaining a posterior fulcrum and body weight through the heel.

When this is not *sufficient*, multiple muscle *transfers* to the heel (tibialis anterior (TA), tibialis posterior (PT), peroneus longus or brevis (PL or PB), flexor hallucis or digitorum longus (FHL or FDL)), heel cord tenodesis, and/or calcaneal osteotomies are options. *Varus foot* deformities, more common in hemiplegics, can be treated with a variety of surgeries including PT frost lengthening, split PT tendon transfer, split TA tendon transfer, hindfoot/midfoot osteotomies, or triple arthrodesis. One of the more effective osteotomies includes a closing varus wedge and medial *slide osteotomy* of the calcaneus, which restores the line of weight bearing through the calcaneus. On the other hand, *valgus foot* deformities are more common in diplegics and quadriplegics. Surgical *treatment* options include PB tendon lengthening, calcaneal lengthening, subtalar arthrodesis, talonavicular arthrodesis, and again triple arthrodesis (through here it would include a

plantar lateral closing wedge for multiplanar correction). *Lastly*, there are bunions. Dorsal *bunions* often present with hallux valgus deformities. In CP patients, soft tissue transfers are not as reliable, so we tend towards fusion for definitive stability. Again, when *strategically* planning surgical fixation for foot and ankle deformities in adult patients with CP, we are faced with the questions: Who should do these adult procedures? Where should they be done? Who oversees coordinating the perioperative care? Who does the intensive rehab after? (See Table 40.1.)

Table 40.1 Orthopaedic care in adult diagnosis and treatment

	Adult diagnosis	Treatment
Spine	Dystonia	Medical management
	Cervical stenosis	PSF ± anterior
	Lumbar stenosis	Laminectomy and fusion
	Scoliosis	PSF often to pelvis
Hip	Hip dysplasia	McHale, Castle
	Degenerative joint disease	THR
Knee	Knee flexion contractures	DFEO
		SEMLS
Foot/ankle	Equinus	Strayer Baker Vulpius TAL
	Calcaneus	Muscle transfers to heel Heel cord tenodesis Calcaneal osteotomies
	Varus	PT frost lengthening Hindfoot/midfoot osteotomies Triple arthrodesis
	Valgus	PB tendon lengthening Calcaneal lengthening Subtalar arthrodesis Talonavicular arthrodesis Triple arthrodesis
	Bunions	Joint fusion

40.6 Term Follow-Up: Gait and PROMIS

Recently, the *multidisciplinary* CP team at Nemours Children's Health published an article exploring the long-term outcomes of conservative and surgical treatment during childhood on adults with CP [36]. They used a combination of gait analysis and patient-reported outcomes to objectively and subjectively evaluate 120 ambulatory adult CP patients (*ages 25–45*) who had undergone multi-level surgeries and other "standards of treatment" during their paediatric and adolescent care periods. The follow-up evaluations of these patients included comprehensive chart reviews, physical exams, PROMIS questionnaires, and gait analysis. From the ***PROS*****,** they found that physical function was significantly lower in the full study group and in groups classified as GMFCS II and III, and 4.32% of patients reported a moderate to great extent of chronic pain, and 38.2% reported an extent of joint/muscle pain. Regarding *gait characteristics*, there were no clinically meaningful changes from adolescence to adulthood. There were several *statistically* significant differences that were not clinically significant including gait velocity and kinematic motion of the hip, knee, and ankle. Other statistically significant changes included hip rotation, hip extension max in stance, knee extension max in stance, ankle dorsiflexion max in stance, foot progression angle, and hip *power* generation.

Upon further *analysis*, when compared with the MCID, 40% of adults with CP decreased in gait velocity, 41% decreased in GMFM-D, and 26% decreased in GDI, while 37% improved in gait velocity, 40% improved in GMFM-D, and 44% improved in GDI. Overall *adolescent* function predicted adult function. The *adolescent* gait velocity predicted 61.3% of variation in adult gait velocity, adolescent GMFM predicted 82% of the variation in adult GMFM, and adolescent GDI predicted 47% of the variation in adult GDI.

The *overall stability* of the gait and gross motor function is more aligned with the findings of Gannotti et al. compared to others who have referenced broader declines with age. This may be *attributed* to the fact that our sample had special-

ized orthopaedic care in childhood in addition to coordinated multidisciplinary teams. There was variability among individuals, and there was more severe neurologic involvement, represented by GMFCS, correlated to decline in GMFM and gait. This is also consistent with the literature [37].

Interestingly, the *study* showed similar amount of pain interference, depression, and satisfaction with participation, compared to the general population. One *theory* is that growing up with a childhood disability promotes good coping skills and resiliency in adulthood. There were several more thought-provoking *findings* in this study that call for further research to understand the relevance and applicability of the findings, so that we can use this to *improve* the early care provided to children with CP and better tailor our adult care.

40.7 Conclusion

The rate of literature on care for the adult CP population lags in comparison to the increasing rates in the general population. The *advancements* and *concerted* efforts to improve care for our CP adults further lag, and we see the negative effects of this in the inability of many of these patients to reach their full potential as active members in society. This *chapter* provides a summary of the *multifactorial* challenges these patients face and the most common lower extremity pathologies seen along with treatment options. Through our research on the *long-term* effects of standardized, comprehensive care for children with CP, we hope to motivate others to critically look at what have we been doing right, what can we do better, and *what* can we introduce to the care of our CP population that we have yet to consider.

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Rehabilitation Principles of Adults with Cerebral Palsy

41

Mintaze Kerem Günel, Cemil Özal, and Yeşim Sücüllü Karadağ

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 individuals with CP to participate in 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. *Physiotherapy* and *rehabilitation* programs in CP vary based on the individual's age and functional status. The physiotherapy, rehabilitation, and terms of physical and motor functions are reviewed in this chapter.

Keywords

Cerebral palsy · Adult · Physiotherapy · Rehabilitation · Motor function

41.1 Introduction

The popular Turkish saying "*Whoever is born grows*" reflects the hopes 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). Although *frequently* regarded as a pediatric disorder, today, the majority of individuals with CP are adults [1]; *additionally*, with the improvements of medical care, survival rate and life expectancy of adults with CP have increased, and by that development, adults with CP are now considered as one of the world's largest populations with a physical impairment [2]. Today, *majority* of children with CP reach adulthood; on the other hand, adulthood and aging with CP bring about various health and functional challenges, leading to an increased focus on adults with CP in rehabilitation practices [3].

The *limitations* associated with CP persist from childhood through the elderly years. The transitional periods from childhood to adoles-

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cence 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 control; skeletal deformities due to the adverse effect of gravity; and hypertonia and dystonia all might further limit ambulation and physical independence over time [4]. While most individuals easily adapt to the physiological growth of their body during transition to adulthood, this poses many additional problems and barriers for individuals with CP which physicians and physiotherapists treating CP patients have to address [1–4]. Individuals with CP in *adulthood* also need specific management: their condition amplifies the physiological and psychological results of aging, often causing "*premature aging*" which tends to have a quicker decline in mobility and walking skills as compared with otherwise healthy population, and with aging many adults with CP are in danger of several health problems including osteoarthritis, myelopathy, 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 [1, 4, 5]. 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 children 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.

41.2 Cerebral Palsy and Age

Many people with CP survive well into adulthood, and it is reported that survival to 58 years is similar to that of the general population in 22% of individuals with CP and mild impairment. Further, early childhood mortality has decreased for those with severe CP since 1990; shifting to adulthood. Therefore, rehabilitation needs for adults with CP have increased considerably in the last decades [3]. Physicians and *physiotherapists* should be aware of changes in mobility, strength, and endurance to be expected during the maturation process of individuals 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 [4]. Significant *deterioration* in the mobility was reported in majority of adults with CP [6]. 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. *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. The presence of sensory and cognitive problems increases the severity of limitations [5].

41.3 Adults with Cerebral Palsy and the International Classification of Functioning, Disability and Health: ICF Perspective

Adults with CP exhibit a wide range of functional *features* and *disabilities* related to participation, activities, and bodily functions. A person's degree of functioning is influenced by a variety of factors, including issues with motor function, intellectual disability, and environmental factors that have become a major focus on clinical practice.

The International Classification of Functioning, Disability and Health (ICF) also makes it easier to comprehend *disability* and *functioning* overall. It breaks down disability and functioning into components, such as body functions, body structures, and activities and

participation, while contextual factors explain environmental factors, personal factors, and activities and participation. It is based on a thorough *biopsychosocial* model of functioning and may be used in clinical rehabilitation practice to help with goal setting and intervention planning in adults with CP. In total, the ICF model contains over 1400 categories, which makes its implementation in clinical practice and research challenging; therefore, to address this challenge, ICF Core Set, which includes the ICF categories that are most relevant for describing functioning of adults with CP, has been developed [7].

Adults with CP experience activity limitation and difficulty in participation, which are increased with aging. In addition, young adults with CP are less often employed or live independently less than young adults without CP [8]. A recent population-based study found that, from an ICF viewpoint, 79–90% of the diversity in early adult participation in domestic life and interpersonal relationship of individuals with CP may be attributed to childhood experiences (Table 41.1). Young adults with limited manual abilities and restricted motor function may encounter activity limitations as they transition into adulthood. *Additionally*, there was a substantial correlation between engagement in this age group and manual competence, communication, social functioning, and mobility. *Therefore*, concentrating intervention on these skills at an earlier age could promote involvement in later adolescents and transitions into adulthood, given that the predictors of participation were communication, social function, manual ability, and mobility [9].

41.4 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. Although the majority of adults with CP, who are without intellectual disability, are ambulatory (58% overall), an average 35-year-old adult with CP begins

Table 41.1 ICF framework for adults with CP (*created by authors: Mintaze Kerem Günel, Cemil Özal)

Adults with cerebral palsy*		
ICF domains		
Body functions and structure impairments	**Activity limitations**	**Participation limitations**
Premature aging	Mobility reduction	Decreased social participation
Mental health problems (anxiety, depression)	Decrease of physical activity and fitness	Decline in self-care
Musculoskeletal and postural deformities and degenerations	Communication problems	Unemployment and educational problems
Muscle tone and voluntary movements problems	Dexterity reduction of manual abilities	Intimate, family relationships and sexual problems
Muscle strength problems	Eating and drinking problems	Recreation and leisure limitations
Pain	Transfer problems	Poor quality of life
Chronic fatigue	Restricted motor function	Housing limitations
Metabolic disorders, gastro-urinary system problems	Toileting problems	Mobility-related limitations (driving, journey)
Sleep disturbances	Balance problems and falls	Problems in making decision and personal responsibilities
Environmental factors: barriers	**Personal factors: barriers**	
Physical and architectural barriers	Cognitive level	
Lack of community opportunities	Low motivation and self-confidence	
Limited awareness of adult healthcare services	Comorbidities (epilepsy, diabetes, vision and hearing loss)	
Discrimination and social stigma	Fear of not being understood	
Lack of social support	Limited funding mechanisms to support ongoing care	

experiencing reduction in walking ability. Moreover, when compared with adults in the general population, gross motor functional decline occurs earlier in adults with CP [1].

According to *studies*, 25–58% of adults with CP experience decline in mobility, and deterioration of walking ability has been described as early as 35–40 years of age in contrast to typically developing persons who report deterioration after age 75 years. In CP, those with worse initial walking ability, those who are bilaterally affected, and those with higher levels of fatigue experience greater deterioration. In addition, deterioration of walking ability has also been found to be associated with more pain and self-reported reduced balance [6].

Over *one-third* of adults with CP will worsen by GMFCS level during adulthood. According to a longitudinal cohort study of adults with CP, 39% of adults could walk unassisted at age 20 years, and only one-fourth could do so at age 60 years. *A substantial* decline in mobility occurred over 15 years in all age cohorts; moreover, the mobility deterioration risk increases with age. Gross motor functional decline tends to be closely related to associated problems such as pain and fatigue. *Additionally*, people with deterioration in gross motor ability over that period reported greater levels of pain and fatigue than those maintaining their functional status. Notably, adults with higher functional level appear to be less at risk for early decline; however, deterioration occurs more quickly in those with bilateral rather than unilateral involvement and in those who experienced developmentally delayed walking. However, better motor functional ability (i.e., GMFCS Level I vs. Level III) is also associated with a later age of peak mobility [1].

This *possibility* increases with age: progressive risk of deterioration is reported 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; in bilateral CP, deterioration starts earlier than hemiplegic CP [1, 5, 6]. *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 mobility aids to save energy for other activities, to prevent falling, and to feel safer [6]. However, losing the ability to walk affects adults with CP symptoms as well as their social, educational, and professional life, and the level of assistance needed with activities of daily life like personal hygiene or getting dressed [5].

There are several *mechanisms* that cause deterioration including weight gain, deformity, spasticity, and physical growth that results in a disadvantage in biomechanics and weakening of the muscles. *Loss* of energy or fitness can lead to abnormal compensations, such as hip hitching for foot clearance, using the hip adductors to pull through when hip flexor weakness is present, or using the lateral trunk flexion excessively for gait advancement. *Osteoarthritis* is a widespread condition in the general population, with a number of risk factors. It may be expected that arthritis's effects will manifest more quickly and severely in adults with CP, including abnormal gait and joint malalignment; these individuals require more energy to move around and have skeletal malalignment, deformity, and contracture [5, 6].

Additional risks of decline include physiological burnout, which is brought on by fatigue; reduced strength, dexterity, and mobility; concurrent illness; and injury. Extended fractures of the bones, extended periods of immobility, and cognitive and depressive problems could also be significant; however, they might have a relationship. The psychosocial factors most closely associated with dysfunction across the samples included *catastrophizing* cognitions; task perseverance, guarding, and resting coping responses; and perceived social support and solicitous response. Therefore, psychosocial factors are also significant predictors of functioning in adults with CP. *Spasticity* leads to various secondary impairments including contractures, muscle stiffness, muscle spasms, and increased muscle stress as well as is frequently related to pain and fatigue. *Secondary* musculoskeletal and neurological conditions can lead to premature aging of adults with CP. Spasticity is also a possible mechanism for accelerating problems with osteoarthritis.

Progressive chronic conditions in adulthood are related to increased spasticity and mobility impairments. *Therefore*, adults with CP require spasticity management to reduce muscle and joint impairments and minimize the accelerated decline in functional performance [5].

Balance disorder and falls are the most commonly reported problems; adults with CP consistently report poor balance, which may contribute to reduced mobility with approximately 60% of adults affected; *progressive* postural instability can be due to factors associated with aging, such as impaired balance, progressive loss of muscle strength, and deterioration in mobility that may contribute to the increased risk of falls observed in adults with CP as well as spasticity and joint limitations. *Additionally*, adults with CP are more likely to fall; they had 3.64 times the odds of experiencing a fall compared to adults without CP and fall more frequent than adults without CP, wherein adults with CP experienced 5.83 times more falls than adults without CP. Falls or other unwelcome experiences may discourage the older adults with CP. Therefore, the *causes* and *consequences* of falls in adults with CP need examination. Falls may be related to injury, disability, and even death in adults with CP. *Fractures* are among the fall-related injuries that can cause a long-term worsening of disability due to deconditioning and ongoing weakness following the immobile period for bone repair (see Chap. 32). Because individuals with CP have a higher-than-average chance of developing musculoskeletal conditions like osteoporosis, falling can have more severe effects on them. Young individuals with CP frequently experience a decline in their mobility, which may also be attributed to falls. Impaired balance, a *decrease* in mobility, and deconditioning are the major causes of falls; for this reason, these variables should be investigated as soon as possible. In addition to the negative effects on their health, falls can cause people to lose confidence in their ability to avoid falling and develop a fear of falling, which limits participation [10].

Physical fitness, in addition to the natural decrease associated with aging and the tendency to reduce energy loss, leads to gradual reduction in physical activity and fitness, and in adults with CP, physical activity was reported to decrease with increasing GMFCS levels [4]. *Adults* with CP are reported to be less active than their peers who are developmentally normal, to participate in a lesser range of physical activities overall, to have greater rates of sedentary habits, and to pace their activities more slowly. Because of this, a cycle of *deconditioning* is set off by a reduction in muscular strength, endurance, flexibility, and aerobic capacity, which raises the risk of chronic illness and its sequelae. Even though active participation in regular exercise is recommended to control obesity, improve *cardiovascular* fitness, reduce pain, and minimize the development of secondary conditions, only nearly half of adults with CP report being physically active for at least 1 h per week, and the majority of them do not follow a regular exercise program consisting of stretching, strengthening, and aerobics [11].

In adults with CP, physical activity was reported to decrease with increasing GMFCS levels [4]. *Additionally*, a combination of functional capacity and social, psychological, and environmental barriers may have an impact on participation in physical activity in adults with CP [12]. Enhanced physical fitness in young adults with spastic CP was effective in decreasing fatigue, mental health, and social participation without a substantial change in gross motor function, despite the fact that few researches have looked at the benefits of physical fitness in adulthood [4].

*Musculoskeletal deformitie*s: Adults with CP experience premature deterioration and deconditioning of the musculoskeletal system, and nearly 25–30% of adults with CP report deterioration in gross motor function [5]. Adults with more severe mobility restrictions have a highly increased risk of developing musculoskeletal morbidities, and multiple musculoskeletal morbidities among adults aged 31–40 years were 1.9-fold higher compared with adults aged 18–30 years, 4.3-fold in adults aged 41–50 years, and 6.1-fold higher than those above 50 years (see Chap. 21) [4]. Hip dislocation is related to pain, scoliosis, and decreased mobility. Contractures develop over time, increasing joint

stress and muscle pain [5]. 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 (see Chap. 22) [13].

Especially, nonambulatory adults with CP experience postural asymmetry associated with windswept hips, scoliosis, pelvic obliquity, and limb contracture, even though postural asymmetry is an important aspect of health care for adults with CP. The *development* of postural asymmetry of the thorax that affects respiration function may result in respiratory diseases, especially for the severely affected adults. *Difficulty* seating, decreased participation, as well as pain have been described as consequences of a postural asymmetry. Besides that, *complications* like hygiene problems, problems in swallowing and sleep, and pressure injuries can also be seen. Postural asymmetries may be most evident in non-ambulant adults with CP with low motor function typically described as Levels IV–V according to the GMFCS who are up around 20% of the total population of people with CP, exhibiting the highest risk for secondary issues and potential for a shorter life expectancy. Therefore, the common postural asymmetries of windswept hips, *scoliosis*, pelvic obliquity, and limb contracture require to be checked. Among this group, more than one-third have hip migration percentage in excess of 30%, more than 75% demonstrate "scoliosis," and more than 40% experience pelvic obliquity. Estimates ranged from 14 to 100% hip and 32 to 87% knee contractures. Although scoliosis is more frequent among severe affected adults with CP, the prevalence in total adult CP is quite high as 46% [13] (see Chap. 23).

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. *According* to a population-based cohort study, risk of osteoporosis and osteoarthritis in people with CP increased. Studies report that osteoarthritis is more frequent, more severe, and earlier in individuals with CP. The prevalence of osteoarthritis is reported as one-fourth among nonambulatory adults and one-third among ambulatory adults that may related to postural control and mobility. *Additionally*, low back problems are an important issue in adults with CP; the prevalence of spondylosis is reported as 29.5%, and the prevalence of spondylopathies is 61.5% [4, 14].

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. *Additionally*, the rate of complications after surgical intervention is higher in CP compared to non-CP patients. Moreover, the prevalence of musculoskeletal disease in young adults with CP is more than ten times higher than in those without CP. Nevertheless, surgery for hip joint misalignment and degeneration improves pain and walking function. The timing of the operation is very important, and cases require close follow-up by the orthopedic surgeon, the physiotherapist, and the caregivers. *Physiotherapists* should start strengthening the hip and trunk muscles, by standing up and ambulation, in the early postoperative period [13].

Pain is a very common complaint in adults with CP, according to a meta-analysis estimating an overall pain prevalence of 65–70% that contributes to the decline in motor functional capacity. More people experienced pain as they aged; 22% were pain-free initially, but only 17% were pain-free 7 years later [1]. Pain is associated with lower participation involvement and increased incidence of behavioral issues. The lower limbs, back, and neck are high-risk areas of pain for adults with CP who can walk [1, 4]. Pain is associated with contractures, orthopedic deformities, fractures, pressure from sitting on bony prominences, as well as spasticity [4].

Pain gets worse due to fatigue, staying in a certain position for extended periods, especially

on early morning hours. As people age, they may experience increased pain and acquire painful secondary disorders including osteoarthritis, neuropathy, or joint dislocations or contractures, as well as spinal canal stenosis. *Additionally*, pain in the arms increased with age, which may have been associated with overuse related to reduced walking ability and using walking aids or a wheelchair (see Chaps. 37 and 38). Chronic pain syndromes can occur as a consequence of these secondary disorders. Apart from the physical and sensory causes, there is mounting evidence that the development or maintenance of this multimodal pain in individuals with long-term disability may be influenced by psychological issues including depression. Pain is concerning as it can worsen functional decline and negatively impact an adult's quality of life who has CP [15]. Therefore, comprehensive pain management should be instigated to minimize the likelihood of secondary behavioral problems from developing as well as physiotherapy programs are recommended to focus on pain-reducing exercises, and preventive treatment aimed at correcting skeletal and muscle abnormalities early in life may help to avoid progressive deterioration [5].

Chronic *fatigue* is an important physical condition associated with CP, which is defined as a decrease in the muscle force-generating capacity of the neuromuscular system during a prolonged or ongoing activity or as excessive tiredness or exhaustion, one of the most bothersome and undertreated physical conditions, which is still a significant issue for this group [1]. Chronic *pain* and fatigue are the most common causes for deterioration in mobility for adults with CP, and they are typically experienced together during prolonged, taxing muscular contractions, and both can limit muscle performance; pain and fatigue were the most common health challenges faced by adults with CP [4], and studies indicated that 80% of adults with CP experience severe pain and fatigue that worsen over time [4, 5]. *Fatigue* is associated with gross motor function levels in adults with CP. Furthermore, it impacts activities, mobility, health lifestyle, and quality of life during adulthood [4, 5]. The most common reasons of fatigue are activity-related factors, general demands of life, sleep/rest, general health concerns, CP-related factors, mental health concerns, and environmental factors [16]. Fatigue appears to be highly related to other adverse symptoms of CP, including pain and poor walking ability [1]. Although fatigue is present among all functional levels, it is worse on average for those with greater gross motor impairment. *Additionally*, there is evidence that shows the role of physical activity in fatigue. Some surveys show a relationship between fatigue and inactivity; moreover, higher body mass index and larger waist circumference correlate significantly with fatigue severity [4, 5, 16].

The *strategies* for management of fatigue in CP comprise education and support to integrate self-management techniques, such as:

- planning and pacing,
- rest and relaxation,
- sleeping,
- changing activities,
- being physically active,
- making specific adaptations or assistive devices etc.

These measures could form a basis for the prevention and management of fatigue in adults with CP [16].

41.5 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 [1, 4, 5].

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. *Physiotherapy* can be applied at home, in clinics and hospitals as outpatients, in rehabilitation hospitals as inpatients, or even at the workplace of the patient, and plans should include specific goals, objectives, and measurable short-term priorities (Table 41.2). These short-term goals allow therapists and patients to have a clear understanding of the process [17]. Adult physiotherapy programs should be supported by physical and sport activities, and also aquatic exercises, hippotherapy, and therapeutic horseback riding are recommended to improve gross motor function as well as participation [18] (see Chap. 1).

Table 41.2 Physiotherapy and rehabilitation interventions (*created by authors: Mintaze Kerem Günel, Cemil Özal)

Physiotherapy and rehabilitation interventions*	
Conceptual interventions	
• Bobath approach	
Activity-based intervention	**Motor learning strategies**
Task-specific training:	Strategy development
• Goal-directed therapy	Feedback
• Activities of daily living	Practice
• Functional mobility skills	Transfer of learning
Environmental context	
Behavioral shaping	
Safety awareness training	
Impairment-specific and augmented intervention	
Impairment interventions	**Augmented intervention**
Strength and endurance training	Neuromuscular electrical stimulation
Mobility	Orthosis
Coordination	Biofeedback
Postural control and balance	
Gait and locomotion	
Aerobic capacity/endurance	
Pain management	
Complementary interventions	
Substitution training	Virtual reality
Alternate movement strategies	Serious games
Assistive/supportive devices	
Environmental modification	
Alternative daily life activity modification	

Physiotherapy and *rehabilitation training* involve 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 benefits from strength training and improvement in cardiorespiratory fitness with physical endurance training, which may contribute to reaching higher levels of physical activity. According to a guideline for individuals with CP, gait training, physical activities, upper limb training, strengthening exercises, and ankle-foot orthoses for motor impairment of the feet and the ankles are recommended for adults with CP [18].

Functional *exercises* combining aerobic and anaerobic capacity and strength training significantly improve physical fitness, 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. Different *interventions* include exercise, active video games, recreational activities, behavioral coaching, and motor skill training as well as tele-health technology, and community resources may enhance physical activity [19].

Training programs on static bicycles or treadmills can be beneficial for gait and gross motor development [18, 20]. The treadmill is a functional training method that may be effective for gait endurance, gait speed, and limb support time than cadence and step length. For nonambulatory

CP patients, treadmills that support body weight can be used [21].

Recommendations on the type, frequency, and duration of exercise are tailored for adults 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 reducing the likelihood of depression and anxiety that accompany aging.

The *Bobath concept* provides a framework for understanding the problems for individuals with adult CP as well. The Bobath concept is based on a thorough analysis and understanding of the individual's problems that are resulted by impairment in central nervous system and its impact on sensory-motor, cognitive, perceptual, social, and emotional condition (see Chaps. 11 and 19). Bobath employs a framework for understanding the major problems, and it takes a holistic approach to the body as it develops an understanding of how different muscle groups, senses, speech, and hearing interact and work with the individual to develop strategies of coping to prevent the condition from getting worse or at least stabilize it. It explores an individual's sensory-motor function, tone and patterns of movement, and the way these affect the individual's ability of participation in daily life. It relies on the knowledge of how the clinical features evolve and working to minimize secondary problems. It is *based* on one-to-one treatment, and therapists work with the individual to design tailored treatment programs which aim to enhance and develop functional skills [22]. Other ultimate elements of Bobath are the transdisciplinary approach for therapy (physiotherapists, speech and language therapists, and occupational therapists working together); the understanding of the complexity of CP with its motor, sensory, perceptual, cognitive, emotional, and behavioral components; and the adoption of a lifespan perspective [23] (see Chap. 30).

The *development* of clinical reasoning based on Bobath's approach will prioritize the establishment of interventional objectives that are focused on each individual's primary difficulty, which is a critical part in both defining and accomplishing these same objectives. The approach provides for a global treatment designed according to the difficulties and needs of each individual based on observing, analyzing, and interpreting the motor performance of a task [23].

Goal-*directed therapy* (GDT) aims to gradually increase independence in daily activities and improve functional performance with the most promising outcomes on improved function and self-care. This approach is based on the neuronal group selection theory and dynamic systems theory that make up the theoretical framework of motor control. It *includes* activities directed at the individualized goals, taking the individual's learning potential into account. Phased grading of the individual design enables developing an individualized plan to learn goal-directed activities and reach the goals and also makes it possible to individually evaluate treatment results. In GDT, the important part of planning a rehabilitation program is to identify barriers for participation and target functional activities and adaptions in the environment in order to overcome these barriers. Therefore, setting specific goals together with the individual is essential [24].

Muscle strength training: Most of the young adults with CP experience a deterioration in mobility as they age, which may be attributed to progressive loss of muscle strength and reduced gait efficiency [4, 5].

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 progressive resistance. This is highly *emphasized* to increase power generation capacity and improve muscle performance, motor skills, and range of motion. 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 [25]. It is recommended that individuals with CP participate in a muscle-strengthening program twice a week for at least 12–16 weeks [11]. *Electrical* stimulation is proposed as a useful modality when selective muscle control is required for specific strengthening programs [26].

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 Levels 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. Among *strength* programs, progressive resistance training has the potential to improve gait efficiency and muscle strength and hence prevent or delay deterioration immobility in young adulthood [27, 28]. Besides the progressive resistance training, functional training exercises, which are appropriately designed, targeted resistance training especially for the lower limbs, may lead to greater improvement in mobility given the specificity of the training modes. *Among* lower extremity muscles, ankle plantar flexor strength is a strong predictor of walking endurance, step cadence, and gross motor function among young people with CP, and therefore, a training program targeting ankle plantar flexors may improve walking function and gross motor function as well as gait efficiency through biomechanical mechanisms. *Moreover*, increasing the size and strength of the plantar flexor muscles may improve knee extension in the stance phase of gait and help propulsion of the lower limb in pre-swing, resulting in greater walking efficiency with a more erect alignment [27]. On the other hand, more research is needed to explore muscle strength training in non-ambulant people.

Functional gait training allows for repetition of motor task to enhance skill acquisition. Targeting improved walking ability, with training, may lead to gains in increased independence as well as increased participation in daily life. Functional gait training encompasses a range of diverse interventions with the same treatment goal. It can be defined as actively practicing the task of walking, to improve walking ability. This can involve overground gait training or treadmill-based gait training (see Chap. 1). The addition of a treadmill allows a greater repetition of stepping in a safe, controlled environment, increasing intensity. Both methods may incorporate the use of partial body weight support systems that act to reduce load on lower limbs, allowing upright posture and gait facilitation [29].

A *meta-analysis* found that most of the evidence points to the benefits of functional gait training for enhancing walking capacity in young adults with cerebral palsy across a wide range of ages and degrees of mobility impairment. Numerous reports of improvements in walking speed and gross motor function exceeded the clinically significant threshold. *Functional* mobility, spatiotemporal gait metrics, and walking endurance all showed additional improvements. Therefore, findings support the safe treatment strategy of functional gait training for young people with CP in order to enhance walking-related outcomes [29].

Electrical stimulation can also be applied as a purely muscle-strengthening application during physiotherapy, simply known as neuromuscular electrical stimulation (NMES). According to studies, NMES increases muscle strength and motor performance in CP and is an important alternative for selective motor control in muscles

and strengthening of weak structures. *Although* it has positive effects on its own, NMES is often incorporated into physiotherapy and adaptations with other therapy models in CP. NMES has been used as a means to strengthen muscles in CP and has been found to increase muscle fiber diameter and muscle size as well as strength [26].

When *NMES* is applied to achieve functional movements, the general term functional electrical stimulation (FES) is often used. FES refers to electrical impulses that are sufficient to evoke muscular contractions that are delivered to the muscles via surface electrodes at an intensity. FES, also known as the functional neuromuscular electrical stimulation (FNS) or NMES, is a method of applying safe levels of electrical current to activate the damaged or disabled neuromuscular system. The potential for *FES* is to aid in the functional ability (FES can be used in different forms; for instance, FES cycling provides a solution to an individual who has limited ability to pedal due to muscle weakness, spasticity, and deconditioning). When applied during cycling, FES can provide sensory cues to help to contract the muscles at the correct point in the cycling phase, with the aim to improve the timing and synergy of contractions. Alternatively, it can evoke stronger muscle contractions to achieve full cycling revolutions. NMES combined with physical therapy is more effective than physical therapy alone [20].

Virtual reality (VR) *intervention* is a technology that provides a sense of presence in a real environment with the help of 3D pictures and animations formed in a computer environment and enables the person to interact with the objects in that environment. In other words, VR described as an improved form of human-computer interaction that allows the user to be part of and interact with a computer-generated environment and VR has been used in the treatment of patients with CP. *Rehabilitation* with VR enables training at different levels of complexity with feedback in a safe and controlled environment; *additionally*, VR can enable clinicians to control the duration and intensity of tasks not performed in the real world. At the same time, VR offers meaningful learning experience by providing encouragement and motivation during rehabilitation. Additionally, VR, besides conventional rehabilitation, can improve upper limb function as well as lower limb strength, postural control, balance, and lower limb function in young adults with CP [22].

The serious games are the games to generalize to improve real-life outcomes that differ from entertainment games designed. *Interventions* in serious games used in contexts support the generalization of learning, which focuses on the integration of educational objectives with known, specific, evidence-based game mechanics and appears to have positive effects on persons with CP. *Game-based* rehabilitation in serious contexts should include desirable features for rehabilitation, meaningful and motivational elements, and adaptability feedback to increase the capabilities in persons with CP; moreover, it may induce increased motivation and social interaction. Game-based rehabilitation may improve balance and gait function as well as independence in participation of adults with CP [28].

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 [1, 17] (see Chaps. 27, 28, and 29). Deep brain stimulation might also be used to reduce dystonia and improve motor function [1].

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 for the patient's side [24]. *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 incompatibility with maintenance or prevention programs.

41.6 Conclusion

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, foreseeing and preventing functional decline with increasing age. *Adults* with CP need specific information in order to make their own decisions. 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. It is very important for them to participate in life and to continue being active and happy in life, and these individuals should be supported with a multidisciplinary team approach.

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