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Cerebral Palsy

Clinical and Therapeutic Aspects

Edited by Isam Jaber Al-Zwaini

CEREBRAL PALSY - CLINICAL AND THERAPEUTIC ASPECTS

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Notice

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Meet the editor

Professor Isam Jaber AL-Zwaini was born January 4, 1963, in Baghdad, Iraq. After graduation from AL-Mustansiryia College of Medicine 1987, he worked as a house officer in different hospitals in Baghdad for 15 months followed by military service for three years. He started his pediatric studies in 1991 and gained the Fellowship of Iraqi Commission for Medical Specializations in 1996. He started work as a lecturer in the Department of Pediatrics, AL-Anbar Medical College, from 1996 to 2001 where he upgraded to the degree of assistant professor. In 2005 he started working in the Department of Pediatrics, AL-Kindy Medical College, University of Baghdad, and upgraded to the degree of professor in 2008. He attained associate membership of the Royal College of Paediatrics and Child Health, UK, in 2007. He has been head of the pediatric department in AL-Anbar and AL-Kindy Medical College for many years. He has published more than 30 scientific papers in different pediatric fields. He has a special interest in pediatric hematology, neurology, and nutrition.

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Preface

Cerebral palsy (CP) is a common pediatric problem and is the leading cause of childhood disability. It occurs at a rate of 3.6 cases per 1000 children. Spastic CP is the most common form accounting for about 77%. It represents a major social and psychological impact on both family and society, and is a group of disorders with movement difficulties being common for all affected patients. Its severity and extent are variable from one patient to another. Additionally, the impacts of CP on daily activities, communications, and requirements are also variable. So, probably each patient is unique in his or her presentation and requirements. Wide-spectrum problems in CP are furthermore compromised by many associated medical problems, including epilepsy (40%), visual impairment (15%), hearing impairment (7%), and communication difficulties (25%). Recent advances in clinical research increase our knowledge and understanding of causal pathways, possible preventive measures, specific intervention strategies, and the value of new treatment modalities such as botulinum toxin and intrathecal baclofen in the management of cerebral palsy. Therefore, I am extremely honored to present this book with its four sections and 10 very interesting chapters, which cover various fields in CP.

The first chapter by assistant professor Ali A. AL-Mayahi discusses the early markers for anticipating CP. Since cerebral palsy is a permanent disorder in the development of movement and posture in the developing fetal or infant brain, which usually manifest before 18 months of age, the most challenging tasks for medical practitioners is to identify specific risk factors in early infancy and predict severe impairment that manifests later in development. So, early detection of signs of motor impairment is crucial to assist physicians to give close follow-up of those infants and to reassure parents whose children are normal. It has been shown that intervention may be most efficient when the plasticity of the brain is high, and an early detection of brain impairment is therefore crucial. An earlier follow-up and training program can have a positive effect on the motor development of a child with CP, in particular through prevention of limb contractions, and might make a difference in the child's ability to handle everyday challenges. In addition, an early detection of CP gives the parents more time for adjustment and preparation. Since clinical manifestations of CP do not emerge before a child is at least six months, the general movement is considered the most reliable early marker for monitoring fetal and infant movement. Abnormal general movement carries a high risk of developing CP. In addition, the absence of so-called fidgety movements at 3–5 months post-term age. Besides high sensitivity (>91%) and specificity (>81%), the assessment of general movement is quick, non-intrusive, and easy to acquire.

In the second chapter, Dr. Ogoke Christian gives a review of the clinical classification of CP. Classification of CP remains a debatable issue. In this chapter, the author discusses the various classifications of CP, highlights the clinical features used in the various classifications,

outlines the recent functional classifications of CP such as the Gross Motor Function Classification System, Manual Ability Classification System, Communication Function Classification System, and Eating and Drinking Ability Classification System and finely highlights how these recent classifications guide the current management of CP. Each classification used alone is incomplete. Therefore, multiaxial classification gives a more comprehensive description of a child with CP. The recent WHO International Classification of Functioning, Disability, and Health emphasized the importance of focusing on the functional consequences of various states of health and has stimulated the development of newer functional scales in CP. Currently, there are functional scales for some of the functions impaired in CP. It is widely accepted that functional classification is the best classification for the patient because it guides management.

Dr. Day Steven et al. in the third chapter discuss the survival, mortality, and life expectancy of patients with CP. The level of disability in CP ranges from immaterial to profound. In concert with the continuum of level of severity of disability/independent functioning, healthcare needs, therapies, medications, surgical interventions, costs of care, daily demands on parents and other family members, and expectations for the future in terms of education, employment, and other milestones of life all vary widely. Similarly, life expectancy in CP follows a continuum, from far lower than to potentially as high as the general population life expectancy, and parallels the continuum of levels of disability. The authors review the literature documenting this and examine the specific factors that are known to be strongly associated with mortality and longevity in CP. They also examine the evidence regarding the causes of death in CP, and present some new findings related to this. They finely outline important methodological considerations for future research in this area.

Dr. Kholin Alexey in the fourth chapter discusses the problem of epilepsy in children with CP. Different types of epilepsy occur in about 40% of children with CP. It will aggravate the clinical course of CP, complicate rehabilitation, affect prognosis of the motor and intellectual functions, and could be life threatening. The spectrum of epilepsies in CP is wide ranging from favorable combinations with benign idiopathic forms to extremely severe epileptic encephalopathies. Frequent combinations of epileptic and non-epileptic paroxysms cause difficulty in their interpretation and differential diagnosis. Video-EEG monitoring is a "golden standard" for differential diagnosis of epileptic and non-epileptic events and is very useful for investigation of patients with CP. Treatment of epilepsy in combination with CP strictly requires an individual approach due to the form of epilepsy, seizure types, the age of the patient, comorbidity, and the somatic and mental condition of the patient.

In the fifth chapter, Dr. Akhter Rahena et al. give a description of the oral health status and factors affecting dental caries in children with CP. Oral health can be significantly affected in children with CP. Many factors operate, including changes in the structure of the orofacial region, feeding problems, and difficulties with maintaining oral hygiene. Difficulties and barriers in accessing oral health care are additional factors. Caries rates in CP have been examined by several studies but to date no population-based studies have been published defining the risk factors for dental caries among children with CP. There is a high prevalence of orofacial motor dysfunction among people with CP, which can hinder oral hygiene and hence increase dental biofilm formation and retention. Factors such as food consistency, snacking between meals, and associated oromotor dysfunction have also been reported to contribute to the high incidence of caries found in those with CP. The chapter also provides preventive and restorative recommendations to combat the prevalence of this problem.

Dr. Adel A. Kareem in the sixth chapter reviews his experience in using botulinum toxin in children with CP. In the last 25 years, botulinum toxin type A (BTX-A) has been proved as an effective medicine strategy to decrease hypertonia in children with CP. Nowadays, BTX-A has a major role in the multidisciplinary treatment of spastic CP, in addition to physiotherapy, occupational therapy, speech therapy, casting, ankle-foot orthoses and knee-ankle-foot orthoses, surgical application of intrathecal baclofen, selective dorsal rhizotomy, and different other orthopedic interventions. Its use after the age of two years has been adopted by most experts all over the world. Botulinum toxin use in the management of CP is recommended to improve function and to support motor development. Furthermore, botulinum toxin injection has an additional role in the decrease of pain associated with focal spasticity.

The seventh chapter by Dr. Moneer Faraj discusses relatively new treatment modalities for CP, namely intrathecal baclofen. He discusses the rationale for the use of this mode of treatment in spasticity. Different treatment options are used to reduce spasticity and increase the range of motion in CP, including non-pharmacological methods (splints or braces, electrical or vibratory stimulation, physical and occupational therapy, massage, heat or ice, and serial or inhibitory casting), pharmacological methods by different medications (nerve block, anesthetics injection, alcohol or phenol, neurotoxins, and oral medications such as oral baclofen and anticonvulsant), surgical methods such as dorsal entry zone rhizotomy, and augmented therapy such as baclofen pump implantation (a surgical procedure performed to permanently implant a pump that delivers baclofen to the spinal fluid to treat severe to moderately severe spasticity that is refractory to oral medications). As compared to oral medications, the direct infusion of baclofen into the intrathecal space minimizes the amount of drug needed to be effective and it will limit or eliminate the common undesirable side effects associated with taking oral medications for spasticity. The pumps can deliver a precise and consistent drug dose throughout the day, so avoiding the peaks and valleys of taking oral medication. Dosing is very flexible and can be programmed as required, from the same dose administered on an hourly basis 24 hours a day to different doses at different times of the day or days of the week.

The eighth chapter by Dr. Alcaraz Jesús discusses the use of plasma growth factors in CP. Nowadays, platelet-rich plasma is a common medical technique within so-called regenerative medicine. Its use in various fields of medicine, especially traumatology, dentistry, and general surgery, has undergone an extraordinary development given the enormous capacity for regeneration, differentiation, and chemotaxis that produce the so-called growth factors, modulating angiogenesis and the cellular plasticity of injured tissues. Among them, the best known are the so-called insulin-like growth factor, transforming growth factor A or B, vascular endothelium-derived growth factor, and platelet-derived growth factor. Neuroendocrinology and neurorehabilitation are the new branches of medicine where plasma growth factor application opens up new expectations. These factors infuse locally or systemically by the intravenous route, and have the capacity for immunomodulation and chemotaxis on neural cells. Furthermore, it has been demonstrated that in patients with neurological degenerative diseases (e.g. Alzheimer's disease, vascular encephalopathy, multiple sclerosis, amyotrophic lateral sclerosis, and hypoxic–anoxic encephalopathy), the plasmatic levels of certain growth factors were below the baseline, so it was hardened that could interfere in the mechanism of cellular hypoxia, producing both a neuroprotection function and regeneration and differentiation of neuronal tissue.

In the ninth chapter, Dr. João Lameiras Campagnolo discusses various aspects of hip surgery in children with CP. He discusses in particular theoretical and practical strategies used to treat specific CP hip dislocation. Hip pathology is one of the main orthopedic problems in children with CP. In several countries, hip dislocation is significantly prevalent and is still a major concern in these patients. Depending on the age, the disability grade, the rehabilitation support, and the surgical strategies, results of hip treatment are variable. The ideal outcome of a stable, reduced, and long-lasting pain-free hip is not always achieved.

Finally, I hope this book with its interesting chapters will shed light on some of the stimulating aspects of this important disease. I would like to thank all authors who contributed with their chapters and for their patience and cooperation throughout the processing of the book. Also, I would like to thank the IntechOpen personnel, especially Ms. Dolores Kuzelj, who helped me through the publishing process of this book.

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Section 1

Predictors of Cerebral Palsy

Chapter 1

Early Markers for Cerebral Palsy

Ali A. Al-Mayahi

Additional information is available at the end of the chapter

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Abstract

Cerebral palsy (CP) is a term referring to a nonprogressive disease of the brain originating during the antenatal, neonatal, or early postnatal period when brain neuronal connections are still evolving. Secondary effects of spasticity on growth may, however, be progressive. There may be additional disturbances of sensation, perception, cognition, communication, and behavior. Babies who are neurologically abnormal as newborns are at increased risk of neurologic abnormality in later months and years. Being born preterm (born <37 weeks of gestation) or with a very low birth weight (weighing <1500 g/<32 weeks of gestation) or extreme low birth weight (<1000 g/<28 weeks of gestation) is associated with significant motor impairment. Which specific signs in the neonate are of greatest predictive power, what long-term disability these signs predict, and how well they predict it remain unclear? Physician's major concern is to identify specific risk factors for severe impairment in early infancy so as to predict the developmental outcome of those children that may manifest later on with neurological deficit especially if they have perinatal insult. Parents on the other hand are also concerned about their growing infants, their development, and neurological outcome. Since cerebral palsy is a permanent disorder, early detection of signs of motor impairment is crucial to assist physicians to give close follow-up of those infants and to reassure parents whose children are normal. It has been shown that intervention may be most efficient when the plasticity of the brain is high, and an early detection of brain impairment is therefore crucial. An earlier follow-up and training program can have a positive effect of the motor development of the child with CP, in particular through prevention of limb contractions, and might make a difference in the child's ability to handle everyday challenges. In addition, an early detection of CP gives the parents more time for adjustment and preparation. Since clinical manifestations of cerebral palsy do not emerge before a child is at least 6 months, the general movement (GM) is considered the most reliable early markers for monitoring of fetal and infant movement. Abnormal General movements and absence of the so-called fidgety movements at 3-5 months post-term carries a high risk of developing cerebral palsy. Beside a high specificity (82–99%) and sensitivity (95–100%), the assessment of the general movements (GMs) is quick, nonintrusive, and easy to acquire.

Keywords: infant, cerebral palsy, early markers, general movement, neuroimaging

1. Introduction

Cerebral palsy (CP) is a permanent disorder in the development of movement and posture in the developing fetal or infant brain which usually manifests before 18 months of age [1]. Prematurity is a major risk factor for later motor impairment, and the prevalence of CP increases from 0.1% in term babies to 14.6% in those born preterm [2, 3].

The physical impairment is often accompanied by disturbances in cognition and perception [4]. Preterm birth, perinatal asphyxia and neonatal encephalopathy, genetic predisposition, white matter disease, deep gray matter lesion, cerebral infarction, and intraventricular hemorrhage are associated with increased risk of CP [5–7].

The ability to predict CP earlier than 2 years of age would have many advantages. Earlier recognition of infants at high risk for neurodevelopmental delay would also benefit families through individualized case management and interventions and may also lead to more focused follow-up and reassure the parents of those children who are unlikely to develop CP. One of the most challenging tasks for medical practitioners is to identify specific risk factors in early infancy and predict severe impairment that manifest later in development. Parents on the other hand still concerned about the developmental perspectives of their infant, especially if he has a perinatal insult. One should consider that overt clinical symptoms of CP usually do not manifest before the child is at least half year old [4]. In addition to that, identification of language and cognitive function delay requires long time follow-up for accurate detection [8]. Early recognition of neurodevelopmental delay needs a good tool for early diagnosis to predict the outcome and to enable early intervention as soon as possible. The plasticity of the brain is at its highest during the first 2 years and decreases gradually thereafter [9]. It has been shown that spontaneous motility is an excellent marker for neural dysfunction caused by brain impairment, which normally would not become evident and clinically manifested for years [10, 11]. The general movement assessment (GMA) developed by Prechtl is a known diagnostic tool for the functional assessment of the young nervous system and has shown good results in predicting CP at an early stage [12–15]. GMA is noninvasive, even nonintrusive, cost-efficient, and easy to learn [12]. During the last 15 years, considerable research has been devoted to GMs, whose quality has proven to be most indicative of functional integrity of the young nervous system, with specificity of 82–99% and a sensitivity of 95–100% [10, 16–17]. GMA conducted at 3 months of corrected age is useful in a clinical setting for predicting CP at 2 years of corrected age for children born <32 weeks of gestation [18]. In its predictive power, the GM assessment is superior to cranial ultrasound (US) or neurological examination and equivalent to MRI (white matter assessment) [19–21].

2. The aim of this chapter

The aim of this chapter is to discuss the early markers of cerebral palsy from the general movement assessment to the neurological examination and then neuroimgaing studies when indicated in assessing high-risk infants to provide opportunity for early detection of any poor motor performance and for early possible intervention.

3. General movements

General movement is a part of spontaneous movement activity that is generated by the developing nervous system; it appears from the 7th week postmenstrual until 3–5 months post-term. The beginning of early fetal movement at the 7th week is correlated with the development of synapsis in the spinal cord, the emergence of neuromuscular contacts, and before the development of spinal reflex pathway at 10–11 weeks postmenstrual [22–24]. It is characterized by a movement that involves the whole body in a variable sequence involving the arm, leg, neck, and trunk. They are complex in nature that wax and wane vary in intensity, speed, and range of motion and have a gradual onset and end. It has been proposed that GMs consist of rhythmic bursts of action potentials [16]. GMs are generated from a large neuronal generator network that extends from the brain stem to the spinal cord [25].

The variable nature of GM is explained by the presence of supraspinal projections that activate, inhibit, and modulate the central generator network [26]. Fetal and neonatal nervous system generates not only a variety of motor patterns such as simple startles or twitches but also more complex patterns such as stretching, yawning, or GM [12, 26]. General movements are movements which involve the entire body, rotations around the limb axes, and slight changes in the direction of movement that gives the GM its fluency and elegancy [10, 27]. The first-stage fetal movement that starts at the 7th week postmenstrual appears as movements that are restricted to the head and trunk, and then the second stage begins with the movement of all parts of the body as slow and simple movement of the arms and legs.

More complex and variable GMs emerge at week 9–10 of postmenstrual age (PMA), where each phase has its own characteristics [28]. Complexity and variation of movements are brought about by the independent exploration of degrees of freedom in all body joints. The variable combinations of movement like flexion-extension, abduction-adduction, and endorotation-exorotation generate a series of changes in movement direction of the involved body parts. GMs are considered as the major tool of assessing fetal and infant brain integrity in which reduced modulation of the central neuronal generators results in less variable GM and may indicate fetal or neonatal motor compromise [25].

3.1. Fetal and preterm general movements

From week 9 up to term age, the GMs are referred to as fetal and preterm general movements. These movements have large amplitudes and fast speed in which the fetus develops the entire neonatal movement, which also includes arm and leg movements, startles, sucking, breathing, and stretching movements [12].

3.2. Writhing movements

From term age onward till the second month post-term, the GM is called "writhing movement" which is characterized by small-to-moderate amplitude and speed. In addition, trunk movements are smaller than previously [29].

3.3. Fidgety movements

At 6 to 9 weeks post-term, the writhing movement disappears where the so-called fidgety movement (FM) appears [10]. It consists of rounded tiny movements of the neck, trunk, and limbs. It is of moderate speed and variable acceleration; they disappear when the infant starts being fussy or cries and is drowsy or sleeps [12, 25]. FM disappear from 3 to 5 months post-term (**Figure 1**) [30].

General movements gradually disappear at 3–5 months post-term, when general movement activity is taken over by goal-directed movements of the arms. The latter consist, for instance, of mutual manipulation of the fingers or manipulation of clothes [10].

3.3.1. Clinical variants of fidgety movement

Prechtl had described a clinical interpretation for FMs into (**Table 1**) [12].

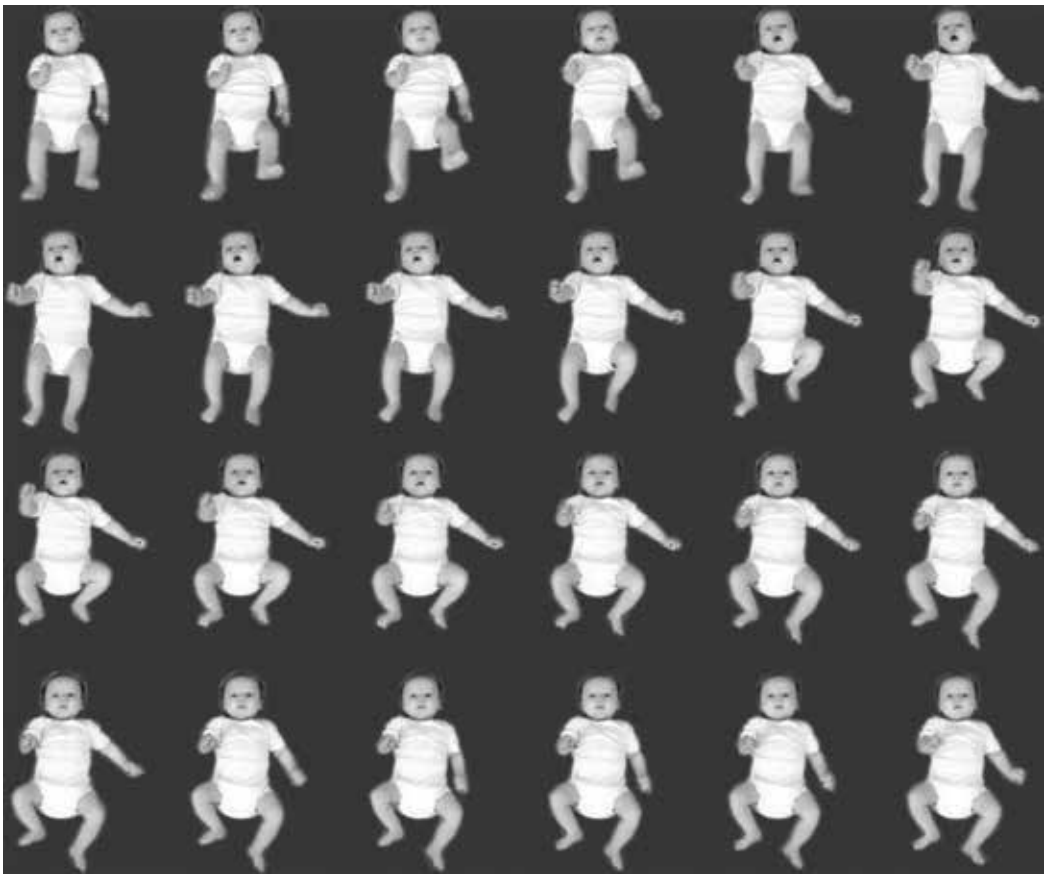

Figure 1. Video print of a 14-week-old infant showing fidgety movements as time evolves from left to right and from top to bottom. A frame rate of 12.5 Hz is used, yielding a total time of 1.92 s [30].

	Normal FM	Abnormal FM
Old	+ +, +, + −	− −, Exagg
New	+ +, +	+ −, −, Exagg

Table 1. New and old Prechtl approach for classification of normal and abnormal FMs, where the FMs are categorized as continual (+ +), intermittent (+), sporadic (+ −), absent (−), and exaggerated (Exagg) [12].

3.3.1.1. Continual FMs

Continual FMs occur frequently with very short pauses (1–2 s). It scores (++). FMs involve the whole body, particularly the neck, shoulders, wrists, hips, and ankles. FMs may occur as asymmetrical movement depending on the position of the head. They are mainly displayed in the hips and ankles but not so much in the shoulders and wrists [31, 32].

3.3.1.2. Intermittent FMs

Intermittent FMs occur often but with longer pauses (up to 10 s) than continual movements, which may indicate that FMs are present only during half of the observation time [31, 32]. Intermittent FMs scores (+).

3.3.1.3. Sporadic FMs

The occurrence of FMs here is less frequent and sporadic with much longer pause up to 1 minute. Sporadic FMs are age-adequate from 6 to 8 weeks post-term until the 5th month when FMs start to wane [31, 32]. Sporadic FM is regarded as abnormal movement according to the new Prechtl approach of general movement assessment (**Table 1**).

The potential biological function of this tiny movement may be attributable to the postnatal calibration of the proprioceptive system [12, 33]. Children and adolescents with fine motor dysfunction had less pronounced or abnormal fidgety movement at infancy [34, 35]. Sporadic FMs score (+ −).

3.3.1.4. Abnormal FMs

Abnormal FMs (score: AF) look like normal FMs, but it occurs with greater amplitude, speed, and jerkiness (exaggerated) [10, 12, 19]. Abnormal FMs are rare; they occur more often in infants born preterm who show uncoordinated sucking [35]. Abnormal FMs have been described in infants with Down syndrome (trisomy 21) [36, 37] and infants who has intrauterine exposure to maternal opiate abuse and/or HIV [1, 38]. Infants with abnormal FMs may develop normally [19, 35, 39, 40] but may also develop CP [19, 32]. Some studies documented an association between abnormal FMs and coordination difficulties and/or fine manipulative disabilities [35, 40]. Recently, an exceedingly high rate of abnormal FMs was described in infants who were later diagnosed with autism spectrum disorder [41].

3.3.1.5. Absent FMs

Whenever FMs are missing altogether from 9 to 20 weeks of post-term age, this abnormality is called absent FMs (score: F−). Infants with absent FMs show other normal or abnormal movements [19]. Absent FMs are highly predictive of later neurological deficits [10], particularly of CP [10, 12, 19, 32, 38, 39]. Further observation allows for determination of the eventual type of CP as well as the anatomical distribution and severity of the activity limitation. Despite the absence of FMs, infants with an increased risk of non-spastic CP showed circular arm movements with or without spread fingers [42, 43]. Asymmetry of distal segmental movements may predict later development of unilateral CP [44, 45].

It has been shown that abnormal and absent FMs increase the risk of development of neurological impairment. Particularly, the absence of FMs has been shown to be highly predictive of CP, while normal FMs are associated with normal neurological outcome [10]. GMs during preterm and term age are considered abnormal if it lacks the variability in intensity, speed, and range of motion which may indicate a poor repertoire general movement. Another form of abnormal GMs that lacks the usual fluency and smoothness is described as cramped-synchronized GMs, a rigid movement of the limb and trunk muscles that contract simultaneously and relax almost simultaneously. Both the presence of cramped-synchronized GM and the absence of fidgety movements are highly predictive of CP [14, 21]. Chaotic movements on the other hand are also considered abnormal GMs in which it is abrupt and occurs with high speed and large amplitude and mostly observed in moderate preterm [10].

4. General movement assessment

Since long-time GMs regarded as standard tool for monitoring and predicting motor compromise like cerebral palsy [14]. It is an easy, noninvasive, and cost-effective method that consists of a video camera and a trained person who analyze the video record. The infant (should be silent, not crying) is monitored with video camera in supine position for 3–5 minutes [12]. There are several computer-based methods for assessing GM in infants with high risk of neurological impairment. The computerized video-based method is divided into two types: the motion capturing system and traditional color camera [46]. The motion capturing system has an advantage in separating healthy infants from the high-risk infants, but it is a costly and expensive and used only in research practice, while the traditional method is used outside the clinical and research practice like the infant's home that is called the GM tool box [47]. Adde et al. described that the GM tool box showed that the variability in displacement of spatial center of active pixels in the image had the highest sensitivity (81.5%) and specificity (70%) in classifying GMs [46]. Another study revealed that this type of computer-based analysis can reliably differentiate between normal (continual) and abnormal (intermittent) GMs [48]. The absence of fidgety movements was never specific for a particular subtype of CP. This fact indicates that intact corticospinal fibers and a normal output of the basal ganglia and cerebellum are necessary to generate normal fidgety movements [27].

Unilateral CP can be identified through GM assessment and application of Hammersmith Infant Neurological Examination (HINE) [49]. These results clearly lead to the conclusion that a 3- to 4-month-old infant with a normal neurological score but an absence of fidgety movements and asymmetric segmental movements is at a high risk of developing unilateral CP [45] (**Table 2**).

GMS during preterm age	Writhing GMs (at term until 8 weeks postterm)	Fidgety GMs (3–5 months)	Neurological outcome
Poor repertoire or normal GMs	Poor repertoire or abnormal GMs	Normal fidgety movements	Normal
Poor repertoire or cramped-synchronized GMs	cramped-synchronized GMs	Absence of fidgety movements; abnormal findings in neurological examination	Bilateral spastic CP
Poor repertoire or cramped-synchronized GMs	Poor repertoire or cramped-synchronized GMs	Absence of fidgety movements and asymmetrical segmental movements; normal or abnormal findings in neurological examination	Unilateral spastic CP
Poor repertoire GMs	Poor repertoire GMs; circular arm and finger spreading	Absence of fidgety movements; absence of foot-to-foot contact; circular arm movements and finger spreading	Dyskinetic CP

CP, cerebral palsy; GM, general movement.

Table 2. Developmental trajectories with a high predictive power for normal development and the development of cerebral palsy [42].

5. Value of neurological examination

Neurological assessment since long time is used as a monitoring system for development of the high-risk infants. The main goal of the high-risk infant follow-up programs is to monitor the development and to provide early identification and treatment of high-risk infants (preterm and those with perinatal insult). These programs are also considered as a referral centers for general providers who have identified delays on routine screenings. Neurological examination is considered a vital tool of neurodevelopmental assessment and follow-up, complemented by various developmental and medical assessments. There are several neurological examination methods available for high-risk infants used for both clinical care and research studies. The well-known methods are the Hammersmith Infant Neurological Examination (HINE) [50], the Touwen [51], the Amiel-Tison [52], the Bayley Scales of Infant and Toddler Development [53], and Dubowitz neonatal neurological examination [54]. These assessment methods have a high predictive value with sensitivity and specificity of 88 and 92%, respectively, in predicting CP [14]. The use of the above neuromotor and developmental assessment is to predict impairments as early as possible and to help physician provide guidance for families about their children development and help in discriminating between normally developing infants from those with abnormal development. It also enables prognostic information on the neurological and motor outcome and when to send those infants showing early impairment for rehabilitation programs.

The HINE is an easily performed and relatively brief standardized and scorable clinical neurological examination for infants between 2 and 24 months of age, accessible to all clinicians, with good interobserver reliability. It has no associated costs such as lengthy certifications or proprietary forms. It consists of 26 items that assess different aspects of neurological examinations such as cranial nerves, posture, movements, tone, and reflexes [53], with a questionnaire instructions and diagrams included on the scoring sheet, similar to Dubowitz neonatal neurological examinations [54]. Each item is scored individually (0, 1, 2, or 3), with a sum score of all individual items (range 0–78), Optimality scores for infants 3 to 18 months are based on the frequency of distribution of neurological findings in a typical infant population: it is considered optimal when an item is found in at least 90% of infants [53].

The sequential use of the HINE allows the identification of early signs of cerebral palsy and other neuromotor disorders, while individual items are predictive of motor outcomes. For example, in preterm infants assessed between 6 and 15 months of corrected age, scores above 64 predict independent walking with a walked sensitivity of 98% and specificity of 85%. Conversely, scores below 52 were highly predictive of cerebral palsy and severe motor impairments [55].

Neurological examination and tools that incorporate it are clinically influenced by the experience of an examiner and a child's state of rest. The neurological examination tools are mostly of value in term age, while general motor assessment has better predictive accuracy at preterm age. Signs that may appear transient during preterm period like jitteriness and dystonia that may be detected through neurological examination are misleading and have poor predictive accuracy of CP [56, 57]. Neurological examination is of value in the prediction of milder cases of CP, during which GMA is less sensitive [58]. The combination of both GMA and HINE at 3 months post-term is valuable in predicting infants at high risk of CP [49].

6. Neuroimaging studies

6.1. Cranial ultrasonography

Cranial imaging is the most well studied of the postnatal clinical findings correlated with CP. Serial cranial ultrasound has been used for nearly 30 years to evaluate CNS structure in infancy. Ultrasonography had been used for assessment of fetal well-being and behavior state in utero. Cranial ultrasound reliably detects germinal matrix and intraventricular hemorrhage, ventricular dilation, and periventricular leukomalacia (PVL). Although cystic white matter injury (WMI) and ventriculomegaly are highly associated with CP, premature infants with normal cranial ultrasound are also at risk for motor abnormalities [59]. Infants born after 28–30 weeks of gestation are not routinely examined with ultrasonography; this is partly due to the low sensitivity of cranial US (66–79%) [60]. Thus, a brain injury that does not present clear clinical signs can go undetected for a long period of time, resulting in an intervention being initiated late.

6.2. Magnetic resonance imaging

MRI, which is often used to reveal anatomic abnormalities, could offer a unique, noninvasive opportunity to predict neurological deficits, even as early as the newborn stage [61]. Also,

MRI has considerably higher sensitivity than cranial ultrasound (US) [62]. Its higher sensitivity is important to detect early damage occurring before reliable US imaging. In addition of hypoxia-ischemia, MRI can also show other patterns of injury, such as central cortico-subcortical damage, diffuse cortical involvement, bilateral parasagittal lesions, as well as brainstem, cerebella, and hippocampus lesions.

The patterns of MRI in children with cerebral palsy are:

1. White matter damage

According to the studies of pathological observations with patient phenotypes, white matter injury (WMI) is often observed in spastic diplegia and quadriplegia. The abnormalities of white matter are particularly frequent in children with CP born premature. Incidence of white matter damage, across all studies, was reported in nearly 30–40% of all subjects; also, myelin abnormalities are quite common in CP [63, 64].

2. Gray matter damage

The gray matter damage is defined as injuries to the basal ganglia, cortical defects, thalamic abnormalities, and diencephalic lesions. The hallmark of acute perinatal hypoxia-ischemia in term infants, central gray matter damage, is an important cause of death and cerebral palsy.

3. White and gray matter damage

The white and gray matter damage, most common among hemiplegics, infarcts are commonly found in both white and gray matter surrounding the middle cerebral artery among subjects with CP.

4. Ventriculomegaly, atrophy, and cerebrospinal fluid abnormalities

The ventriculomegaly, common subjects with CP, includes enlarged, dilated, or reduced ventricles (unilateral or bilateral), abnormalities of the atria, ventricular or occipital horns, and posterior fossa abnormalities [65, 60].

A significant relationship between white matter abnormalities on magnetic resonance imaging (MRI) and absent FMs in infants born at <30 weeks of gestation supports the idea that abnormal GMs reflect white matter injury [66].

Although the white matter damages are the most common abnormality [67, 68], but combined gray and white matter abnormalities are more common among children with hemiplegia. Isolated white matter abnormalities are more common with bilateral spasticity or athetosis and with ataxia. Isolated gray matter damage is the least common finding. In preterm-born infants, periventricular white matter lesions occurred more often than in term-born children (90% vs. 20%) [67]. It has been shown that both GMA and magnetic resonance imaging (MRI) had a sensitivity of 100% in predicting the development of CP by the age of 12 months in preterm infants [21].

The scientists had developed guidelines for early detection and intervention for cerebral palsy; they include recommendations for neurological examinations, neuroimaging, and motor assessments for infants between 5 months and 24 months of corrected age [13].

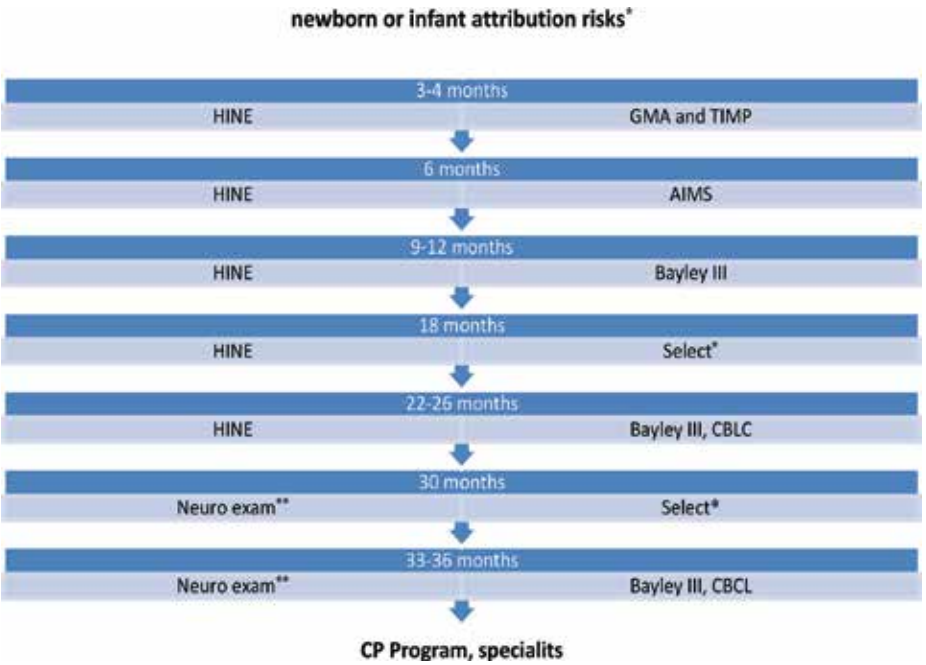

Figure 2. Translation of international guidelines into a clinical practice algorithm in a neonatal intensive care unit follow-up program. *Select examinations target developmental progression and represent the best feasible evidence for specific concern. **Neurological examination after a 2-year visit includes Amiel Tisonorother. Bayley-III, Bayley scales of infant and toddler development-third edition; CBCL, child behavior checklist; GMA, general movement assessment; HINE, Hammersmith infant neurological examination; TIMP, test of infant motor performance [69].

As shown in **Figure 2** [69], the guidelines can be translated into clinical practice by adapting core elements to suit individual clinical settings. As soon as the high-risk infants as a neonate (e.g., neuroimaging findings consistent with neonatal encephalopathy) are referred, they undergo surveillance according to the guidelines at the 3- to 4-month visits. In hospitalized extremely preterm infant with white matter injury, the surveillance occurs at the bedside according to the guidelines with a HINE, a Test of Infant Motor Performance, and a general movement assessment. Referred high-risk infant should start close to the point of the pathway, for example, a high-risk infant referred for the surveillance at 9 months due to inability to sit would start with a HINE and a Bayley Scales of Infant and Toddler Development.

7. Conclusion

This systematic review has shown that there is good evidence that GMA can accurately predict the development of CP. There is reasonable evidence to support the use of MRI at term corrected age, neurological examination in the older infant, and, to a lesser extent, ultrasound in infants of preterm age for early assessment. The great advantage of detecting an increased risk of CP at such an early stage consists of the possibility of intervention long before the emergence of obvious pathological features of CP.

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Section 2

Classification of Cerebral Palsy

Chapter 2

Clinical Classification of Cerebral Palsy

Christian Chukwukere Ogoke

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79246

Abstract

The classification of cerebral palsy (CP) remains a challenge; hence the presence of so many classifications and a lack of consensus. Each classification used alone is incomplete. Therefore, a multiaxial classification gives a more comprehensive description of a child with CP. The recent WHO International Classification of Functioning, Disability and Health (ICF) emphasizes the importance of focusing on the functional consequences of various states of health and has stimulated the development of newer functional scales in CP. It is widely accepted that the functional classification is the best classification for the patient because it guides management. The objectives of this chapter are to review the various classifications of CP, to highlight the clinical features used in the various classifications, to outline the recent functional classifications of CP and to highlight how these recent classifications guide current management. It is expected that at the end of this chapter, the reader should be able to understand the difficulties in classifying CP, enumerate and discuss the various classifications of CP, understand the merits and shortcomings of each classification scheme, clinically evaluate and classify a child with CP multiaxially and understand how functional scales predict current and future needs of children with CP.

Keywords: clinical classification, cerebral palsy, functional scales, management, spastic, extrapyramidal, SCPE, GMFCS, MACS, CFCS, EDACS, multiaxial

1. Introduction

The categorization of children with cerebral palsy (CP) into clinical groups remains a challenge, hence the presence of so many classifications that are not comprehensive and the continued search for a holistic classification [1]. The clinical manifestations of CP are heterogeneous as rightly pointed out in the most current definition of CP [1, 2]. This implies that children with CP differ clinically in many aspects. Therefore, different groupings (classifications) are possible [1].

These classifications (groups) differ in the characteristic(s) used and their individual uses or purposes. A classification may be used for describing the nature of the disability, for predicting current and future management needs, comparing cases in different areas and assessing change following an intervention [1]. Generally, it is desirable that any classification used should be reliable, valid, quantitative, and objective and most importantly assist management [1].

Besides early identification and intervention, the current trend in neurodevelopmental pediatrics is a focus on functional effects of different states of health [3, 4]. This is the outcome of the recent WHO International Classification of Functioning, Disability and Health (ICF) which in the field of CP led to the development of newer measures of functional abilities (functional scales) [3, 4]. There are functional scales for a number of functions impaired in CP. It is widely accepted that the functional classification remains the best classification for a patient with CP because it guides management [1, 5, 6].

2. Overview of clinical classification of CP

Some factors that influence the clinical classification of CP are the age of a child, reliability of the medical history, and extent of diagnostic investigations [1]. This means that the same child may be classified differently at different times (due to changes in peripheral manifestations with age), by different people (due to variable historical data from maternal recall or case notes), and in different regions (due to differences in availability and affordability of neuroimaging and metabolic studies). Therefore, Bax et al. [1] in 2005 proposed that all classification results should indicate these factors at the time of classification.

Children with CP differ clinically in the following characteristics: type/nature of motor disorder, distribution of motor impairment, etiology, presence/number of accompanying impairments, structural brain abnormalities on neuroimaging, degree of severity of impairments, and individual therapeutic needs. These clinical variables form the basis of the traditional classifications of CP. In 1956, Minear [7] and the Nomenclature and Classification Committee of the American Academy for cerebral palsy classification put forward an early classification system that presented seven classification axes based on the aforementioned features.

Subsequent classification systems originated from the Minear classifications and are either a combination or an expansion of the categories. Such classification systems based on multiple variables include the Swedish classification system [8], Edinburgh classification [9] and classification by the Surveillance for Cerebral Palsy in Europe (SCPE) [10].

The current emphasis on the functional consequences of different health states increased interest and research on the functional classification of CP [1, 3, 4]. The result is an evolution of newer measures (functional scales) that objectively and reliably measure and quantify functional abilities. A number of these functional scales have been validated by multiple studies [11–16]. They include Gross Motor Function Classification System (GMFCS) [11] (functional mobility/ambulatory function), Manual Ability Classification System (MACS) [14] (hand and

arm function/manual dexterity), Communication Function Classification System (CFCS) [16] (speech/communication function) and Eating and Drinking Ability Classification System (EDAC) [17] (eating and drinking/oropharyngeal function). They are mainly used for predicting current and future management needs of children with CP, and their use agrees with current thinking in management of CP.

Advances in management of CP including the biopsychosocial method of service delivery that recommends liberal use of assistive devices require additional characteristics or variables to be added to traditional classifications in order to assist management and satisfy other important purposes like clinical description and research [1, 4, 5]. Such a classification would be called holistic, comprehensive or standardized. A consensus on what characteristics/components such holistic classification should incorporate is yet to be reached by experts in the field of CP.

3. Traditional classifications of CP based on single characteristics

The traditional classifications of CP are basically the Minear [7] classifications in seven axes namely:

1. Physiological
2. Topographic
3. Supplemental
4. Aetiologic
5. Neuroanatomic (radiologic)
6. Therapeutic
7. Functional

3.1. Physiologic classification

This is based on the type/nature of motor or movement disorder (quality and changes in tone) and classifies CP into two types: spastic (pyramidal) and non-spastic (extrapyramidal). Generally speaking, neuromotor findings in spastic CP are consistent and persistent while variability is the rule in extrapyramidal CP [6, 18, 19].

The clinical features of spastic CP are as follows [6, 18, 19]:

- Tone is invariably increased (hypertonia), that is, persistently increased with little or no variation in the awake (movement, tension and emotion) or sleep states. This is further confirmed by asking caregivers whether their child feels stiff when touched or held most times of the day even during sleep. The answer is usually a "yes."

- The quality of the increased tone is described as "clasp-knife" spasticity and is elicited clinically by a rapid passive movement at a joint (as rapidly as the time taken to say "one thousand and one"). This produces the classic "clasp-knife" resistance followed by a sudden "give." Spasticity refers to hypertonia due to a velocity-dependent increase in tonic spinal stretch reflex.
- Deep tendon reflexes are markedly increased (more commonly grade 3+ or 4+)
- A positive Babinski sign (extensor planter response), that is, lightly stroking the lateral aspect of the sole and across the foot pads/ball of the foot, results in extension/dorsiflexion of the hallux (up-going big toe) and fanning out/spreading of the other toes.
- Sustained ankle clonus, that is, when the ankle is briskly dorsiflexed on a flexed knee, a rhythmic contraction is observed.
- Non-positional contractures (due to persistent hypertonia)
- Decreased movement
- Localization/limb distribution of neuromotor impairment varies from one child to another and so spastic CP can be further classified topographically.

In contrast, the clinical features of extrapyramidal (non-spastic) CP are [6, 18, 19]:

- Tone is variably increased (varies from hypertonia to hypotonia) depending on the state, that is, tone is increased by activity, agitation, tension, and emotions like crying, but tone is decreased in sleep and when relaxed. Caregiver usually tells the clinician that their child limbs feel normal when asleep or quiet.
- The quality of the increased tone is "lead pipe" rigidity or "candle wax" type and is elicited clinically by a slow passive flexion and extension of a limb. The increased resistance to this passive movement is felt all through the movement. Besides, extrapyramidal hypertonus can be diminished by repetitive movement and this is called "shaking it out."
- Deep tendon reflexes are usually normal or mildly increased (grade 1+ to 3+).
- A negative Babinski sign.
- Unsustained ankle clonus.
- Positional contractures (the variable tone is protective against contractures and so contractures like hip/knee flexion contracture only occur after prolonged periods on a wheelchair).
- Movement is disordered. Thus, extrapyramidal CP is also called dyskinetic CP.
- There is a four-limb functional impairment that precludes further topographic classification. However, extrapyramidal or dyskinetic CP is further subdivided based on the different manifestations of abnormal/involuntary movements (dyskinesia) and tone. The subtypes are choreathetoid CP—characterized by excessive and rapid movements involving the proximal body parts (trunk) (chorea) combined with slow writhing movements of

the distal parts of the body (extremities) (athetosis) and usually with reduced tone. This is the commonest type of extrapyramidal CP. Dystonic CP is characterized by extrapyramidal hypertonia and decreased movement (hypokinesia). Dystonia occurs when there is simultaneous contraction of both agonist and antagonist muscles. Ataxic CP occurs when there are signs of incoordination and hypotonia caused by damage to the cerebellum. This is a rare form of CP [6, 18, 19].

One merit of the physiological classification is that it can suggest the areas of brain damage and possible etiological factors. For instance, spasticity would suggest damage to the cortical neurons (pyramidal cells) due to hypoxic ischemic encephalopathy (HIE) from severe perinatal asphyxia and postnatal central nervous system (CNS) infections like meningitis [19]. In addition, dyskinetic CP points to damage to the basal nuclei by bilirubin encephalopathy and severe perinatal asphyxia at term [19]. Therefore, the physiological classification is still clinically useful.

However, the physiological classification is not reliable [6, 18, 20]. The terms spastic (pyramidal) and extrapyramidal CP are strictly incorrect [6, 18, 20]. It is more accurate to refer to these as "predominantly spastic" and "predominantly non-spastic." Due to the complex interactions of the upper motor neuron system (the pyramidal, extrapyramidal, and cerebellar pathways) with the anterior horn cells to control posture and movement, lesions causing CP in real life usually involve both pyramidal and extrapyramidal pathways [21]. Strictly speaking, pyramidal lesions induce spasticity as a result of concomitant damage to extrapyramidal pathways [21]. This explains the clinical combination of motor/movement abnormalities, for example, spasticity and dystonia, and spasticity and choreoathetosis. This is the so-called mixed CP subtype. From the explanation above, this CP subtype should actually be very common but from published studies [22, 23], spastic CP remains the commonest type thereby exposing the subjectivity and imprecision in assessment of patients based on this classification. Additionally, the physiological classification does not aid therapy or inform management of patients with CP, and this inability to indicate functional abilities remains a major drawback [6, 18, 20].

3.2. Topographic classification

This classification relies on the localization/limb distribution of neuromotor impairment in spastic CP [19]. It subdivides spastic CP into: quadriplegia (symmetric/equal and severe spasticity of all four limbs), diplegia (involvement of the four limbs but greater spasticity and weakness in the lower limbs) and hemiplegia (involvement of the upper and lower limbs on one side of the body) [19]. Other types of spastic CP such as tripegia (three-limb spasticity) and monoplegia (one-limb spasticity) are rare, and double hemiplegia (four extremity involvement with greater spasticity of the upper limbs) is no longer in use [6, 20].

An advantage of this classification is that these topographical subtypes can be linked to some etiological factors. For instance, diplegia suggests periventricular leukomalacia due to prematurity/low birth weight; hemiplegia suggests perinatal stroke, periventricular hemorrhagic infarction or neonatal cortical infarction while quadriplegia suggests severe perinatal

asphyxia at term, postnatal infection (bacterial meningitis) and metabolic/genetic disorders [19]. However, the descriptive terms in the topographic classification cannot be used reliably [6, 20]. One notable source of confusion is distinguishing spastic diplegia from quadriplegia. This distinction is highly subjective since it is unclear how much upper limb spasticity is needed to separate a diplegia from a quadriplegia [6, 20]. Recall that there is involvement of the four limbs in both subtypes. The arm and leg naturally perform different functions, and assessing the relative severity of involvement is difficult [1]. Moreover, the imprecise use of these terms in clinical practice has been reported by Gorter et al. [24] Many experts agree that the use of these terms in classification should be stopped [1]. Furthermore, the topographic classification does not consider functional abilities and so does not aid therapy or inform management of these children [6, 20]. Therefore, the topographic and physiological classifications share similar merits and demerits.

3.3. Supplemental classification

This is an additional grouping that comprises the accompanying impairments in CP and their association with the physiological and topographic classifications [6, 20]. The accompanying physical, mental or physiological impairments in CP include epilepsy, cognitive (intellectual), speech, visual and hearing impairments, behavioral problems and secondary musculoskeletal abnormalities (hip dislocation/subluxation, contractures) [1, 2]. The purpose of linking these supplemental disorders to the physiological and topographic classifications was to identify syndromes with a common etiology that would lead to prevention [6, 20]. Unfortunately, the supplemental disorders correlated poorly with the two earlier classifications. This means that it was only in a few examples like bilirubin encephalopathy that such a link between supplemental disorders, physiology and etiological factor could be established. For instance, the combination of accompanying impairments—vertical gaze palsy, sensorineural deafness and enamel dysplasia—is associated with choreoathetoid CP (physiology) from damage to the basal nuclei by bilirubin encephalopathy (etiological factor) [6, 20].

Though these associations were limited and the aim of the supplemental classification defeated, supplemental disorders (accompanying impairments) remain pertinent to the current management of CP because their presence strengthens the need for multidisciplinary management. This means that the accompanying impairments need to be taken into consideration in planning service delivery. Moreover, the accompanying impairments may cause more functional limitation than the primary motor dysfunction (the core feature of CP) and thus must be addressed to achieve a positive functional outcome. Furthermore, the most recent definition of CP [2] highlights the importance of these accompanying impairments by incorporating them as part of the definition of CP since CP rarely occurs without them. It is generally recommended that the presence or absence of these impairments and the extent to which they interfere with function be recorded in addition to the classifications used [1]. Currently, it is recommended that at least the presence/absence of epilepsy be recorded and intellectual function (IQ), vision and hearing be assessed [1].

3.4. Etiologic classification

The categorization based on the actual cause (etiology) and timing of insult was aimed at prevention, and the association of erythroblastosis fetalis with choreoathetoid CP was the paradigm for this classification [6, 20]. The etiology of CP is multifactorial, and the causal pathways are (mechanisms) multiple and complex. The Collaborative Perinatal Project [25] identified the associated risk factors for CP. Due to the fact that much of the data in these epidemiological studies [25, 26] are still correlational, "risk factors" are more appropriate than etiology. These risk factors or associated etiological factors in CP include genetic abnormalities, cerebral dysgenesis, multiple gestation, intrauterine/congenital infection (TORCHS), maternal infection (UTI), prematurity, low birth weight, perinatal asphyxia (HIE), bilirubin encephalopathy, postnatal CNS infections, etc. [19, 25, 26]. These associated etiological factors can be classified according to the timing of insult as prenatal (commonest), perinatal and postnatal [6, 19, 20].

Identifying both the disturbances or events and causal pathways or processes that led to the damage to the developing motor system remains a challenge [6, 20]. This is compounded by the fact that most of these factors are prenatal in timing. Therefore, the etiological classification was severely limited and failed in addressing prevention [6, 20].

3.5. Neuroanatomic (neuropathologic) classification

This classification correlates specific radiologic findings (brain structural alterations) with types of CP [6, 20]. This implies categorizing CP patients based on neuroradiologic findings. Thus, the neuropathologic classification relies on neuroimaging studies such as magnetic resonance imaging (MRI) and computed tomography scan (CT scan).

Neuroimaging contributes significantly to the understanding of the etiology and pathology of CP and the timing of insults [1, 6, 20]. In a systematic review of neuroimaging for cerebral palsy, Korzeniewski et al. [27] classified abnormal radiological findings and diagnoses into five categories namely: malformations, gray matter damage, white matter damage, ventriculomegaly, atrophy or CSF space abnormalities and miscellaneous findings.

Though the correlations between the neuropathologic substrates and clinical types have been weak and inconsistent, recent advances such as diffusion tensor imaging, magnetic resonance spectroscopy, functional magnetic resonance imaging and fast spin echo imaging have improved greatly the possibility of a comprehensive radiologic classification [6, 20, 27]. A recent study by Hou et al. [28] continues to correlate neuropathologic findings with different clinical types of CP. For example, dyskinesia correlated with lesions detected by MRI in the thalamus and putamen due to HIE and in the globus pallidus and hypothalamus due to kernicterus.

There are also difficulties in estimating the timing of insults in CP using neuroimaging findings. It was initially assumed that the presence of neuronal migrational disorders meant that the insult occurred in the first half of pregnancy while the presence of a glial response indicated insults around the second half of pregnancy [27]. However, there is evidence that cell

migrational disorders can occur in the last 2–3 months of pregnancy [27]. Nevertheless, malformations are more likely to occur earlier in gestation, and thus, neuroimaging confirmation of their presence can help establish that the cause of CP is unrelated to perinatal events [27].

Categorizing patients with CP based on neuroradiologic findings implies that neuroimaging studies be carried out on all patients. Therefore, it will be difficult to apply such classification in resource-poor countries where neuroimaging facilities are not readily available or affordable and the professional expertise needed may be lacking. Despite this, the American Academy of Neurology (AAN) recommends neuroimaging studies on all children with CP whenever possible [27]. The bottom line is that neuroimaging can be used to identify the neuropathologic substrates of the various etiologic and risk factors of CP, possibly provide information about timing of insults and detect cerebral dysgenesis or malformations but, at present, a comprehensive neuropathologic classification is still in the pipeline.

3.6. Therapeutic classification

This scheme categorizes CP cases based on treatment needs into four groups namely: non-treatment, modest treatment, need for a CP treatment team, and pervasive support groups [6, 20]. Parents/caregivers want their children to receive treatments that will improve their condition, so any classification that is implicative of treatment is important to the patients and their caregivers and relevant to clinical practice. There is a consensus in the literature that the therapeutic and functional classifications are the most important to the patient [1, 6, 20].

However, the therapeutic classification simply identifies how much treatment or the extent of interventions a given child requires without specifying what is actually needed to improve function. This explains the little emphasis on the therapeutic classification.

3.7. Functional classification

Functionally, CP is classified into levels of severity based on functional (motor) abilities and/or limitation of activity [1, 6, 20]. Currently, the emphasis on the functional classification is due to its important role in the management of CP. So there is a rekindled interest in this scheme.

The functional classification remains the best classification of CP because it is a useful guide to providing care for patients appropriate for their functional level and helps clinicians set and discuss with parents/caregivers realistic rehabilitation goals [1, 4, 5, 11, 12]. The functional classification satisfies the needs of patients and parents/caregivers by informing the current and future service needs of children with CP [5]. It provides information that will permit comparison of CP cases in different locations. It provides information that will allow evaluation of change at different points in time in the same patient such as after an intervention [1].

However, it falls short of giving full descriptive information about a child with CP that clearly delineates the nature of the problem. It does not indicate the nature of the motor abnormality, the topography, the etiology, or neuropathologic substrates which in their own respects are

important descriptive information. Besides, it does not indicate supplemental disorders that are necessary for assessing the service delivery needs of patients with CP.

Iloeje and Ogoke [29] in 2017 reported that the type of CP (physiology and topography), etiological factors and the number of accompanying impairments (supplemental disorders) were positively associated with the severity of gross motor dysfunction and walking ability of children with CP. In that study [29], children with spastic quadriplegic type, bacterial meningitis as etiological factor or many (five or six) accompanying impairments all had severe gross motor dysfunction and were non-ambulatory. Therefore, the other classifications may suggest functional abilities in children with CP.

4. Traditional classifications of CP based on multiple variables

These are the Swedish classification [8], Edinburgh classification [9] and Surveillance for Cerebral Palsy in Europe (SCPE) classification [10].

4.1. The Swedish classification

CP subtypes based on the Swedish classification (1989) [8] are spastic (hemiplegic, tetraplegic, and diplegic), dyskinetic (dystonic and athetotic), ataxic and unclassified/mixed. It is immediately obvious that this classification combines the Minear's Physiologic and Topographic schema. Thus, it shares the same merits and demerits as the physiological and topographic classifications as earlier discussed.

4.2. The Edinburgh classification

According to the Edinburgh classification [9], there are six subtypes of CP namely hemiplegia, bilateral hemiplegia, diplegia, ataxic, dyskinetic and other forms of CP including mixed forms. This classification is a combination of classifications based on topography and physiology and so has the same advantages and shortcomings as the topographic and physiologic classifications.

4.3. The Surveillance for Cerebral Palsy in Europe (SCPE) classification

The SCPE [10] classifies CP into the following four subtype groups: spastic (bilateral and unilateral), dyskinetic (dystonic and choreoathetotic), ataxic, and non-classifiable. This grouping also combines the physiological and topographic classifications. The classification tree of the SCPE for subtypes of CP is shown in **Figure 1**.

Due to the lack of reliability of the terms used in Minear's topographic classification, SCPE [10] introduced two new terms to replace quadriplegia, diplegia, and hemiplegia. These terms are bilateral and unilateral used to describe involvement of both sides and one side of the body, respectively. By this classification, spastic quadriplegia and spastic diplegia are classified as bilateral spastic CP (BS-CP) while spastic hemiplegia is termed unilateral spastic CP. This

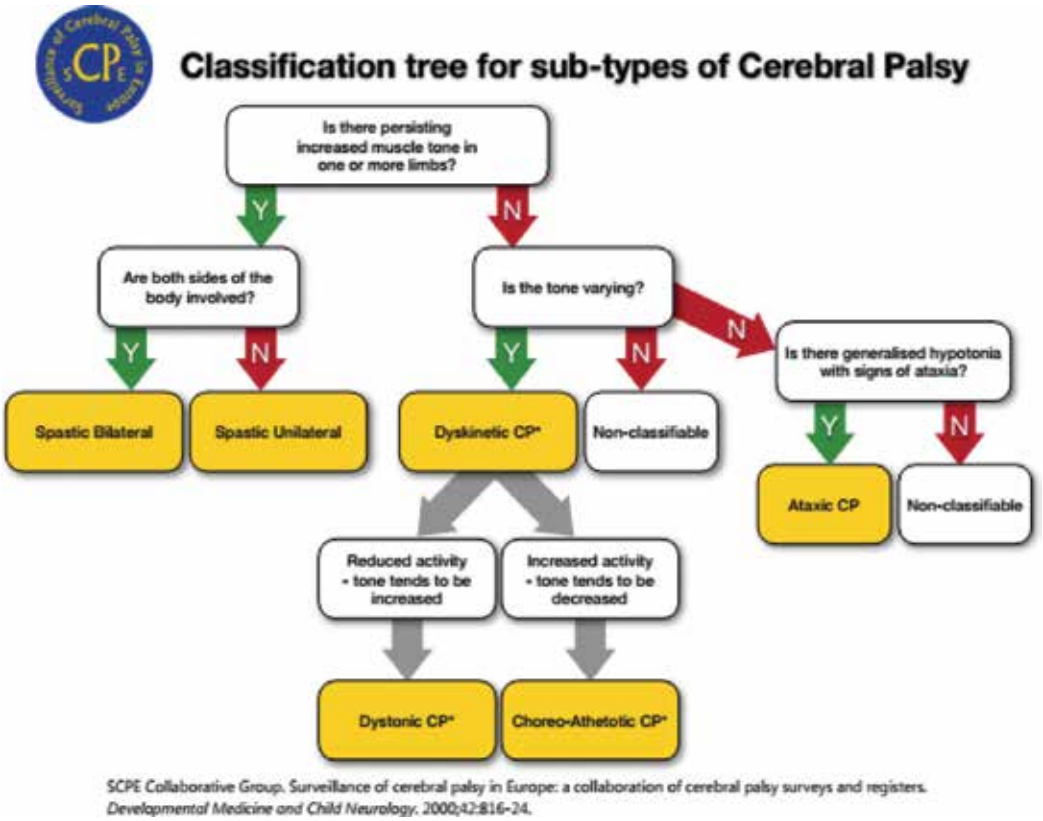


Figure 1. Classification tree for sub types of CP by SCPE.

classification is easy to apply and is more reliable than the earlier traditional classifications. Therefore, by improving the reliability of the terms used in the topographic component of this classification, the SCPE currently seems to be the best traditional classification for description of patients with CP.

However, the SCPE classification [10] does not include functional abilities and so does not aid therapy for patients with CP. Hence, this classification currently has not had a similar level of advocacy as the functional classifications.

5. Current classifications of CP

Currently, functional classification of each case of CP is internationally advocated due to its important role in management. Thus, current classifications of CP are functional scales for various functions impaired in CP such as communication, gross motor, fine motor, and oromotor/oropharyngeal functions. They are basically ordinal scales to categorize functional abilities or severity of limitation of activity and are not used as outcome measures, tests or

assessments [14, 30]. They are simple and easy to apply both by healthcare professionals and care givers and are good for clinical use and patient stratification for research purposes [5, 11, 30]. They have been validated by studies [12, 13, 15] and shown to be objective and reliable clinical classification systems for CP. They have replaced previously used imprecise and subjective functional classifications of CP into mild, moderate and severe.

Their development resulted from the paradigm shift from a focus on body structure and function (impairment-based assessments and treatments) to current emphasis on activity or participation (function and social engagement) [3–5]. These concepts are contained in the ICF [3]. The ICF is a new classification system for health and disease that is universal (for everybody not only people with disabilities) [3]. It is a new way to consider health conditions and posits an interactive relationship between health conditions and contextual factors (environmental and personal factors) in which all components are linked together [3, 4]. It represents a coherent view of health from biological, individual and social perspectives (a biopsychosocial approach to health, functioning and disability) [4]. The ICF model has been used to guide clinical thinking and service delivery to patients with CP [4]. This conceptual change introduced by the ICF is topical.

The functional classifications are analogous and when used together complete the description of daily functional activities in CP at the activity or participation level of the ICF [3, 30]. They include

a. Gross Motor Function Classification System (GMFCS) [11]

b. Manual Abilities Classification System (MACS) [14] & Mini—MACS [31]

c. Communication Function Classification System (CFCS) [16]

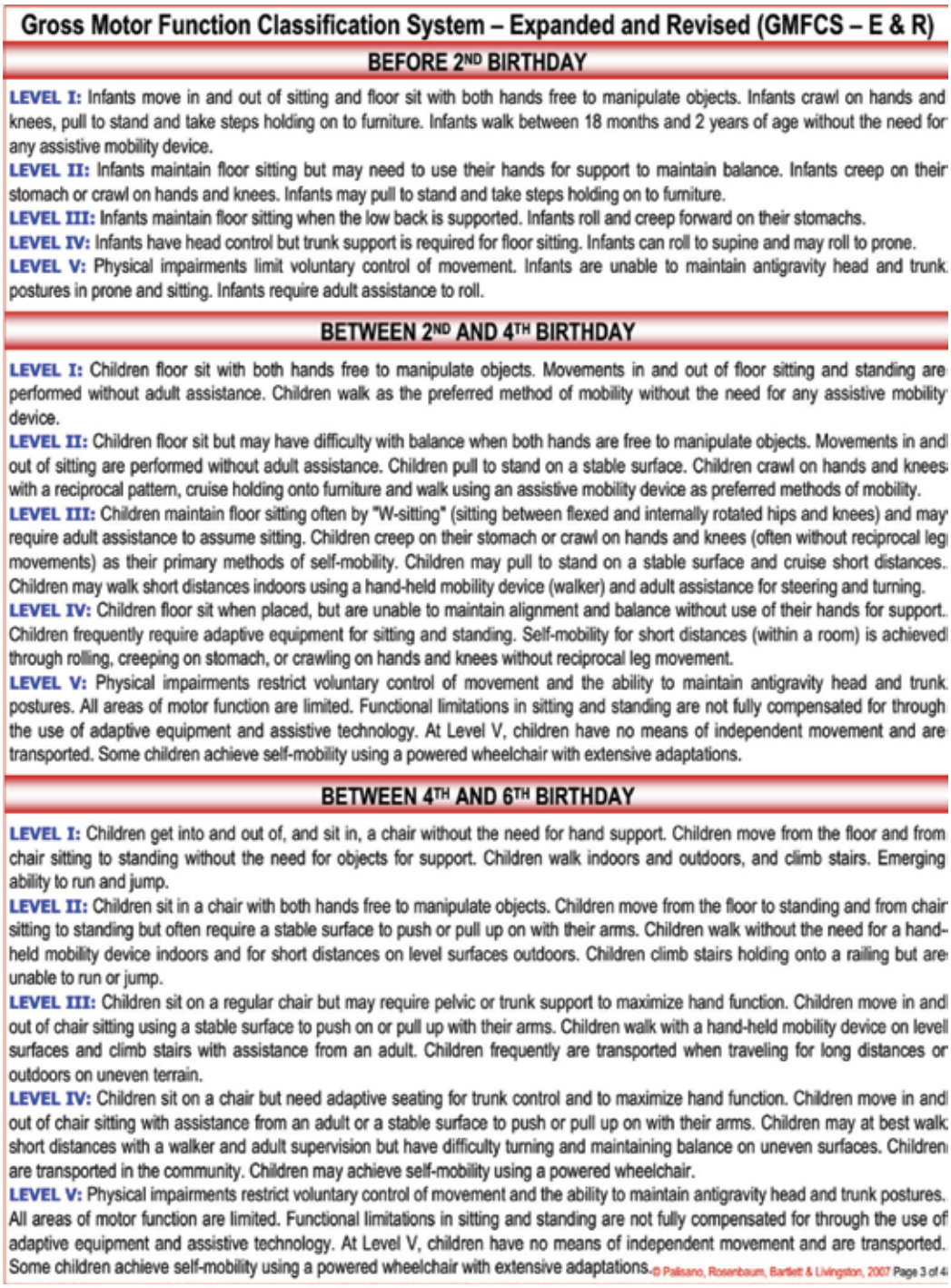
d. Eating & Drinking Ability Classification System (EDACS) [17]

There are other functional scales like the Functional Mobility Scale (FMS), Bimanual Fine Motor Function (BFMF), Functional Assessment Questionnaire (FAQ), the Pediatric Orthopaedic Society of North America Outcomes Data Collection Instruments (PODCI), etc.

However, the first four are more commonly used and will be discussed here.

5.1. Gross Motor Function Classification System (GMFCS)

This is the most widely used clinical functional classification of CP [1]. It is an ordinal scale that categorizes a child's mobility/ambulatory or lower limb function in five levels ranging from walking without restrictions (level I) to inability to maintain antigravity head and trunk postures (level V) [11]. The first version of GMFCS was published in 1997 by Palisano et al. [11] and described gross motor functional abilities and limitations in children aged less than 12 years. The upper limit of 12 years (before end of adolescence) was a limitation of the first version, and the GMFCS was revised and expanded in 2007 by Palisano et al. [32] to include an age group for youths 12–18 years. This current version of GMFCS [32] emphasizes the concepts inherent in the WHO's International Classification of Functioning, Disability and Health (ICF). The GMFCS—ER [32] is shown in **Figure 2**. A summary of the criteria for the GMFCS [11, 32] is as follows:



Gross Motor Function Classification System – Expanded and Revised (GMFCS – E & R)

BEFORE 2ND BIRTHDAY

LEVEL I: Infants move in and out of sitting and floor sit with both hands free to manipulate objects. Infants crawl on hands and knees, pull to stand and take steps holding on to furniture. Infants walk between 18 months and 2 years of age without the need for any assistive mobility device.

LEVEL II: Infants maintain floor sitting but may need to use their hands for support to maintain balance. Infants creep on their stomach or crawl on hands and knees. Infants may pull to stand and take steps holding on to furniture.

LEVEL III: Infants maintain floor sitting when the low back is supported. Infants roll and creep forward on their stomachs.

LEVEL IV: Infants have head control but trunk support is required for floor sitting. Infants can roll to supine and may roll to prone.

LEVEL V: Physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting. Infants require adult assistance to roll.

BETWEEN 2ND AND 4TH BIRTHDAY

LEVEL I: Children floor sit with both hands free to manipulate objects. Movements in and out of floor sitting and standing are performed without adult assistance. Children walk as the preferred method of mobility without the need for any assistive mobility device.

LEVEL II: Children floor sit but may have difficulty with balance when both hands are free to manipulate objects. Movements in and out of sitting are performed without adult assistance. Children pull to stand on a stable surface. Children crawl on hands and knees with a reciprocal pattern, cruise holding onto furniture and walk using an assistive mobility device as preferred methods of mobility.

LEVEL III: Children maintain floor sitting often by "W-sitting" (sitting between flexed and internally rotated hips and knees) and may require adult assistance to assume sitting. Children creep on their stomach or crawl on hands and knees (often without reciprocal leg movements) as their primary methods of self-mobility. Children may pull to stand on a stable surface and cruise short distances. Children may walk short distances indoors using a hand-held mobility device (walker) and adult assistance for steering and turning.

LEVEL IV: Children floor sit when placed, but are unable to maintain alignment and balance without use of their hands for support. Children frequently require adaptive equipment for sitting and standing. Self-mobility for short distances (within a room) is achieved through rolling, creeping on stomach, or crawling on hands and knees without reciprocal leg movement.

LEVEL V: Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent movement and are transported. Some children achieve self-mobility using a powered wheelchair with extensive adaptations.

BETWEEN 4TH AND 6TH BIRTHDAY

LEVEL I: Children get into and out of, and sit in, a chair without the need for hand support. Children move from the floor and from chair sitting to standing without the need for objects for support. Children walk indoors and outdoors, and climb stairs. Emerging ability to run and jump.

LEVEL II: Children sit in a chair with both hands free to manipulate objects. Children move from the floor to standing and from chair sitting to standing but often require a stable surface to push or pull up on with their arms. Children walk without the need for a hand-held mobility device indoors and for short distances on level surfaces outdoors. Children climb stairs holding onto a railing but are unable to run or jump.

LEVEL III: Children sit on a regular chair but may require pelvic or trunk support to maximize hand function. Children move in and out of chair sitting using a stable surface to push on or pull up with their arms. Children walk with a hand-held mobility device on level surfaces and climb stairs with assistance from an adult. Children frequently are transported when traveling for long distances or outdoors on uneven terrain.

LEVEL IV: Children sit on a chair but need adaptive seating for trunk control and to maximize hand function. Children move in and out of chair sitting with assistance from an adult or a stable surface to push or pull up on with their arms. Children may at best walk short distances with a walker and adult supervision but have difficulty turning and maintaining balance on uneven surfaces. Children are transported in the community. Children may achieve self-mobility using a powered wheelchair.

LEVEL V: Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent movement and are transported. Some children achieve self-mobility using a powered wheelchair with extensive adaptations.

Figure 2. Gross Motor Function Classification System—Expanded & Revised (GMFCS—E & R). Reproduced with permission.

a. Level I—Walks without limitations.

b. Level II—Walks with limitations.

c. Level III—Walks using hand-held mobility device.

d. Level IV—Self mobility with limitations; may use powered mobility.

e. Level V—Transported in a wheelchair.

These general headings or titles for each level represent the method of mobility or highest level of mobility that a child with CP is expected to achieve after 6 years of age [11].

Current management of CP involves a liberal use of adaptive/augmentative equipment in addition to impairment-based treatment approaches to achieve independence [5]. A major goal in the management of CP is to ambulate the children and enable independent living; this gave birth to the changing concepts and the GMFCS. So, how GMFCS is a useful guide to providing care appropriate for the functional level and age of a child with CP?

A child on GMFCS level I will walk independently and so requires no adaptive mobility equipment but appropriate stimulation. The child on level II may need hand-held mobility device when first learning to walk (younger than 4 years) and eventually walks with limitations (after 6 years). Thus, a hand-held mobility device may be provided initially for the child on level II. Therefore, the management of patients on GMFCS levels I and II would focus on appropriate stimulation, preventing complications from occurring and treatment of accompanying impairments. The child on GMFCS level III will require adaptive equipment for low back support for floor and chair sitting and at about 6 years, a hand-held mobility device for walking indoors and a self-propelled manual wheelchair for mobility outdoors and in the community. The management is multidisciplinary depending on the nature and number of accompanying impairments. It is important to note that the child on GMFCS level III may be added to children on levels I and II (walking at least indoors) or to children on levels IV and V (wheeled mobility at least in the community). Nevertheless, GMFCS level III is usually classified as ambulatory because the child is independently mobile in some settings irrespective of the need for assistive mobility device. This need or use of adaptive mobility equipment is acceptable (current thinking) [5]. In addition to multidisciplinary care, the child on GMFCS level IV requires initially a body support walker that supports the pelvis and trunk for floor and chair sitting and later powered mobility and a manual wheelchair for transportation outdoors, at school, and in the community. The management of a child on GMFCS level V involves pervasive supports and a manual wheelchair for transportation in all settings (physical assistance at all times) [11].

5.2. Manual Abilities Classification System (MACS) and mini-MACS

The MACS [14] and the mini-MACS [31] are five-level scales for classifying arm and hand function (manual abilities/manual dexterity) in children with CP aged 4–18 years and 1–4 years, respectively. They classify children's usual performance in handling objects with two hands (not best use or individual hand function) in important daily activities (**Figures 3** and 4).

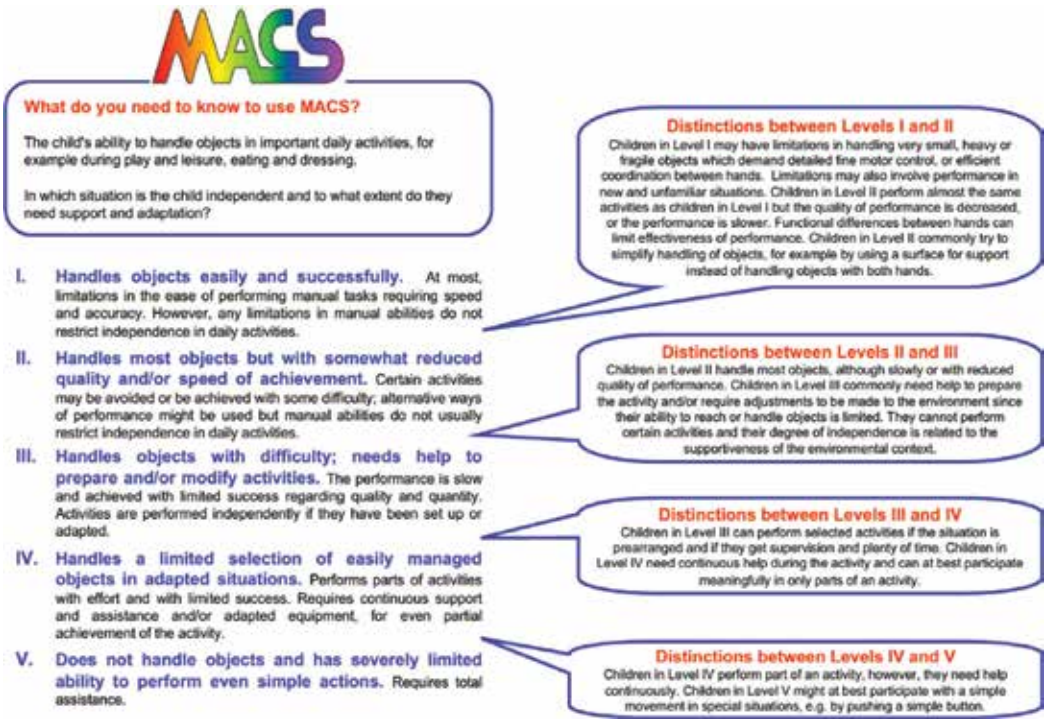


Figure 3. The Manual Ability Classification System (MACS). Reproduced with permission [14].

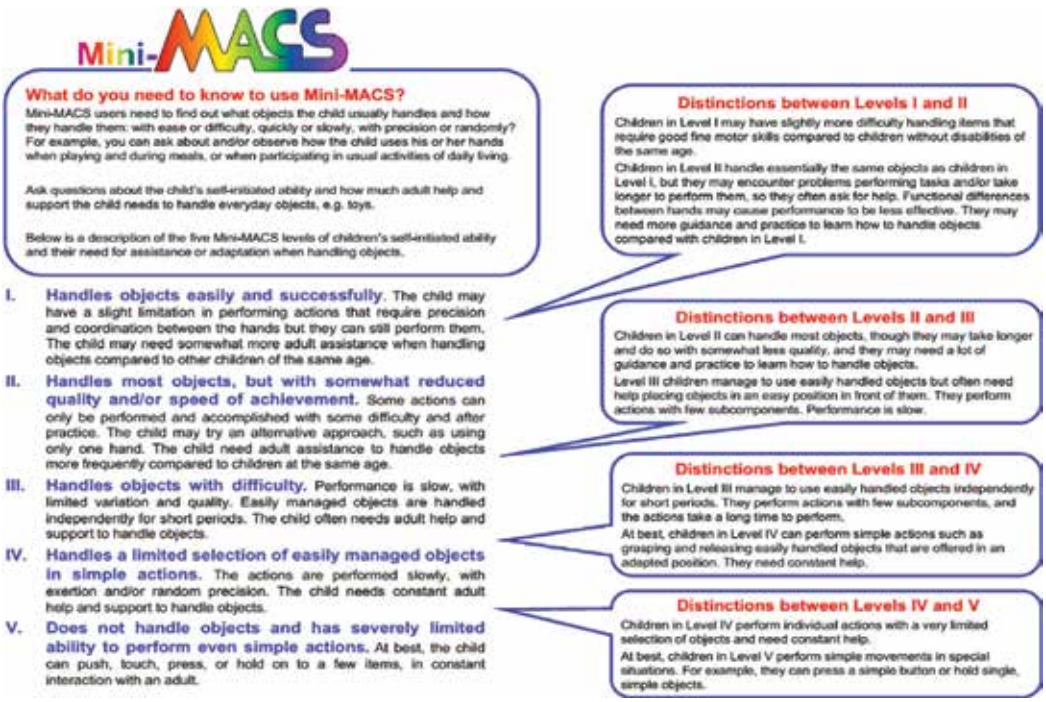


Figure 4. The mini-Manual Ability Classification System (mini-MACS). Reproduced with permission.

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The MACS, developed in 2006 by Eliasson et al. [14] and modeled on the GMFCS, has been shown by various studies to be valid and reliable. However, a study in 2009 by Plasschaert et al. [33] reported lower inter-rater reliability of the MACS when used in children aged 1–5 years (linear weighted Kappa (k) of 0.67 and 0.55 for 2–5 years and 2 years, respectively). Thus, the MACS was adjusted in 2016 by Eliasson et al. [31] to obtain the mini-MACS which was shown to have excellent inter-observer reliability. The adjustments were simply to obtain descriptions that are applicable to children less than 4 years of age. The mini-MACS differs from the MACS due to the need for assistance in handling objects in children 1–4 years and the nature of the objects they are expected to handle.

The MACS is used to ascertain the child's needs and inform management decisions such as choosing an appropriate upper limb intervention. That is, they are used like the GMFCS to guide functional intervention. For instance, children on MACS levels I and II handle objects independently and do not require any adaptive device to handle objects. The children on level III require some assistance and sometimes adaptive equipment for independent handling of objects. Children on level IV require continuous assistance and adaptive equipment while those on level V need total assistance. Eliasson et al. [31] posited that the mini-MACS is probably not sensitive to changes and should therefore not be used to evaluate development or intervention, but rather to categorize how suspected CP affects the manual abilities of children 4 years and younger.

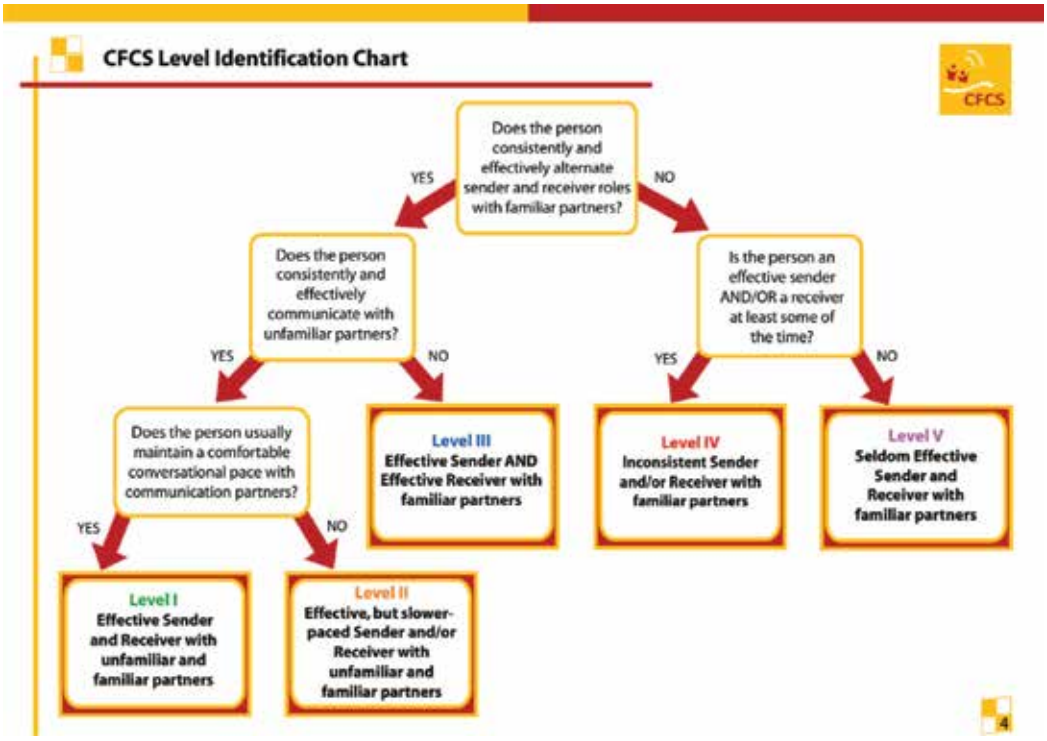

Figure 5. The Communication Function Classification System (CFCS). Reproduced with permission [16].

5.3. Communication Function Classification System (CFCS)

The CFCS was developed and validated by Hidecker et al. [16] in 2011. It classifies everyday communication performance of an individual with CP into five levels ranging from effective communication in all settings (level I) to ineffective communication even with familiar partners (level II). The categorization of the effectiveness of current communication is based on the performance of sender and receiver roles, the pace of communication, and the type of conversational partner. In ascertaining the current level of communication, the CFCS aptly considers and includes use of all methods of communication. This implies that it describes both use of normal verbal and non-verbal communication (speech, gestures, behaviors, eye gaze, and facial expressions) and use of augmentative and alternative communication systems (AACs) (manual sign, pictures, communication books, communication boards and talking devices such as speech generating devices and voice output communication aids) [16]. The CFCS level identification chart is shown in **Figure 5**.

5.4. Eating and Drinking Ability Classification System (EDACS)

The EDACS was developed by Sellers et al. [17] in 2014 and comprises two ordinal scales that describe eating and drinking ability in people with CP from 3 years of age. The five-level scale classifies the safety and efficiency of eating and drinking while the three-level scale classifies level of assistance required to bring food and drink to the mouth. The five-level

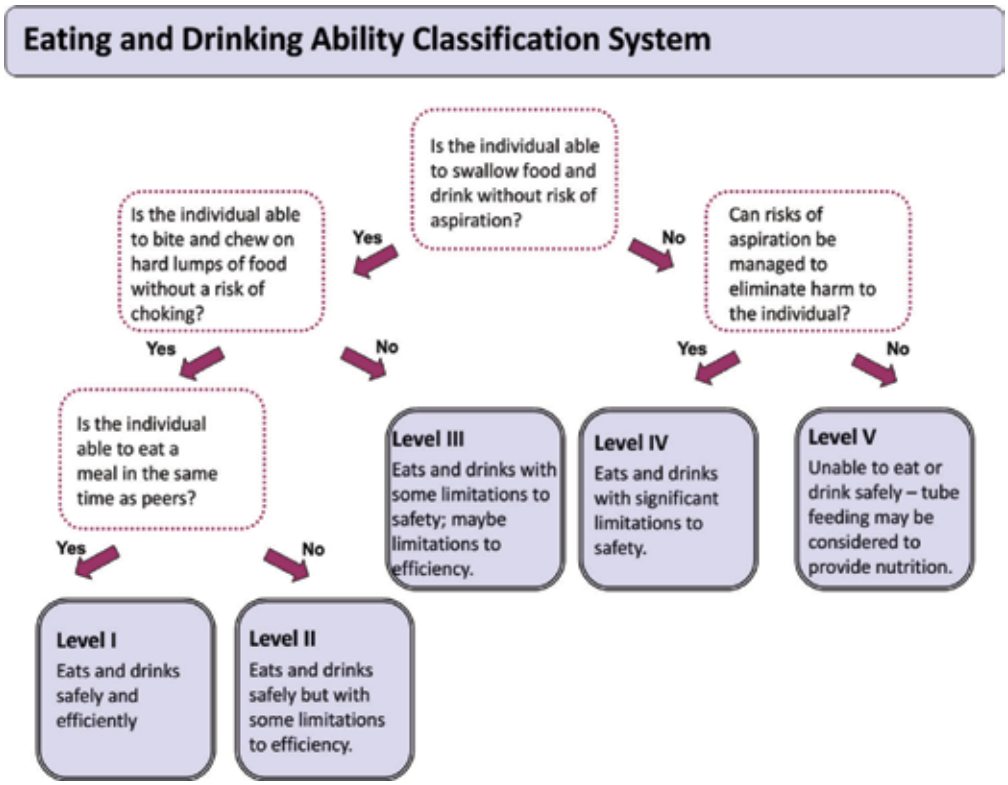

Figure 6. Eating and Drinking Ability Classification System (EDACS) algorithm. Reproduced with permission [17].

scale is based on the range of food textures eaten, the presence of cough and gag when eating or drinking, and the control of movement of food and fluid in the mouth. The three-level scale is categorized into independent, requires assistance, and dependent for eating and drinking. Thus, the EDACS ranges from independent ability to safely and efficiently eat and drink like peers on a wide range of textures (level I) to total dependence for eating and drinking and reliance on tube feeding (level V) [17]. The EDACS algorithm is shown in **Figure 6**.

6. The importance of the current classifications

The final goal of a managing doctor and the final hope of a patient and his family is an ambulatory self-dependent individual. Using the functional classifications to guide management helps the pediatrician, the occupational therapist, the physiotherapist, the speech and language therapist and all involved in the care of children with CP to achieve this goal. For instance, the GMFCS is used to ascertain the requirements for ambulation appropriate for the age of the child and gross motor functional abilities while the MACS helps ascertain appropriate upper limb interventions for independent performance of activities of daily living. The CFCS by classifying communication effectiveness in CP is useful in service delivery. It helps identify those that will require augmentative and alternative communication systems to improve their communication. The EDACS assists in identifying the appropriate food texture to give a particular child, need for assistance, the risks involved in eating and drinking and the appropriate method of feeding (oral/tube feeding). Therefore, in simplistic terms, these current classifications tell us what to do to the child with CP. A summary of all groups of classifications is shown in **Tables 1–3**.

Classification axis	Criterion/characteristic used	Inter rater/ inter observer reliability	Suitability for research (description, comparison/ stratification) (on a scale of 1–5)	Indication of functional abilities	Aiding/ guiding current management
Physiological	Type of motor/movement abnormality (quality and changes in tone)	Poor	++	No	No
Typographic	Distribution/localization of motor impairment	Poor	++	No	No
Supplemental	Accompanying impairments	Not reported	Not reported	No	Yes
Aetiologic	Actual cause and timing of insult	Not available	Not available	Not available	No
Neuroanatomic	Brain structural alterations on neuroimaging	Not available	Not available	Not available	No
Therapeutic	Individual treatment needs	Not reported	Not reported	No	No
Functional	Degree of severity/ activity limitation	Good	+++ (good)	Yes. Its major advantage	Yes. Its strength

Table 1. Comparison of traditional (Minear's) classifications based on single variables.

Classification	Minear's classifications combined	Criteria/characteristics used	Inter rater/ inter observer reliability	Suitability for research (on a scale of 1–5)	Indication of functional abilities	Aiding/ guiding current management
Swedish classification	Physiological and topographic	Type of motor abnormality + localization of motor impairment	Poor	++	No	No
Edinburg classification	Physiological and topographic	Type of motor abnormality + localization of motor impairment	Poor	++	No	No
SCPE Classification	Physiological and modified topographic	Type of motor abnormality + localization of motor impairment as unilateral and bilateral only.	Fair	+++	No	No

Table 2. Comparison of traditional classifications based on multiple variables.

Classification	Criterion/ characteristic used	Inter rater/ inter observer reliability	Suitability for research	Indication of functional abilities	Aiding/ guiding current management	Age range included (year developed)	Nature of scale(s)
GMFCS	Gross motor/ ambulatory/ lower limb function (current gross motor abilities/activity limitations)	Good	Yes (valid and reliable)	Yes	Yes	GMFCS (birth–12 years) (1997) GMFCS-E&R (birth–18 yreas) (2007)	Ordinal (5-level)
MACS	Manual dexterity/ upper limb function (usual performance in handling objects with two hands).	Good	Yes (valid and reliable)	Yes	Yes	MACS (4–18 years) (2006) Mini-MACS (1–4 years) (2016)	Ordinal (5-level)
CFCS	Communication function (everyday communication performance)	Good	Yes (valid and reliable)	Yes	Yes	≥3 years. (2011)	Ordinal (5-level)
EDACS	Eating & drinking ability/ oropharyngeal/ swallowing function (safe and efficiency of eating and drinking and level of assistance required)	Good	Yes (valid and reliable)	Yes	Yes	2–12 years. (2014)	Two ordinal scales (one 5-level, one 3-level)

Table 3. Comparison of current (functional) classifications.

http://dx.doi.org/10.5772/intechopen.79246

7. A holistic (standardized) classification of CP: the future

The development of a standardized or holistic classification of CP is topical and in tandem with advances in understanding of CP, imaging techniques and quantitative motor assessments [1]. Bax et al. [1] in 2005 proposed a standardized CP classification scheme with four major components namely:

1. Motor abnormalities (a. nature and typology of motor disorder and b. functional motor abilities)
2. Associated impairments
3. Anatomic and radiologic findings
4. Causation and timing.

Currently, there are obvious limitations with categorization of neuroimaging findings and identifying specific causes of CP. Therefore, as we await comprehensive and acceptable neuroanatomic and etiologic classifications, the minimum acceptable multiaxial classification of CP for both developed and developing countries should include:

1. Classification of motor abnormalities according to SCPE.
2. Accompanying impairments
3. Functional classification levels for: gross motor/ambulatory function (GMFCS), manual abilities (MACS), communication, (CFCS) and eating and drinking ability (EDACS).

This implies that only the first two components of the standardized classification proposed by Bax et al. [1] are applicable currently. The classification by SCPE provides enough clinical descriptive information about children with CP while the supplemental and functional classifications are useful for management and service delivery. The use of the functional scales in clinical context (to aid management) and in research is in accordance with current thinking and the reconceptualization of the management of CP.

8. Conclusions

Each classification system used in CP has its merits and shortcomings. Therefore, the clinical classification of CP needs to use many axes to be comprehensive. Currently, it must include the functional scales so as to guide management.

The neuropathologic classification is being awaited, and due to its contribution to the assessment of etiological factors and timing of insults in CP, it is critical to the development of a holistic or standardized classification of CP.

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Conflict of interest

None.

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Section 3

Clinical Aspects of Cerebral Palsy

Chapter 3

Survival, Mortality, and Life Expectancy

Steven M. Day and Robert J. Reynolds

Additional information is available at the end of the chapter

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Abstract

Cerebral palsy (CP) is a heterogenous condition, with level of disability ranging from immaterial to profound. In concert with the continuum of level of severity of disability/independent functioning, health care needs, therapies, medications, surgical interventions, costs of care, daily demands on parents and other family members, and expectations for the future in terms of education, employment, and other milestones of life all vary widely. Similarly, life expectancy in CP follows a continuum, from far lower than to potentially as high as general population life expectancy, that parallels the continuum of levels of disability. Here we review the literature documenting this, and examine the specific factors that are known to be strongly associated with mortality and longevity in CP. We also examine the evidence regarding causes of death in CP, and present some new findings related to this. Finally, we outline important methodological considerations for future research in this area.

Keywords: cerebral palsy, life expectancy, survival, mortality, developmental disability

1. Introduction

Just as Americans headed home for the year-end holidays, the Centres for Disease Control and Prevention (CDC) issued its annual report on mortality—which had no news to celebrate. According to the report, published on December 21st, life expectancy in America fell in 2016, for the second year in a row. An American baby born in 2016 can expect to live on average 78.6 years, down from 78.9 in 2014. The last time life expectancy was lower than in the preceding year was in 1993. The last time it fell for two consecutive years was in 1962-1963. - The Economist, 4 January 2018 [1].

The concept of life expectancy is familiar to most people by virtue of reports in newspapers, online sources, or on television or radio. Comparisons of life expectancy at birth in various industrialized countries are common, and thus many people may know or will not be surprised to find that life expectancy is higher in Japan than it is in the US, or that in Russia it is lower than in most countries of Europe. Many may also have some general ideas as to why such differences may exist: diet, exercise, smoking prevalence, access to healthcare may all contribute. Mortality is the ultimate endpoint for studies of health and wellbeing, and life expectancy is one way to summarize the survival and mortality experiences of different groups of people.

Few give much thought as to how exactly we can know that life expectancy in America fell in 2016, as The Economist reports [1]. To fully understand how we can know that (or know that life expectancy in Japan is higher than it is in the US, or that life expectancy for the Hispanic population in the US is greater than it is for people in the US overall, or that women have a greater life expectancy than men almost universally), one needs to understand what life expectancy is, and how it is calculated. In this chapter we will begin with a brief review of the life table, the principle tool used by demographers, actuaries, biostatisticians and epidemiologists in examining questions of life expectancy. In these contexts, life expectancy has a very specific meaning, and must not be confused with the actual survival time of a given individual.

Just as it is known that life expectancy in Japan is greater than in the US, it is also known that life expectancy for groups of people with differing medical conditions, behavior patterns, or professions can differ. It is probably not surprising, for example, that children born with complex congenital heart defects have a lower life expectancy than that of any general population (GP) of age- and sex-matched children (including all comers, with or without heart defects). Similarly, persons with various types of cancer have life expectancies that are lower than those of age- and gender-matched populations (including all comers with or without cancer). Within the population of children born with congenital heart defects, or persons with cancer, variation in life expectancy exist as the group is sub-divided according to level of complexity of heart defects, or site/stage/grade/histology of tumor. Similar statements apply when considering the life expectancy in cerebral palsy (CP). That people with cerebral palsy compose a heterogeneous group will be well understood by most readers of this chapter; as we shall see, the life expectancy of the group as a whole and of meaningfully defined subgroups differ dramatically as a consequence.

The life expectancy of persons with cerebral palsy (CP) is of interest to many audiences for varying reasons. Parents would like to know how long they might have to fulfill the often-challenging physical, emotional, and monetary demands of caring for a child with special needs; they wonder how long they might get to enjoy the rewards of that relationship and wonder and worry whether their child might outlive them. Resource allocation for long-term care facilities depends in part on their residents' longevity, a fact of interest to governments or private insurance companies providing funding for such facilities. Life insurance and structured settlement underwriters must consider life expectancy and other information in a life table in pricing insurance or annuities. Finally, and perhaps most controversially, in cases of litigation related to medical care and treatment alleged to have contributed to an outcome of

CP, life expectancy can be a critical factor in developing and valuing a life-care plan, the expected present value of which may be a large part of potential damages in such litigation.[1] Our interest in this chapter is to provide information based on sound scientific principles and evidence.

2. The life table and survival curve

Life expectancy (LE) is the arithmetic average survival time remaining for a cohort, hypothetical or real. In more technical statistical terms, it is the expected value of a population of random survival times. Alternatively, one can think of it as the average survival time for an individual member of a given population or cohort if such an individual could (hypothetically) live life over and over again.

In order to understand the meaning of life expectancy, and to gain insight into the questions posed above, a basic understanding of the life table is extremely helpful. As we shall see, information presented in a life table can also be set out in, or gleaned from, a survival curve. An understanding of the relationship between the life table and its corresponding survival curve will be helpful in understanding life expectancy *per se*, and in understanding the connection between many studies of long-term survival of children and adults with cerebral palsy, many of which report survival curves or the equivalent, and life tables and life expectancy.

2.1. The life table

Table 1 is an abbreviated version of the latest life table (2017 table based on 2013 data) for all US persons (males and females combined) from the US National Center for Health Statistics (NCHS) [2]. Life expectancy at each whole integer age is given in the column labeled *e(x)*. We can see from **Table 1**, for example, that the LE in the US is 78.8 years at birth; 50.1 remaining years at age 30 years; 23.2 remaining years at age 60; and 2.3 remaining years at age 100. Generally, the meaning of LE is the average remaining lifespan from a given age. This is not to be confused with the age to which a cohort of a given age is expected to live. Thus LE is 78.8 remaining years, to age 78.8, for newborns of age 0; it is 2.3 remaining years, to age 102.3, for those fortunate enough to survived to age 100.

In addition to LE, a life table provides other information, including (for example) (1) the likelihood that a person born today will be alive at age 50, 80, or 100; (2) the 5-year survival probability from any age; (3) the probability of surviving beyond age 70; (4) the median survival time, that is, the time at which half of the hypothetical cohort will have died and beyond which half will continue to live; and (5) the conditional probability of living to age 65 given one has already lived to age 40. Depending on the context, any of these figures may be of greater interest or importance than the LE at a given age; however, LE is the most often cited

[1]For full disclosure, we acknowledge that we, the authors of this chapter, have provided expert opinions on behalf of both plaintiffs and defendants in such legal cases, and will undoubtedly do so in the future.

summary measure of survival. For further details about the columns of the life table and their inter-relationships, the reader is directed to the many references included below [2–6].

2.2. Survival curves

We now focus on age and the column *l(x)* of **Table 1**. If we divide the figures in the *l(x)* column by the radix of the table (*l(0)* = 100,000), we obtain the probability of survival to each age. **Figure 1** plots the resulting survival probabilities against age, the survival curve corresponding to the full US life table (males and females combined).

The unabbreviated version of the life table [2] and the corresponding survival curve (**Figure 1**) provide essentially the same information. The area under the survival curve equals the LE calculated in the life table; if a line vertical line is drawn at any given age in the survival curve figure, the area under the curve (and bounded by the x- and y-axes) from that point to the right will be the life expectancy at that age. In **Figure 1**, the area under the curve from age 70 to age

Age	l(x)	d(x)	q(x)	m(x)	L(x)	T(x)	e(x)
0	100,000	596	0.006	0.0060	99,702	7,882,920	78.8
1	99,404	42	0.000	0.0004	99,383	7,783,218	78.3
2	99,362	25	0.000	0.0003	99,350	7,683,835	77.3
3	99,337	18	0.000	0.0002	99,328	7,584,486	76.4
4	99,318	16	0.000	0.0002	99,311	7,485,158	75.4
5	99,303	14	0.000	0.0001	99,295	7,385,847	74.4
6	99,288	13	0.000	0.0001	99,282	7,286,552	73.4
7	99,275	12	0.000	0.0001	99,270	7,187,270	72.4
8	99,264	10	0.000	0.0001	99,259	7,088,000	71.4
9	99,254	9	0.000	0.0001	99,249	6,988,742	70.4
10	99,244	9	0.000	0.0001	99,240	6,889,493	69.4
20	98,953	70	0.001	0.0007	98,918	5,898,013	59.6
30	98,062	105	0.001	0.0011	98,009	4,912,689	50.1
40	96,811	165	0.002	0.0017	96,729	3,937,892	40.7
50	94,352	390	0.004	0.0041	94,157	2,980,312	31.6
60	88,788	785	0.009	0.0089	88,395	2,061,381	23.2
70	78,308	1475	0.019	0.0190	77,570	1,220,609	15.6
80	57,879	2854	0.049	0.0506	56,453	528,563	9.1
90	24,208	3443	0.142	0.1534	22,486	110,867	4.6
100	1971	703	0.357	0.4411	1620	4540	2.3

Table 1. Life table of the US general population, 2017 [2].

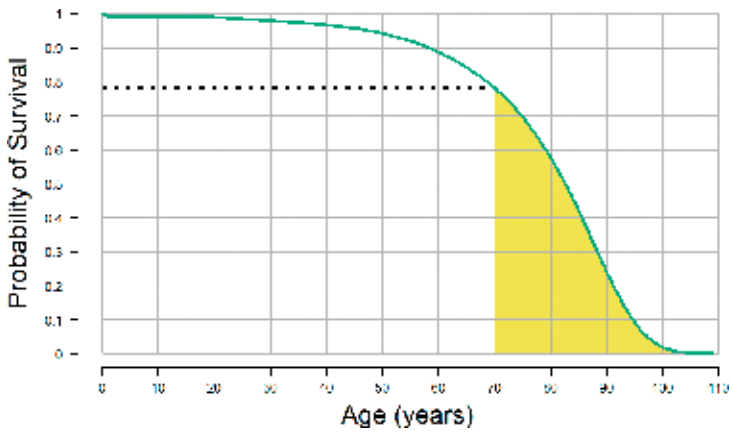

Figure 1. Survival curve for the US GP, 2013. Total area under the survival curve is equal to the life expectancy at birth. Area under the curve from age 70 (shaded in yellow) is estimated by *T(70)* ÷ 100,000 in the life table, 1,220,609 person-years ÷ 100,000 persons = 12.2 years. This can be estimated in the figure by counting rectangles in the shaded area. This area, normalized by dividing by the probability of survival to age 70, 0.78308, is equal to the life expectancy at age 70: 12.2 years ÷ 0.78308 = 15.6 remaining years.

110 (the end of the figure) has been shaded. If one counts the shaded rectangles (and fractions thereof) and divides by the probability of survival to age 70 (0.78308), one will find a number close to the *e(x)* number for age 70 in the life table, namely 15.6 remaining years (which would be to age 85.6).

This connection between the life table and the area under the survival curve gives a way to visualize the implications for life expectancy of evidence provided in many studies of CP survival. **Figure 2** provides a hypothetical, but typical, survival curve for children with relatively severe CP

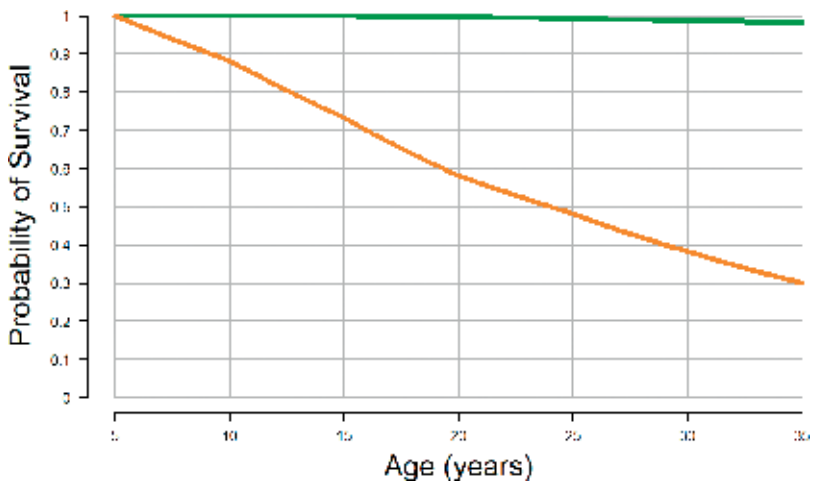

Figure 2. Survival curve for US GP (green) and a cohort with relatively severe CP (orange), from age 5 to age 35. The area under the CP survival curve must clearly be less than that under the GP curve, even if we extend the curves to ages above 100. Methods for extrapolating the CP curve to old ages have been discussed and tested in the literature [3, 5–7].

from age 5 to 35 years. On the same figure, we include the corresponding GP survival curve over the same ages. One can immediately see that the area under the CP curve has to be less than that below the GP curve, and this would be true even if both curves extended to ages over 100 years. Published studies of survival of CP (or almost any medical condition) provide estimates of survival across a limited age span - but survival to all ages is needed to estimate life expectancy. Thus some method of extrapolating information to ages 100 or beyond is necessary to use such empirical evidence to estimate life expectancy.

An in-depth explanation of the issues involved in such extrapolations is beyond the scope of this chapter. Descriptions and comparisons of various methods may be found in the references cited below [3, 5–7]. In the next section, we review the factors that have been shown to be strongly associated with long-term survival in CP.

3. Factors associated with long-term survival, mortality risk, and thus with life expectancy in CP

In the preceding section, we provided a general introduction to the concept of life expectancy and touched upon the idea that persons with various medical conditions may have life expectancies lower than those of age- and gender-matched general populations. In this section we identify the main factors associated with longevity and life expectancy in CP. We will delineate these factors roughly in order of importance, beginning with those having the greatest potential impact on life expectancy. The reader should keep in mind, however, that everything is relative in this regard. Thus, while gross motor functioning may rightly be identified as a major factor, and often the most significant factor effecting life expectancy in CP, for those with only minor deficits in gross motor functioning, another factor may in fact be more relevant. Thus, for any given individual or group, the factors identified in this section may need to be re-ordered for importance.

3.1. Gross motor functioning

> *"The contraction of the muscle…causes dilation of the arterioles, capillaries, and lymph spaces, allowing more oxygenized blood to flow to the muscular fibers, which abstract from it what they require for their nutrition and let the remainder, together with used-up material, pass partly into the veins, partly into the lymph spaces and the lymphatic vessels. By this process the muscle is nourished, the products of decomposition are removed, metabolism is promoted, and heat is produced. …*
>
> *The most natural of all muscular exercises, as pointed out by Hippocrates, is walking exercise. A great part of all the muscles in the body is activated by it; the action of the heart and respiratory organs is increased; the blood is passed with greater force from the heart into the blood vessels of the body, which are obliged to contract more vigorously, carry more blood to the different organs of the body, nourish the latter, and are themselves nourished through their work."* Sir Herman Weber, *On the Influence of muscular exercise on longevity.* 1918 [13].

It has long been understood that voluntary physical activity helps promote health and longevity, and that, conversely, a sedentary lifestyle leads to elevated risk of morbidity and mortality [8–13]. The negative consequences of involuntary inactivity, after injury, illness, or surgery, have also been documented [14]. That the limitations in volitional gross motor functioning that often manifest in persons with CP might negatively impact survival and life expectancy should therefore come as no surprise. Nevertheless, clear evidence of this association for CP and other encephalopathies affecting gross and fine motor functioning was not published before 1990.

In 1990, a *Special Article* published in the New England Journal of Medicine reported on the life expectancy of severely neurologically disabled people [15]. Drawing on the recent work that had identified severe intellectual disability (or mental retardation, as it was called at the time) as a marker for mortality rates far exceeding those of age- and gender-matched GPs [16], the study provided life tables stratified by level of disability. For the first time in a major medical journal, level of gross motor functioning emerged as a profound indicator of elevated mortality risk: Life expectancy for immobile children were reported to be less than 10% of age-matched GP life expectancy, and less than 20% that of ambulatory children with comparable levels of intellectual disability. Unfortunately, the article had a serious flaw that rendered all actual life expectancy figures too low, and all mortality rates too high by something on the order of a factor of 3.

Subsequent evaluations of life expectancy of CP specifically based on the same source of data (but without errors of arithmetic) have subsequently been reported and have confirmed what was perhaps the primary finding in the NEJM Special Article: life expectancy varies on a seeming continuum with level of independent gross motor functioning. Evidence in support of this hypothesis is abundant now, coming from numerous countries around the globe. Examples are easily found in the references at the end of this chapter. A summary of life expectancy estimates per se will be found in a recent review of literature from 1990 to 2014 [7]. Life expectancy for young children range from as low as 15 remaining years for those with little or no purposeful gross motor functional ability, to nearly as high as that of their peers in the GP for those who are able to walk without difficulty (and who have no other significant comorbidities related to their CP).

3.2. Fine motor functioning and feeding ability

In published studies, the ability to dress independently and to feed oneself have served as surrogates for overall fine motor functioning, and the connection to longevity is again straightforward: The greater the independent abilities in these areas, the longer the life expectancy. Numerous studies from California have focused on feeding ability [17–21]. Studies from England have focused on combinations of self-feeding and dressing abilities [22–27], and one study from Israel accounted for independent/non-independent feeding ability [28]. The association of mortality risk with fine motor functioning is not nearly as strong as with gross motor functioning, and a number of studies have not addressed this factor at all. Thus, if one is able to account for a specific category of gross motor functioning, a further adjustment for precise levels of fine motor functioning would be expected to have a smaller impact, all else being equal.

As we have alluded to above, the issue of enteral nutrition (via gastrostomy or otherwise) deserves special attention, and a number of studies have addressed this to one degree or another [17–20, 28–32]. Taken as a whole, these studies provide evidence of a strong association between placement of (and need for) a feeding tube with elevated mortality risk, all else being equal. Of course, association is not causation, and a number of reviews have pointed out the difficulties in interpretation of this association [33–37]. As one noted, "Mortality rates range from 7 to 29% but there is no way to ascertain the degree to which mortality can be attributed to the intervention" [33].

3.3. Intellectual disability

Historically, level of intellectual disability has been considered a strong driver of mortality rates and survival of people with a wide variety of neurological disabilities. Within the category of CP, level of intellectual disability may be of great importance for those whose gross and fine motor functional abilities are high; for those who are immobile and unable to feed themselves, the further impact of level of intellectual disability is small.

3.4. Epilepsy/seizures

Many studies have addressed the association of epilepsy, including remote symptomatic epilepsy, with elevated risk of mortality as a general medical condition, irrespective of any underlying disability [38, 39]. For remote symptomatic epilepsy, comparisons of mortality with the GP may be misleading, as some of the excess may be associated with an underlying brain injury or other neurological condition precipitating the seizures. A California study attempted to measure excess mortality risk associated with seizures by focusing on people with mild developmental disabilities and comparing mortality among those with and without a history of seizures [40, 41]. In studies of CP seizures have also been shown to be markers for excess mortality, above and beyond the excess mortality risk associated with limitations in mobility or feeding ability and other CP-associated disabilities [17, 18, 42, 43]. The relative impact of epilepsy on life expectancy is greater for those with greater levels of independent gross motor functioning.

The reason for the elevated risk of mortality in CP associated with seizures is likely multifactorial. First, as we will see in a subsequent section, seizures and convulsions do manifest as a cause of death in CP, and thus a direct link with mortality is evident. The presence of seizures may also be a marker for overall more involved brain injuries, which in turn may be associated with greater risk of long-term morbidity and mortality. And finally, some anti-epileptic drugs are associated side-effects that can be life threatening, including toxicities, liver failure, anemia, metabolic acidosis, and thrombocytopenia, among others [44, 45].

3.5. Visual and auditory disability

There is little evidence to suggest that auditory or visual disabilities impact directly on mortality risk in cerebral palsy. One Australian study did include deafness and blindness among five "additional impairments" that they found to have a significant impact on mortality rates after

Factor	Comment
Hydrocephalus	Level of risk diminishes with age but risk of infection and malfunction of ventriculoperitoneal shunt may persist across the lifespan.
Scoliosis, kyphosis	Severe cases may impact heart and lung function; surgical intervention is relatively safe and effective in such cases.
Frequent aspiration	Related to swallowing dysfunction, dysphagia, paletopharyngeal incoordination, or gastroestophageal reflux; leading to aspiration pneumonia or other respiratory infections.
Contractures	May impact negatively on survival given that they can further limit volitional movement.
Decubitus ulcers	Pose infection risk. More common among less mobile, and are part of the reason for excess mortality risk associated with immobility.
Tracheostomy	Poses infection risk. At least one study of people with developmental disabilities reported an excess mortality risk of about 1% across all ages.
Ventilator	Poses risk independent of tracheostomy.

Table 2. Other issues that may be associated with excess mortality risk beyond the major factors discussed in preceding sections.

accounting for level of gross motor impairment [43]. A number of studies from the UK identified severe visual disability as marker for elevated mortality [23, 25–27]. It may be that these disabilities are more common among more severely disabled people, and thus they may serve as a marker for overall level of brain injury.

3.6. Other issues

There are any number of additional factors relative to survival and mortality of persons with CP that have, to date, not been studied extensively. Factors that may well have some further impact on life expectancy, beyond the major known factors discussed above, are listed in **Table 2**.

4. Causes of death in CP

Life expectancy in CP is lower than expected in age- and gender-matched GPs. The question naturally arises as to what causes of death are driving the higher mortality rates and lower life expectancies, in this population? A number of studies have addressed this question, most focusing on either *underlying* cause of death or *immediate* (*principal, primary*) cause of death [24, 27, 42, 46–51]. At least two studies were vague as to whether an immediate cause or underlying cause was identified [52, 53]. Most of these studies relied on information reported in death certificates, [24, 27, 42, 46–51, 54] with at least one basing cause of death on a review of medical records from the time of death [53]. An *underlying* cause of death is meant to be the medical condition or other event that started a chain of events ending in death due to an *immediate* cause. In this section we will highlight some of the main underlying and immediate causes of death that have been found to be more common in CP than in the GP, and a few that are in fact less common.

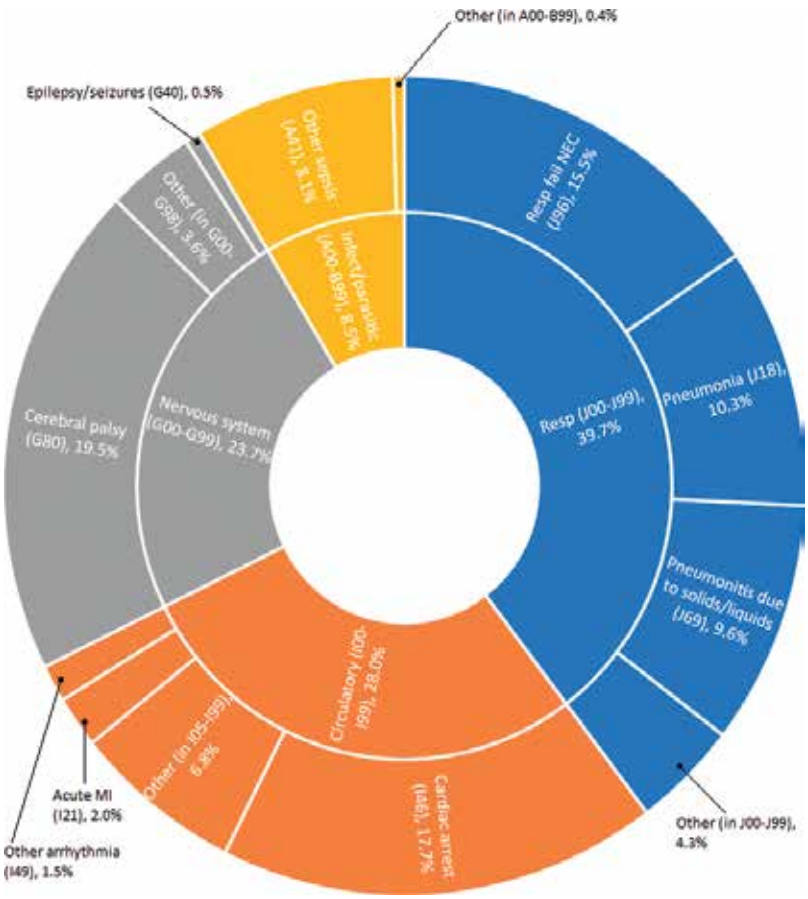

Figure 3. Top four broad categories and corresponding subcategories of immediate cause of death among deaths with a mention of CP on the death certificate.

Figures 3 and **4** shows the distribution of the leading immediate and underlying causes of death among 26,677 deaths in the US from 2005 to 2014 that mentioned CP anywhere on the death certificate (immediate cause of death, underlying cause, contributing cause, or other significant condition).[2] **Figure 3** shows the top 4 broad categories of immediate cause of death (accounting for 73% of all 26,677 deaths) as originally reported on death certificates [55], and as coded in the National Center for Health Statistics (NCHS) Multiple Cause of Death Records [56]. **Figure 4** similarly reports the distribution of the leading underlying causes of death (top 5 broad categories, accounting for 74% of all 26,677 deaths), but recoding some underlying causes originally attributed to CP on death certificates and in the NCHS death records (see next section for details on the recoding). **Figures 3** and **4** both report primarily broad categories

[2]Such analyses of death certificate information do not capture all deaths of people with CP, of course, as in some cases (cases of very mild CP, or when a death clearly had no connection to CP) CP is not mentioned on the death certificate. Other studies have estimated that approximately 40-50% of deaths of people with CP include no mention of CP on the death certificate [24, 43, 47].

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Figure 4. Top five broad categories and corresponding subcategories of underlying cause of death among deaths with a mention of CP on the death certificate.

of causes of death as classified by the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD 10) [57], though in some of the studies to be referenced, an earlier revision of the ICD was employed.

4.1. Cerebral palsy as immediate or underlying cause of death in CP

As **Figure 3** (immediate causes of death) illustrates, CP (ICD 10 G80) was identified in US national death records as being the immediate cause of death in a substantial number of cases (19.5% of the leading causes, or 14.5% of all deaths). CP was far more common as an underlying cause of death among deaths including CP as any cause or contributing factor: initially, 59% of underlying causes of death were attributed to CP. We recoded these, when possible, to be (a) the last cause listed in Part 1 of a death certificate if that cause was not CP; or (b) the penultimate cause in Part 1 if one existed. After recoding, CP accounted for 10% of all underlying causes, or 13.8% of the top 5 leading causes (**Figure 4**). Many studies of causes of death in CP that have relied on death certificate information have reported CP itself to be among the most common underlying causes [24, 27, 46, 47, 49, 50]. Some authors have considered CP to

be "uninformative", or "not valid", as an underlying or principal cause of death [46, 58], and various methods of recoding such deaths have been undertaken [47, 51, 58]. That CP is often recorded as the underlying cause of death on death certificates may be unfortunate, as it is indeed somewhat uninformative.

4.2. Respiratory diseases (ICD 10 J00–J99)

Respiratory diseases have consistently been reported to be among the leading causes of death among children and adults with CP [24, 27, 43, 46–53]. **Figures 3** and **4** shows that, among deaths with any mention of CP on a death certificate, respiratory diseases were the most common immediate cause of death (39.7% of the top 4 causes of death, 29.5% of all deaths) and also the most common underlying cause after recoding many deaths originally attributed to CP (32.4% of the top 5 causes, 23.7% of all deaths).

Those with more severe levels of disability are at greater risk of mortality due to respiratory diseases. Standardized mortality ratios (SMRs) have been reported from as low as 10 or below in older ages for those with less severe disability, to as high as 600 or more at younger ages for those with more severe levels of disability [46]. Among respiratory diseases, pneumonias, and in particular pneumonia related to aspiration of solids or liquids, are common [24, 42, 43, 46–49, 52, 53] and the excess in observed deaths due to this cause is again more pronounced in those with greater levels of disability [46].

4.3. Circulatory diseases (I00–I99)

Circulatory diseases are also elevated in frequency as a cause of death in CP, and is a common cause of death in this population, though this is primarily evidenced in deaths that occur at older ages (as is the case in the GP as well) [27, 46, 47, 51]. **Figures 3** and **4** show circulatory diseases to be the second leading immediate cause of death, and the fourth leading underlying cause (the latter after recoding of underlying causes of death with underlying cause originally attributed to CP).

4.4. Diseases of the nervous system (G00–G99)

The broad category of diseases of the nervous system includes CP itself (G80), as we have discussed above. Even after recoding deaths that are attributed to CP, it remains as a significantly common underlying cause of death (**Figure 4**), but other nervous system diseases become more prominent. Among the most common underlying causes of death within this broad category other than CP itself are seizures and hydrocephalus [51, 52].

4.5. Sepsis

Sepsis is an often life threatening condition caused by the body's system-wide inflammatory response to infection. Sepsis is a common cause of death in CP and in the GP, particularly in the elderly, the very young, or in those with severe disabilities or compromised immune systems. Because the ICD 10 classifies disease according to body system or, in the case of

infection, according to specific organism, sepsis is spread throughout its hierarchy, and across many of the broad categories of causes of death illustrated in **Figures 3** and **4**. Among the 26,677 deaths in the US from 2005 to 2014 that included CP anywhere on the death certificate, sepsis was noted to be the immediate cause in 1628 deaths (6.1%). Among these deaths, 98% were coded as ICD 10 A41 (other sepsis), of which most (97%) were coded as A41.9 (sepsis, unspecified organism).

4.6. Neoplasms, cancer (C00–D46)

Cancers, including both malignant and benign tumors, were an underlying cause of death in only 924 records out of the 26,677 deaths contributing to the analyses of **Figures 3** and **4**, thus not a leading immediate or underlying cause of death, and not included in those figures. Nevertheless, some interesting results have been reported regarding cancer mortality in CP. A large California study reported that those with CP were at greater risk of death due to cancer of the esophagus (SMR = 5.4, 95% CI 3.1–8.8), colon (2.2, 1.4–3.3), liver (2.2, 1.1–4.1), breast (1.8, 1.2–2.6), and bladder (4.6, 2.1–8.7); but at a five-fold decreased risk of death due to cancer of the trachea, bronchus and lung (SMR = 0.2, 0.1–0.4) [59]. The number of cancer deaths is likely small due primarily to its typical manifestation in older ages, ages to which many with more severe levels of CP do not live owing to competing risks.

4.7. Other "uninformative" causes of death

Another category of causes that appears frequently on deaths certificates of persons with CP is "symptoms, signs, and abnormal results of clinical and laboratory tests, not classified elsewhere," (ICD 10 R00–R99). These causes have been considered to be uninformative (or perhaps uninteresting) [46]. Referring again to **Figure 4**, we see that this category was the second leading underlying cause in US deaths from 2005 to 2014 (after recoding as described above), accounting for 22.2% of the top five leading cause categories, or 16.3% of all 26,677 deaths. However, given that this category includes "convulsions, not elsewhere classified," (ICD 10 R56) which in some cases account for up to half of deaths in this category, and also includes deaths related to unspecified respiratory and circulatory system problems, which in one study accounted for more than half of all deaths in this category (ICD 10 R56) [51, 58], more careful scrutiny of this broad category may be warranted. When comparing results from various studies as to the most common underlying or immediate cause of death in CP, it should be borne in mind that some studies omit this, and other, categories from consideration.

5. Methodological considerations for future research

The studies cited and discussed in the foregoing sections of this chapter provide a wealth of information about long-term survival, mortality, and life expectancy of people with cerebral palsy. Many questions remain to be answered, however, and more studies will undoubtedly be carried out in the future in an attempt to answer them. The questions such researchers will face in planning and executing their studies will be many and complex, and a full discussion of all

factors that ought to be considered is beyond the scope of this chapter. In this section, we mention a few of the most important methodological considerations for future studies in the broad context of questions about CP survival and life expectancy. We will also point to a few areas of research that remain poorly explored but important.

5.1. External validity

In previous sections of this chapter, we have identified a number of risk factors that are known to be strongly associated with survival and life expectancy in CP. One of the most important factors is gross motor functioning, and any study of survival in CP must account for this. However, as the literature to date has demonstrated, there are many ways to form cohorts based on combinations of this and other functional abilities. Therefore, for the sake of comparing results across time and place, we advise forming cohorts according to Gross Motor Function Classification System (GMFCS) [60] level or other commonly employed measures of gross motor functioning. For similar reasons, when possible, scales such as the Manual Ability Classification System (MACS) [61], the Communication Function Classification System (CFCS) [62], and the Eating and Drinking Ability Classification System (EDACS) [63] should be utilized. Other factors to account for can be gleaned from Section 4, perhaps chief among them gastrostomy status. Some studies will be limited by data that has been collected historically, but prospective studies should seize the opportunity to measure and report results in a more standardized fashion.

5.2. Time-based biases

Consider the 2000 UK study by Hutton et al. [24] **Figure 1D** in this study illustrates survival for children with severe ambulatory disability (i.e., no independent walking ability) and for children without severe ambulatory disability. The survival curves begin at age 0. This is problematic. Was walking ability really measured at age 0? Surely all children would be considered to have severe ambulatory disability at age 0, by the definition employed in this study. Furthermore, CP is rarely diagnosed in any child before a year or two of age. These issues are important: be as precise as possible with regard to when any time varying covariates are measured, and also as to precisely when (at what age) CP was diagnosed. Failure to do so can lead to a phenomenon known as immortal time bias, a surprisingly common error in reports of survival in a variety of populations, [64] including at least one study of survival of children with neurological disabilities [65].

5.3. Methods for causal inference

Researchers in the fields of Epidemiology, Biostatistics, and Computer Science have collaborated in recent years to develop a framework for robust causal inference [66]. This framework provides the analytic techniques and needed assumptions for interpreting results obtained from observational (i.e. non-experimental) studies in a causal way. The framework also provides tools for thinking more clearly about hypotheses and identifying potential sources of bias and confounding in conventional analyses. Applying these methods to studies of mortality in CP may help to unravel complex questions which have thus far been impossible to address [67]. For example, on the subject of gastrostomy feeding, we might wonder several

things: (a) how much of the increase in mortality for people with a gastrostomy tube is caused by the need for a tube versus the placement and presence of the tube itself; (b) what if all children with CP of a given functional profile were given a gastrostomy tube; or (c) what if no children with CP of a given profile were given gastrostomy tubes? Given the right data and careful analysis, even in the absence of an ethically impractical randomized clinical trial [35], the causal inference framework could help answer these and other important questions.

6. Conclusions

In this chapter we have reviewed the general concepts of life expectancy, life tables, and survival curves. We reviewed the important predictors of mortality and life expectancy in CP, as well as the major causes of death common in CP.

Mobility is a strong predictor of mortality in CP, and as a consequence, a strong predictor of cause of death; in young and old with CP, respiratory diseases figure prominently as a cause of death, and circulatory diseases become more relevant in older ages. Neurologic disorders are also a major category of cause of death, even after reclassifying underlying causes initially attributed to CP to more informative causal categories. Seizures and hydrocephalus are important causes in this category as well.

Future research in the mortality and life expectancy of CP should focus on analyzing data using as many of the previously-identified risk factors as possible and should stratify patients using widely replicable scales of those factors, such as GMFCS. New tools of causal inference should be employed to help control bias and confounding in observational studies.

Though much has been learned about life expectancy and causes of death in CP, there is undoubtedly much to be learned. It is our hope that this review and our recommendations will help guide future research in its quest to answer the many open questions related to long-term mortality and survival, and life expectancy in cerebral palsy.

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Chapter 4

Cerebral Palsy and Epilepsy

Alexey Kholin

Additional information is available at the end of the chapter

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Abstract

The frequency of epilepsy in children with cerebral palsy is 40 times higher than the common population rate. The presence of epilepsy aggravates the clinical course of cerebral palsy, complicates the rehabilitation, affects the prognosis of motor and intellectual functions, and could be life-threatening. Another problem is the possibility of aggravation of epileptic seizures and their appearance de novo due to application of some neurorehabilitation methods (electrophoresis, acupuncture, nootropic drugs, brain stimulators, etc.). Children with cerebral palsy have a broad spectrum of epilepsies—varying from favorable combinations with benign idiopathic forms to extremely severe epileptic encephalopathies. Frequent combination of epileptic and non-epileptic paroxysms causes difficulty in their interpretation and differential diagnosis. Video-EEG monitoring is the "golden standard" for differential diagnostic of epileptic and non-epileptic events, and it is very useful for investigation of patients with cerebral palsy. Treatment of epilepsy in combination with cerebral palsy strictly requires an individual approach due to the form of epilepsy, seizure types, age of the patient, comorbidity, and somatic and mental condition of the patient.

Keywords: cerebral palsy, epilepsy, epileptic seizures, EEG, AEDs

1. Introduction

The actual problem is the presence of epileptic seizures in children with cerebral palsy that caused deterioration of disease, complicates the rehabilitation, affects the prognosis of motor and intellectual functions, and could be life-threatening. Also, the presence of epileptiform discharges with high index can cause progression of cognitive defects and also with possible increasing of motor deficits. These phenomena violate such a core criterion of cerebral palsy as nonprogressive process.

The frequency of neonatal seizures in children with cerebral palsy in 17 times is higher than common population rate, febrile seizures (2.5 times), and epilepsy (more than 40 times higher) [1].

Epilepsy in cerebral palsy occurs according to different authors data in 28% [2], 36.4% [3], 44% [4], 43.2% [1], 62% [5], and even 75% [6].

2. Cerebral palsy and epilepsy

2.1. Risk factors for epilepsy in cerebral palsy

Among infants at group of risk for the development of cerebral palsy and among those who had formed cerebral palsy are advisable to identify also the group of risk for development of epilepsy.

Risk factors for epilepsy in cerebral palsy are [1, 7–10]:

- The presence of neonatal seizures.
- Low Apgar score (≤4 points).
- Extremely preterm infants (≤31 weeks of gestation).
- Neonatal resuscitation.
- Family history of epilepsy.
- Cerebral palsy caused by prenatal factors, especially cerebral dysgenesis.
- Intrauterine infection (especially herpes encephalitis).
- Hemiplegic and tetraplegic forms of cerebral palsy.
- Severe mental retardation.
- The presence of epileptiform discharges on the EEG.

2.2. Characteristics of epilepsy in cerebral palsy

Despite the wide polymorphism of clinical cases, epilepsy in combination with cerebral palsy epilepsy has a number of common characteristics.

They can be expressed as the following features [1, 5, 7–11]:

1. In the majority of cases (up 74.2%), epilepsy in children with cerebral palsy debuted at the first year of life.
2. Children with cerebral palsy have a broad spectrum of epilepsies—varying from favorable combinations with benign idiopathic forms to extremely severe epileptic encephalopathies.

3. Non-rare cerebral palsy is combined with epileptic encephalopathies of infancy and early childhood (Ohtahara, West, Markand-Blume-Ohtahara, Lennox-Gastaut syndromes, etc.).
4. The prevalence of the clinical picture of complex focal, secondarily generalized, and so-called pseudo-generalized epileptic seizures (atypical absence, tonic spasms, and bilateral myoclonic seizures with focal origin).
5. Frequent combination of epileptic and non-epileptic paroxysms, as well as possible similarity of their kinematics, causes difficulty in their interpretation and differential diagnosis. For example, the "dystonic attacks" with kinetic type of asymmetric tonic neck reflex (ATNR) and versive tonic epileptic seizures.
6. The presence of epilepsy aggravated motor and cognitive impairment in cerebral palsy. Frequently, epileptic seizures and epileptiform discharges with high index caused cognitive epileptiform disintegration or partial cognitive defects, as well as a possible increase of motor deficits and progressive loss of certain motor and speech skills.
7. Frequent combination of cerebral palsy and benign epileptiform discharges of childhood (BEDC) on the EEG. Children with periventricular leukomalacia (PVL) and diffuse myelination defects had favorable prognosis for epileptic seizures but in combination with drug-resistant epileptiform discharges (including BEDC) and disintegrative epileptiform processes.
8. In children with cerebral palsy (unless caused by cerebral dysgenesis) may not be a correlation between the sites of epileptiform activity and the area most pronounced structural changes in neuroimaging.
9. There is often a reflex provocation under the influence of audiogenic seizures and somatosensory stimulation (including epilepsy of feeding). The problem of differential diagnosis of startle reflex and startle epilepsy in children with cerebral palsy.
10. Increased risk of recurrence of epilepsy in children with cerebral palsy after antiepileptic drug (AED) discontinuation.

Children with cerebral palsy have a wide spectrum of epilepsies which varies from favorable combinations with benign idiopathic forms to extremely severe epileptic encephalopathies.

So, in the total of 231 pediatric cases of cerebral palsy observed and treated on the Department of Psychoneurology N2 Russian Children Clinical Hospital (Moscow) at 2007–2012 years, 84 children (36.4%) had a combination of cerebral palsy and epilepsy [3].

The following forms of epilepsy were fixed: symptomatic focal frontal lobe epilepsy (25 patients (29.7%)), temporal lobe epilepsy (15 patients (17.9%)), parietal lobe epilepsy (3 patients (3.6%)), occipital lobe epilepsy (8 patients (9.5%)), SE-MISF (severe epilepsy with multifocal independent spike foci or Markand-Blume-Ohtahara syndrome) (7 patients (8.3%)), other multifocal epilepsies (4 patients (4.8%)), West syndrome (5 patients (6%)), focal epilepsy

of childhood with structural brain changes and benign epileptiform discharges of childhood on the EEG (FECSBC-BEDC) (10 patients (11.9%)), and cognitive epileptiform disintegration (CED) with ESES (electrical status epilepticus at slow-wave sleep) (7 patients (8.3%)) [3].

2.3. Epileptiform activity in children with cerebral palsy and epilepsy

Morphologic characteristics of epileptiform activity in children with cerebral palsy and epilepsy are very different and depend on the form of epilepsy, patient age, severity, and nature of brain damage.

In children with cerebral palsy, the high frequency of so-called benign epileptiform discharges of childhood pattern ("BEDC," "BEDOC," or "Rolandic" spikes and spike-wave complexes) was noted and could be found in epileptic (**Figures 1** and **2**) and also non-epileptic patients.

Over the past decades, the world's scientific and clinical experience accumulates the observation of patients with the so-called double pathology—the presence of structural brain damages with motor deficit in combination with epileptic idiopathic component including "BEDC."

Mukhin et al. proposed the definition "focal epilepsy of childhood with structural brain changes and benign epileptiform discharges in EEG" ("FECSBC-BEDC") for the group of children with focal epilepsy, associated with BEDC on EEG and perinatal organic brain damage, which has a special "interim" position between idiopathic and symptomatic epilepsies due to its clinical electrical and neuroimaging characteristics [12].

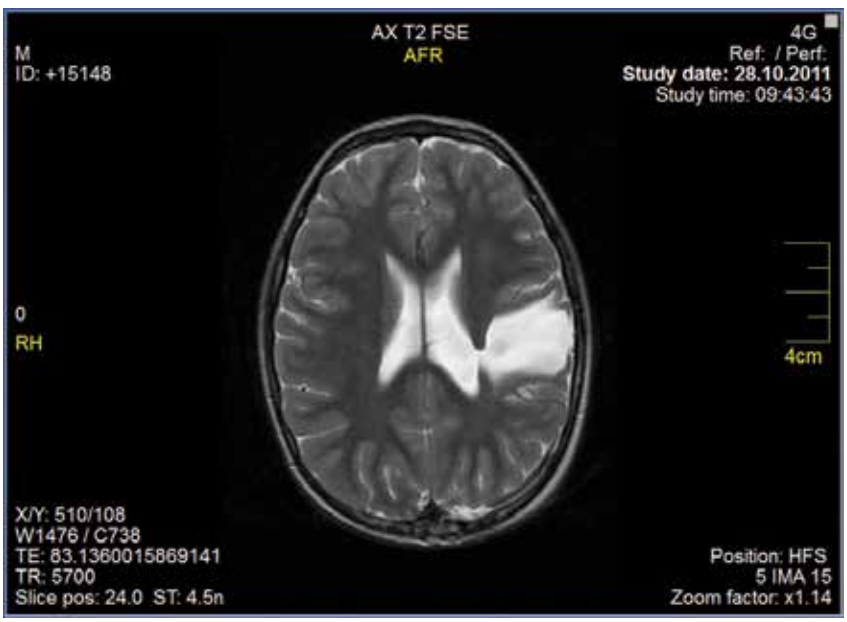

Figure 1. Boy Sh.I. (7 years old). Hemiparetic form of cerebral palsy (right-side hemiparesis). Symptomatic focal epilepsy with right-side hemiconvulsive, versive, dialeptic, and myoclonic-astatic seizure types. Porencephalic cyst in the left hemisphere (parietotemporal region).

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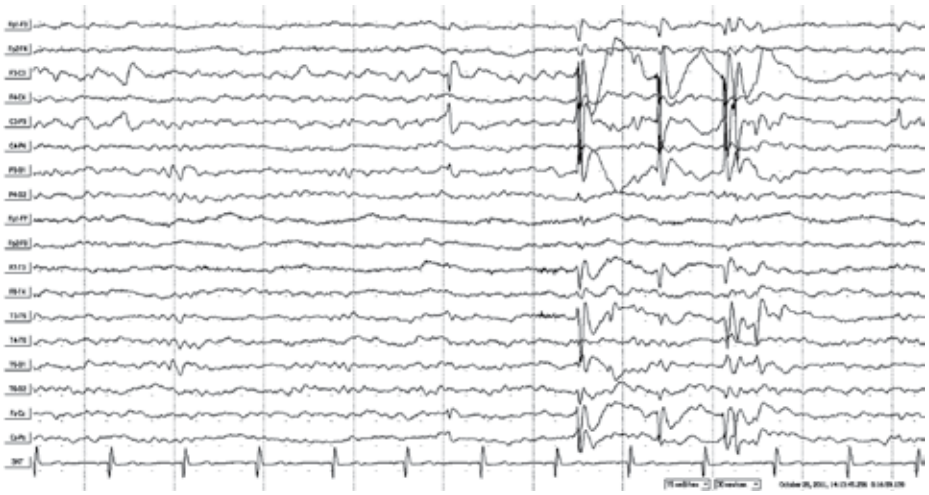

Figure 2. Boy Sh.I. (7 years old) (the same patient). Wake EEG. Regional epileptiform activity in left central and centro-parietotemporal region in the manner of spike-wave with "BEDC" morphology and sharp- and slow-wave complexes in combination with regional slowing.

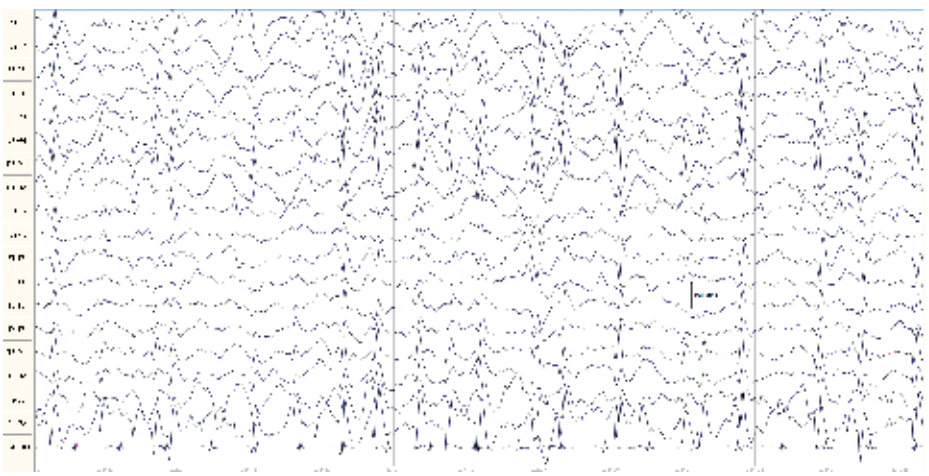

Figure 3. Girl V.M. (11 years old). Cerebral palsy, moderate right-side hemiparesis. Sleep EEG-ESES pattern.

High index (85–100% of recording) of such spikes-waves in sleep formed EEG patterns of CSWS (continuous spikes-and-waves during sleep) and ESES (electrical status epilepticus in sleep) in cases of diffuse spreading of epileptiform discharges (**Figure 3**). It usually correlates with severe speech and cognitive deficit in children.

Sometimes, early appearance on the EEG "BEDC"-like complexes is prognostically unfavorable and preceding the development of hypsarrhythmia. Five-point epileptiform complexes as "Rolandic" at the first months of life in children with hypoxic-ischemic brain damage and periventricular leukomalacia could precede hypsarrhythmia, epileptic spasms, and the development of epileptic encephalopathy (**Figures 4–7**).

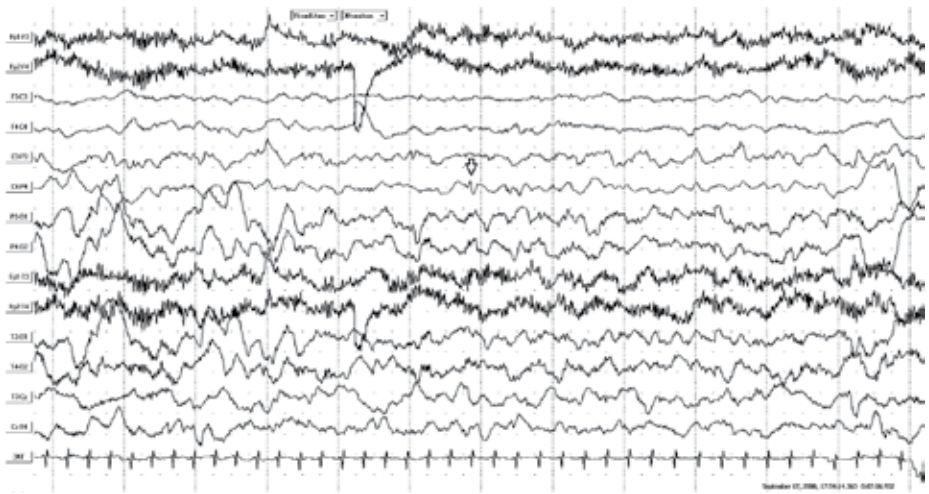

Figure 4. Boy B-H.A. (4 months old). Retardation of psychomotor and preverbal development due to perinatal brain damage. Risk of cerebral palsy. EEG during wakefulness 2 months before the onset of infantile spasms. In the center-right parietal region, low-amplitude five-pointed epileptiform complexes are observed, similar in morphology to the "Rolandic" complexes.

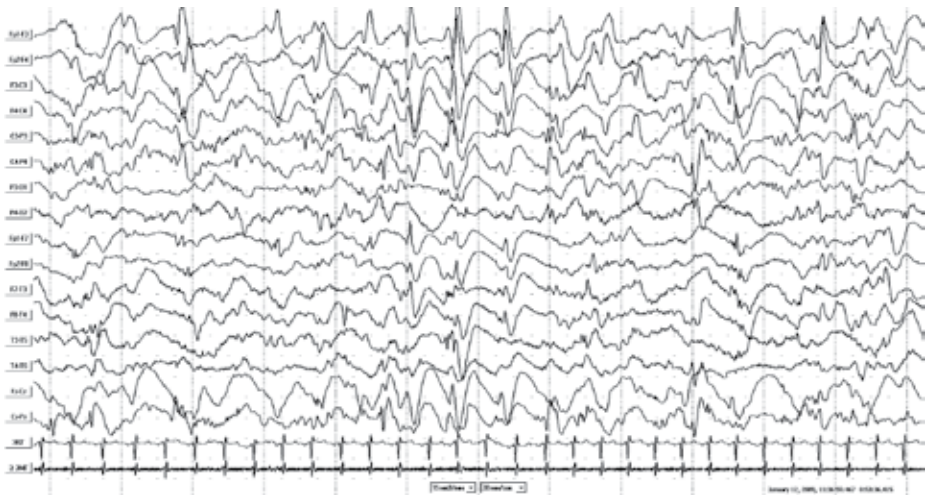

Figure 5. The same patient (4 months later; age of 8 months). Spastic tetraparesis. Infantile spasms. Psychomotor retardation. EEG during wakefulness: modified hypsarrhythmia with a multiregional component (right parietal, left and right frontal areas).

Frequent combination of epileptic seizures and non-epileptic events, as well as possible similarity of their kinematics, causes difficulty in their interpretation and differential diagnosis. For example, we can see EEG illustrations (**Figures 8–12**) of the girl N.A. (age 1 year and 3 months); we can see her interictal EEG pattern and patterns of non-epileptic event and ictal recording. Surprisingly, events considered as asymmetric tonic versive seizures were diagnosed as non-epileptic, but video-EEG also demonstrated minimal motor seizures of temporal

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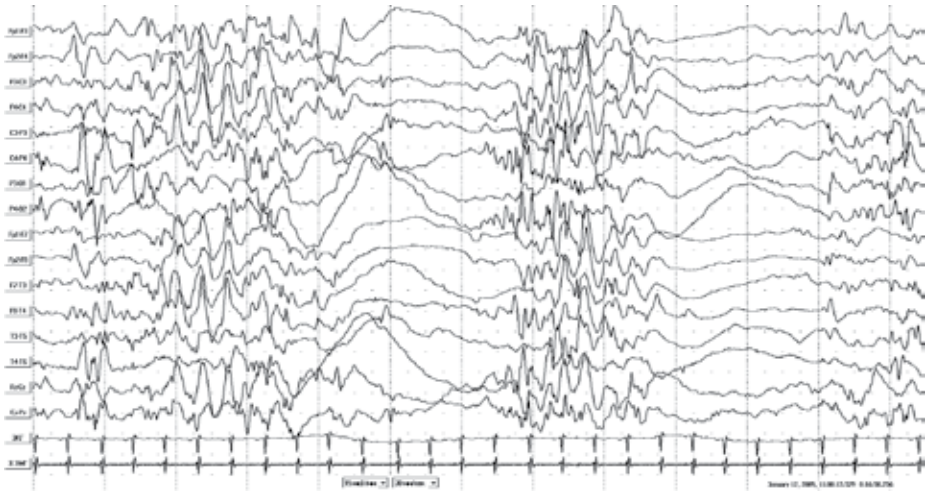

Figure 6. The same patient (age of 8 months). EEG during sleep: modified hypsarrhythmia with persistence of suppression burst pattern and main regional focus in the right parietal area.

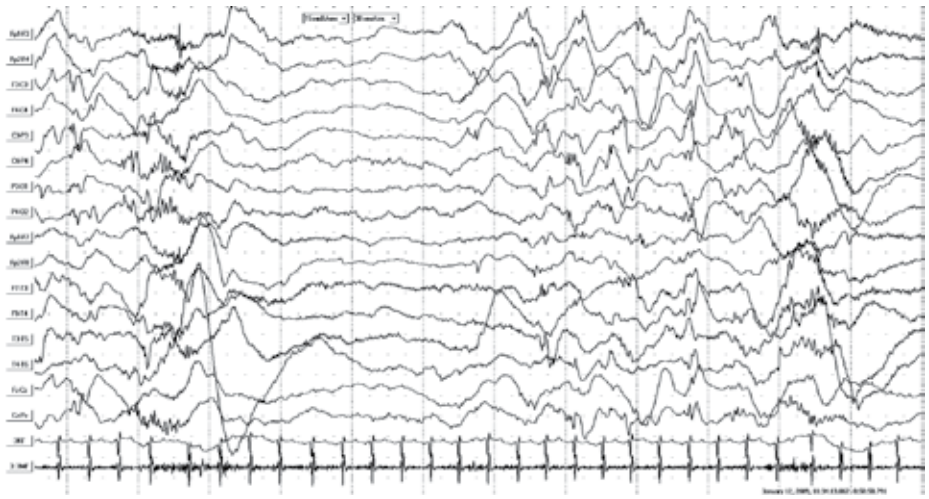

Figure 7. The same patient (age of 8 months). EEG during a series of tonic axial and axiorhizomelic flexor epileptic spasms. Marked diffuse ictal runs of "low-amplitude fast activity" ("lafa") and "fast activity" with predominant right-hemisphere parietal involvement and postictal partial inhibition of bioelectric activity.

lobe genesis not considered by the father of the child and even the physicians. The girl had spastic tetraplegic-type cerebral palsy, microcephaly, symptomatic focal epilepsy, pseudobulbar syndrome, chronic aspiration syndrome, and severe delay of psychomotor development. According to the anamnesis data, the mother 34 years old, and the father is 50 years old. The girl from the first physiological pregnancy, delivery at the 40th month of gestation. Her mother died during status epilepticus of bilateral tonic-clonic seizures. Mechanic extraction of the child with obstetric forceps from dying mother. The girl was born with weight 3510 g,

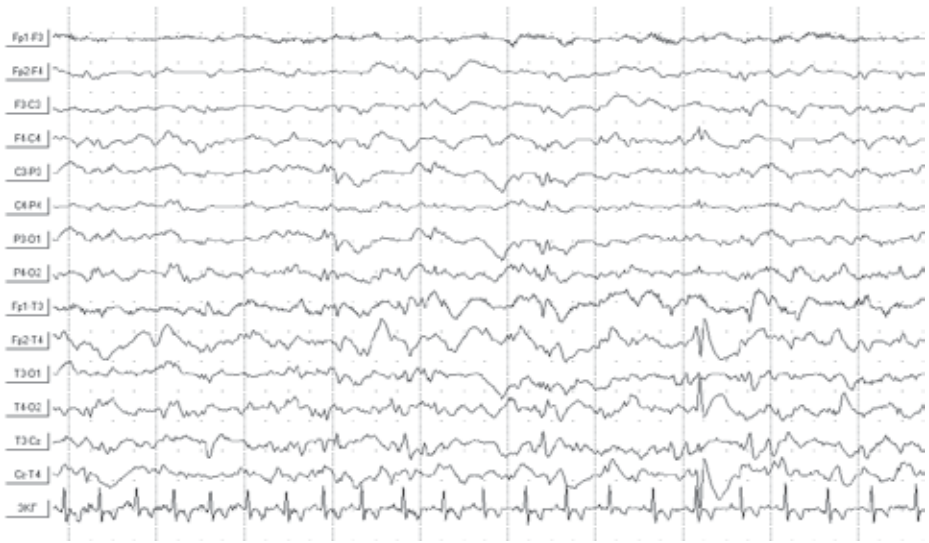

Figure 8. Girl N.A. (1 year and 3 months). Cerebral palsy. Interictal EEG with "BEDC" complexes of the left and independently right temporal, temporo-central, and temporoparietal localization.

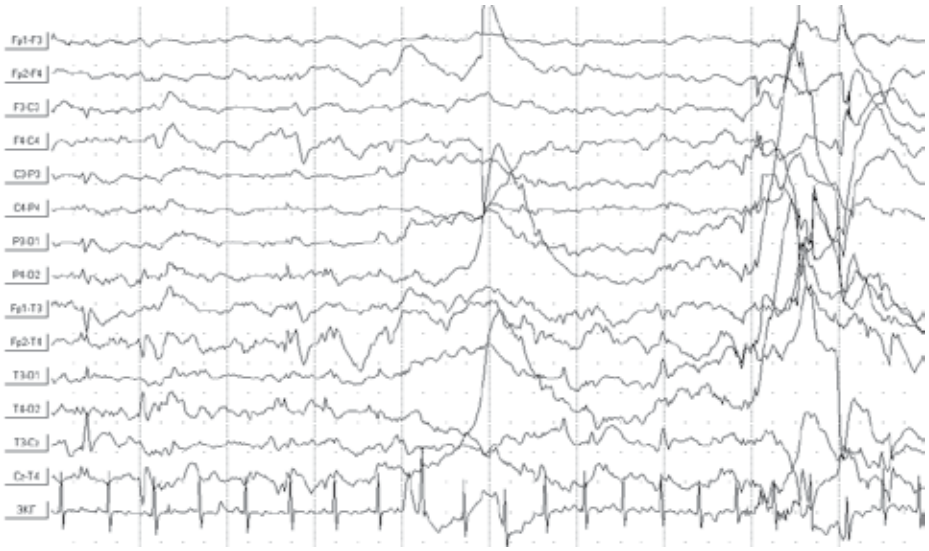

Figure 9. The same girl and EEG record. EEG of non-epileptic paroxysm (the beginning)—"dystonic attacks" with kinetic type of asymmetric tonic neck reflex (ATNR). No ictal pattern. Movement artifacts with the same background interictal "BEDC" complexes.

length of 53 cm, and Apgar score of 4/5 degrees. She was on the artificial lung ventilation for 3 weeks. Neonatal seizures appear from the first days of life.

Esipova E.S. and coauthors (2017) have analyzed video-EEG monitoring results of 133 children (87 boys and 46 girls) with spastic forms of cerebral palsy who underwent examination and

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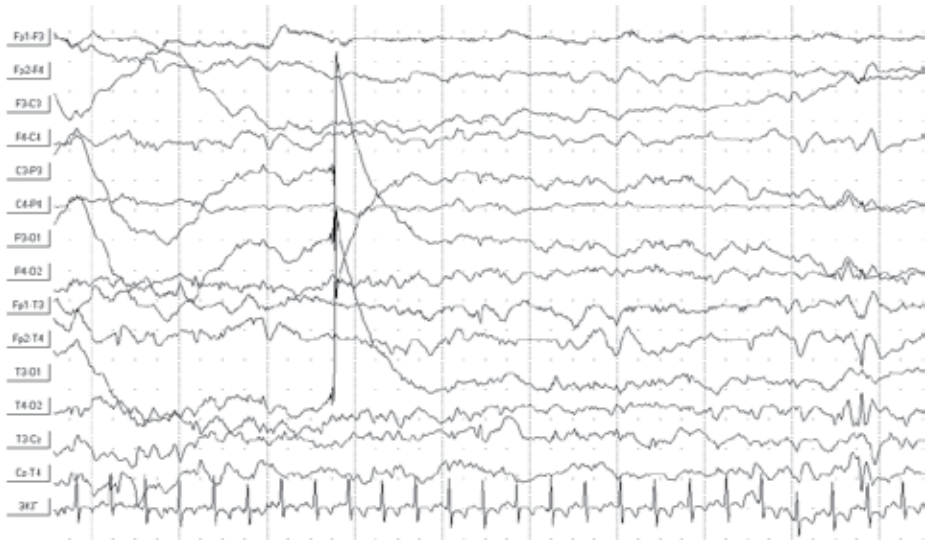

Figure 10. The same girl and EEG record. The end of non-epileptic paroxysm.

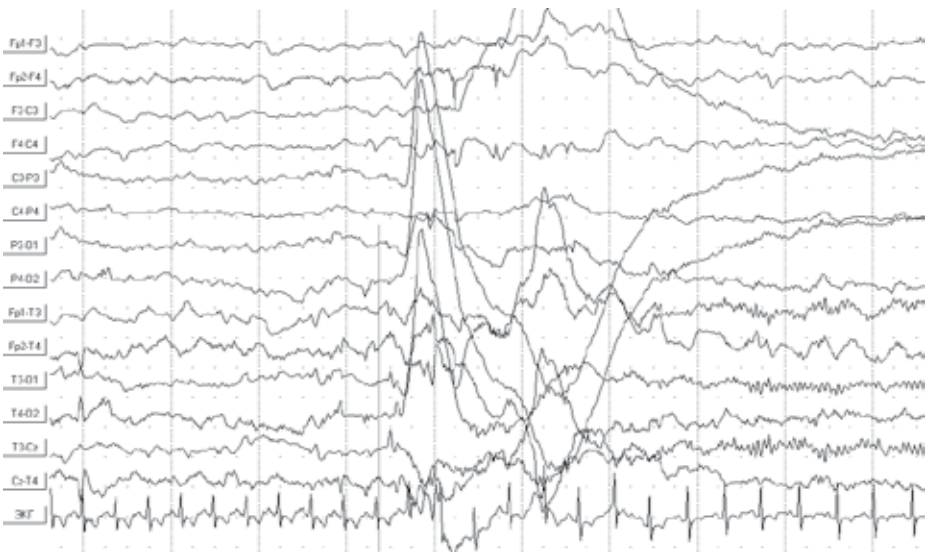

Figure 11. The same girl and EEG record. The ictal event—minimal motor seizure ("subtile" bilateral spasm with dystonic set of the right hand) with "fast activity" pattern in the left temporal region.

treatment at the Department of Psychoneurology N2 Russian Children Clinical Hospital in 2014–2016 years. In a group of spasic tetraparesis (n = 79), the presence of epilepsy was 54.43% (n = 43), and the presence of epileptiform activity on the EEG was 72.15% (n = 57) including 24 children (30.38%) with "benign epileptiform discharges of childhood" ("BEDC"). In a group of spastic hemiparesis (n = 18), the presence of epilepsy was 27.78% (n = 5), but the presence of epileptiform activity on the EEG was 61.11% (n = 11) including 8 children (44.45%) with

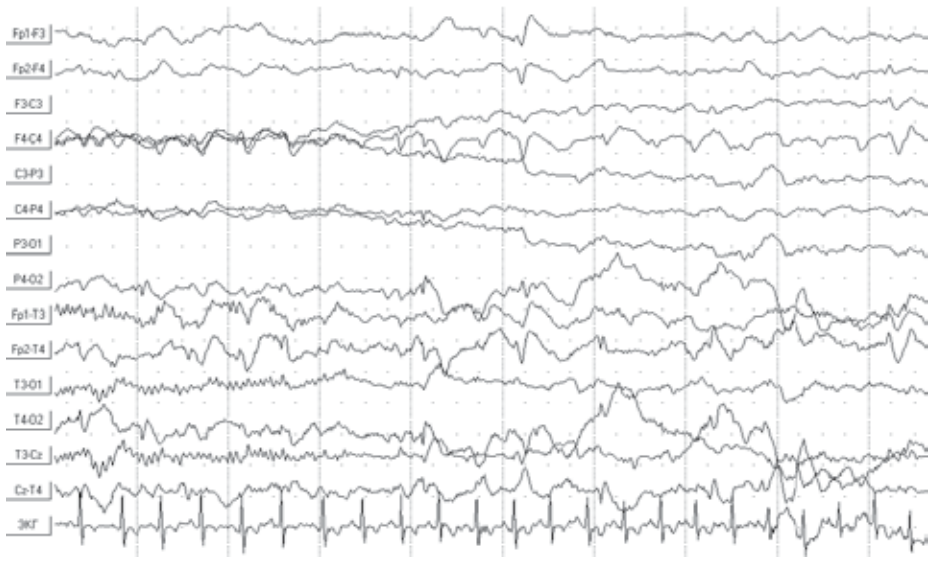

Figure 12. The same girl and EEG record. The end of ictal event—"fast activity" pattern in the left temporal region stopped.

"BEDC." In a group of Little's disease (spastic diplegia) (n = 25), the presence of epilepsy was 20% (n = 5), and the presence of epileptiform activity was 48% (n = 12) including 7 children (28%) with "BEDC." Mixed form of cerebral palsy (n = 11) contains seven epileptic patients, and the presence of epileptiform activity was 72.73% (n = 8) including 5 children (45.45%) with "BEDC." Among the 133 children, 72.2% (n = 96) of all the presented patients had non-epileptic paroxysms on the EEG considered by parents and also mentioned by EEG assistants. In 18.1% (n = 24) of patients, a combination of epileptic and non-epileptic events on the video-EEG monitoring was fixed. In 13 patients only epileptic events were fixed (9.7%) [13].

2.4. Treatment of epilepsy in children with cerebral palsy

Drugs of choice in the treatment of epilepsy in children are valproates in doses of 20–100 mg/kg/daily. It should be emphasized that the high incidence of bulbar palsy disorders in children causes serious problems with the use of tablet and capsule forms of antiepileptic drugs (AEDs). This problem has been solved by the use of such forms of valproates such as depakine chronosphere, depakine syrup, convulex in the syrup and drops form, etc.

In cases of atypical absences and BEDC-associated conditions, succinimides (suxilep, petnidan) at doses 20–35 mg/kg/day are appropriate.

In children with cerebral palsy and cognitive epileptiform disintegration with BEDC on EEG, also levetiracetam (keppra, epiterra, levetinol) in doses 20–80 mg/kg/day could be very good.

In application of carbamazepine group, oxcarbazepine, lamotrigine, and topiramate in pediatric patients under the age of 7 years should be considered the high risk of aggravation of the

phenomenon of secondary bilateral synchronization of the EEG, with clinical manifestations of myoclonic seizures, atypical absences, and secondarily generalized seizures. This group of drugs to be combined with a broad-spectrum AED with low aggravation risk (as valproates) and their use requires careful dynamic video-EEG monitoring to detect early signs of aggravation. But carbamazepine, oxcarbazepine, eslicarbazepine acetate, lamotrigine, and topiramate could be very useful in focal tonic and clonic seizures. In older children and adult patients, topiramate is one of the best drugs in frontal lobe epilepsy with secondary bilateral synchronization. Carbamazepine group and oxcarbazepine are better in temporal and occipital localization of epileptic focus.

In frequent epileptic seizures, especially myoclonic types, benzodiazepines are very useful (clonazepam 0.1–0.3 mg/kg/daily, frisium 0.3–1 mg/kg/daily). Benzodiazepines may also be helpful to reduce muscle tonus and decreased expression of dystonic non-epileptic attacks.

In young children with cerebral dysgenesis, vigabatrin may be effective in treatment (30–150 mg/kg/daily). It is useful to give predominant part or total daily dose at the evening for peak of drug concentration in blood at the dark for preventing retinotoxicity.

In prolonged clusters of seizures and status epilepticus - diazepam in rectal tubes, buccal or nasal midazolam, benzodiazepines i.m., i.v. In benzodiazepine-resistant status epilepticus and in tonic-autonomic seizures with apnea and bradyarrhythmia, valproates strictly i.v. (depakin, convulex) is recommended.

In consideration with the high risk of seizure recurrence and severity of epilepsy structural defects of the brain in patients with cerebral palsy, the duration of antiepileptic therapy should be at least 3 years after achieving clinical remission (usually for ≥5 years).

In the presence of drug-resistant epilepsy, it is necessary to decide on the possibility of epileptic surgery, which will be appropriate for cerebral dysgenesis, especially in cases of focal cortical dysplasia. On the contrary, the presence of a structural defect of hypoxic-ischemic or posthemorrhagic genesis and epileptiform discharge "BEDC" type in contralateral (in potentially "healthy" hemisphere as a result of a combination of cerebral palsy and idiopathic epileptic component) is a contraindication for epileptic surgery.

In cases of pharmacoresistance and impossibility or absence of indications for surgical treatment, VNS therapy (implantation of a vagus nerve stimulator) may be considered.

The serious problem is the possibility of aggravation of epileptic seizures and their appearance de novo due to application of some neurorehabilitation methods (electrophoresis, acupuncture, electroretinostimulation, application of nootropic drugs and brain stimulators, etc.). Of course, rehabilitation methods in every child will individually depend on motor and mental skills and the severity of epileptiform process. Reflex locomotion gymnastic (the Vojta method) and neurodynamic rehabilitation therapy (the Bobath method) have minimal epilepsy aggravation risk and are strongly recommended for all children with motor retardation as well as in cases of cerebral palsy with epilepsy and epileptiform activity. Metabolic L-carnitine treatment is very useful for patients with cerebral palsy especially in cases of prolong antiepileptic therapy (extremely important in long-term therapy with valproates causing

carnitine deficiency). Peptidergic nootropic therapy in cerebral palsy associated with epilepsy also demonstrated its efficiency and safety [14].

3. Conclusions

- Epilepsy is non-rare condition in patients with spastic forms of cerebral palsy.
- The presence of epilepsy aggravates the clinical course of cerebral palsy, complicates the rehabilitation, affects the prognosis of motor and intellectual functions, and could be life-threatening.
- Frequent combination of epileptic and non-epileptic paroxysms, as well as possible similarity of their kinematics, causes difficulty in their interpretation and differential diagnosis.
- Video-EEG monitoring as a "golden standard" for differential diagnostic of epileptic and non-epileptic events is very useful for investigation of patients with cerebral palsy. Sleep EEG is very important for detection of epileptiform discharges especially in children with CSWS or ESES pattern.
- Treatment of epilepsy in combination with cerebral palsy strictly requires an individual approach due to the form of epilepsy, seizure types, age of the patient, comorbidity, and somatic and mental condition of the patient.
- The presence of epilepsy is not a contraindication for rehabilitation and nootropic treatment. But we need to use methods with minimal risk of possibility for aggravation of seizures and epileptiform discharges.

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Conflict of interest

No conflict of interest.

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Chapter 5

Oral Health in Children with Cerebral Palsy

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Additional information is available at the end of the chapter

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Abstract

Cerebral palsy (CP) is a neurodevelopmental condition comprising a group of permanent disorders of movement and posture that are attributed to nonprogressive disturbances of the developing brain. The neuromuscular problems inherent in CP can affect oral health significantly in several ways. These can include changes in structure of the orofacial region, feeding problems, difficulties with maintaining oral hygiene; additionally, people with CP can encounter barriers in accessing oral health care. Several studies have examined caries rates in individuals who have CP. However, to date, no population-based studies have been published defining the risk factors for dental caries experience among children with CP. There is a high prevalence of orofacial motor dysfunction among people with CP, which can hinder oral hygiene and hence increase dental biofilm formation and retention. Factors such as food consistency, snacking between meals, and associated oromotor dysfunction have also been reported to contribute to the high incidence of caries found in those with CP. Therefore, this chapter will aim to describe the oral health status and factors affecting dental caries experience of children with CP, while also providing preventative and restorative recommendations to combat the prevalence of this disease.

Keywords: dental caries, motor function, oral hygiene, children, cerebral palsy

1. Introduction

Cerebral palsy (CP) is a neurodevelopmental condition comprising a group of permanent disorders of movement and posture that are attributed to nonprogressive disturbances of the developing brain [1, 2]. In children, CP affects approximately 2.1/1000 worldwide, making it

the most common physical disability of childhood. Although some children might outgrow their CP symptoms due to the maturation of neurons, lesions within the central nervous system often compromise motor development severely through time. The classification of CP often differs according to the gestational age at birth, age, and the distribution of lesions. However, classifications are normally registered using two categories, extremity location and neurologic dysfunction. If extremities are involved, diagnosis is subjective to monoplegia, hemiplegia, diplegia, or quadriplegia. If neurologic dysfunctions are involved, it is subjective to spastic, hypotonic, dystonic, athetotic, or a combination [3]. While commonly diagnosed, it is often shown that CP affects many aspects of a child's health. Common health problems associated with CP are excessive drooling, respiratory issues, nutrition, sleep, and poor oral hygiene. With almost one-third of children with CP having difficulties with chewing and swallowing, it is important to note that oral health is a primitive underlying factor for the majority of these complications.

Oral health in children with CP is impacted significantly by their neuromuscular and neurodevelopmental disabilities, leading them to have a higher risk of dental disease due to the greater difficulty for these individuals to perform or receive effective oral hygiene and oral care [4–6]. Specific attributions can be made to the high prevalence of orofacial motor dysfunction, which can lead to poor oral hygiene, and increase dental biofilm formation and retention [7]. Factors such as food consistency and snacking between meals have also been reported to contribute to the high incidence of dental diseases, like dental caries and periodontitis [8]. Nevertheless, dental caries is one of the most common chronic diseases in childhood. Dental caries are defined as one or more decayed, missing, or filled teeth for permanent teeth. Dental caries can also develop at any tooth site in the oral cavity. Hence, with the combined characteristics of poor oral hygiene and orofacial impairments, children with CP make seamless dental caries inhabitants. Several studies have examined caries rates in individuals who have CP [9–11]. However, most of those studies were conducted on highly selected children (e.g., children attending clinics or rehabilitation centers) and in high-income countries. A study from England did not find any significant differences in the levels of decayed, missing, and filled teeth between children who had CP and a control group of children without disabilities. They did find, however, that the children with CP had more untreated decay than children without a disability. Emphasizing the notion that oral health considerations were avoided or even worse, not accessible, which embarks the path of irreversible dental damage and further consequential health issues impacting overall quality of life. For this reason, society must change its outlook on the correlation between healthcare and oral health status for this population.

The concept of oral health-related quality of life (OHRQoL) is defined as the impact of oral health or disease on an individual's daily functioning and well-being. In the United States Surgeon General's report on oral health, they attribute OHRQoL as, "a multidimensional construct that reflects (among other things) people's comfort when eating, sleeping, and engaging in social interaction; their self-esteem; and their satisfaction with respect to their oral health" [12]. Previous studies have in fact demonstrated that dental diseases and disorders have a negative impact on an individual's OHRQoL and the quality of life (QoL) of their parents or

caregivers. Therefore, improving and understanding the factors contributing to the OHRQoL should be the goal for all children with dental disease including children with CP. For these reasons, the motivating factors of dental caries will be explored in order to identify modifications to the oral hygiene behavior and appropriate diet for children with CP. By pinpointing these improvements, a prospective outlook can be set on the impact training and reorganization of preventative dental care can provide for this challenged population.

2. Oral hygiene

2.1. Oral hygiene and CP

Oral health pertains to the teeth, tongue, gums, and their supporting tissue, but also the upper and lower jaw, chewing muscles, throat, salivary glands, and lips that allow us to explore our five senses [12] through speech, facial expressions, food, smell, or touch. With these valuable assets being compromised under the CP population, it is very common for one to not understand or assume responsibility of a standard oral routine; but it is for this same reason that this specific population must be inspected more heavily. Thus, early oral health preventive care and routines must be explored in order for this population to subside in the category of prevalent dental caries.

Studies have shown that the prevalence of caries experience was higher in individuals who cleaned their teeth less than once a day than those whose teeth were cleaned at least once a day [13]. For this reason, tooth brushing twice a day can provide an effective maintenance of the oral cavity. Alongside with fluoride-containing toothpaste, it is shown to decrease the presence of plaque. Plaque being a microbial biomass is composed of resident bacteria from saliva. If a tooth surface is covered by dental plaque, the metabolic activity alters the chemical dissolution of the tooth surface [14]. Therefore, brushing is essential to disturb and remove plaque in efforts of decreasing the rate cariogenicity.

Tooth brushing and flossing also eliminates the quantity of food debris, which if not removed can lead acid erosion to breakdown enamel and dentin, leaving teeth sensitive and discolored. Being that these are the major factors that promote the increase of dental caries, there are no parts of a tooth that are necessarily, "more or less susceptible." However, the idea of susceptibility is one parent of children with CP must acknowledge that no matter the age, classification of CP, or dietary regime, lesion formation and progression of dental caries can be controlled.

2.2. Fluoride and antimicrobial products and CP

The presence of fluoride within a child's oral practice is essential in the prevalence and severity of dental caries. Fluoride's attraction to calcium inhibits and even reverses the potential of dental caries to form by disrupting demineralization and enhancing remineralization of teeth. Remineralization of teeth increases the acid resistance of the enamel surface structure, thus

preventing the change in pH levels, which are primarily responsible for tooth erosion and the creation of new lesions. Fluoride can be integrated in three main functions, community water fluoridation, pastes, and mouthwashes. Frequent consumption of water containing fluoride can permit a consistent barrier for dental caries to occur among the CP population, with minimal dietary efforts needed. Daily toothpaste use alongside with tooth brushing can provide a direct dosage of fluoride for the enamel to combat acid erosion. Studies relating dental caries risk factors attributed difficulty in the application of fluoride to the oral reflexes, such as biting and vomiting and intraoral sensitivity [7, 15]. As a result, it is advised that parents aide their children in the process of tooth brushing, by altering the child's orofacial position to decrease the probability of these refluxes, thereby promoting the ability to apply the daily dosage of fluoride on all teeth. Antimicrobial products although not noted as often can also be utilized in low concentrations to diminish the role of bacteria within the oral region. With minimal bacterial growth, oral cavities will be less prone to metabolize fermentable carbohydrates. Counteracting the microbial environment will thus set additional inhibitors that these dental caries agents will try and override. Finally, mouthwashes containing low concentrations of fluoride (0.05% neutral sodium fluoride or 0.1% stannous fluoride) and antimicrobial agents can provide an effective mean in increasing salivary production, which will allow a continuous aqueous flow to protect the oral cavity throughout the day.

2.3. Frequent dental visits and CP

Disease preventative measures can be performed within one's home; however, it can also be supported by seeking a professional opinion, at least once a year. Seeking an oral health professional that is an approved medical practitioner in one's estate can provide the family and child with CP, a clear, understandable, and personalized protocol to be followed if the oral health evaluation is not up to par. Oral health practitioners can provide insight on the severity of the dental caries present, and the following steps to be considered if a stronger optical concentrated treatment is needed. Specifically, in low-income and middle-income countries (LMIC), parents and physicians must work together in reassuring the child of an oral evaluation as governmental and service providers are limited in their capacity to quantify current and future resources of this population. This phenomenon has been evaluated by studies in Brazil, Bangladesh, and Japan. Determinations were made on the effects of oral health care access and dental caries progression in LMIC [3, 13, 16]. Results displayed that progression of dental caries was reduced once handicapped children participated in the funded rehabilitative programs of oral health professionals [16]. Practitioners should be specifically trained and equipped to handle CP-related orofacial impairments in order to provide the patient the least amount of discomfort and pain as possible.

The role of oral hygiene in the prevention and decrement of dental caries within the CP population can be reviewed by three major provisions, daily tooth brushing, use of fluoride-containing products, and scheduled dental visits. The combination of tooth brushing and fluoride toothpaste can provide an effective barrier to the ubiquitous degradation of plaque and cariogenic bacteria. Scheduled dental visits can provide a professional review of the child's current oral health status and can deliver an incentive to change oral health behavior if dental examinations are abnormal. Overall, efforts should be emphasized that the role of oral hygiene plays a significant role in the prevalence of dental caries, and caregivers should focus on providing a primal example of daily oral health routines to combat this notion.

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3. Motor and orofacial impairment

Children with CP experience varying degrees of motor impairment as quantified by the gross motor function classification system (GMFCS), which classifies children with CP based on functional abilities and limitations [17]. GMFCS is a classification system intended to enhance communication between families and professionals when describing a child's gross motor function and can be useful when setting goals and making management decisions. The GMFCS levels range from level I of "Walks without limitations" to level V of "Transported in a manual wheelchair." Motor impairment results in difficulty in performing and receiving oral hygiene, which among other factors, such as feeding problems and reduced access to oral health care, increases caries risk. The GMFCS has not traditionally been used to inform dental professionals in their evaluation of dental caries risk and management decisions for children with CP; however, it has recently been identified that children with CP with severe motor impairment are at high risk for dental caries. As a result, this section will focus on motor impairment and its association with worse OHRQoL of children with CP.

3.1. CP type and motor impairment

Motor impairment in children with CP can be communicated in a variety of ways making it difficult to gather information from the literature on the impact of motor impairment. It is commonly described by some combination of location, type, and severity and falls along a continuum with the most severe presentation being of the "quadriplegic spastic type characterized by stiff hypertonic muscles and motor deficits in all four limbs." Location is often described as tetraparesis/tetraplegia/quadriplegia, triplegia, diparesis/diplegia, monoplegia, or hemiparesis/hemiplegia and type is often described as spastic, athetoid, ataxic, hypotonia, or mixed. Recent studies in Brazil found a relationship between increased motor impairment and increased caries experience in children with CP. It has been found that "individuals with mild to moderate mobility disability (GMFCS levels I, II and III) had a 4.2-fold greater chance of having teeth with cavities and those with severe motor impairment (GMFCS levels IV and V) had an eightfold greater chance of having cavities in comparison to individuals without motor impairment" [18]. As a result, attributed difficulty in providing oral hygiene to children with CP can be claimed by the "differences in intraoral sensibility, presence of involuntary physical movements and/or oral pathological reflexes and spasticity in masticatory muscles" [15]. For these reasons, attention must be paid forward in the act of involving primary caregivers in the instrumental role of oral hygiene practices, as they are the main source to provide consistent care and additional oral health care for these children with CP.

3.2. GMFCS and oral health-related quality of life in CP

The OHRQoL instrument has been used in several studies to obtain data from primary caregivers or parents, to reference the effect of their child's current oral health on their daily lives, (i.e., "how often have you had mouth sores because of your teeth/mouth?"). These data points also include the parents' concerns about their child's oral health in regards to being upset, having disrupted sleep, or taken time off work. Studies using this paradigm concluded that compared to children with GMFCS I-III, the group of children with increased motor impairment of GMFCS IV-V had worse outcomes for having difficulty saying words, having trouble

sleeping, having difficulty eating, drinking or chewing firm foods, taking longer to eat a meal, and feeling terrible or frustrated. Furthermore, children were more likely found to feel upset, shy, and avoid smiling or laughing. These main concerns were the elements that resulted with statistically significant differences between the two groups, ranging from 5.2 to 9.1 times more prevalent in the group with increased motor impairment. These components narrate the children's emotional reactions to their oral condition and in particular reflect on their self-esteem, social, and emotional well-being. Having difficulty drinking, eating, or chewing firm foods reflects upon the domain of physical functions while feeling upset and shy reflect upon the individual's social and emotional experience. Concurrent studies in parts of world such as Brazil and Japan also have found that parents of children with CP had greater distress, uneasiness, and lower quality of life, which implicates the attributed complications of motor and orofacial impairments in the performance of quality oral hygiene and life for families worldwide [3, 16].

It is well defined that the health-related quality of life (HQoL) and oral health-related quality of life (OHRQoL) between children with CP are often intertwined. The prevalence of motor deficiencies associated with CP contributes to the inability for this population to perform daily movements and thus making it incapable for children to perform self-care functions such as maintaining adequate oral hygiene, thereby moving the subjective responsibility of oral hygiene, feeding, and overall lively independence to the caregiver. This manner of consistent dependence significantly impacts the physical, social, and emotional well-being of both a child and their caregiver. As a result, an assessment will be made to discuss oral health's multidimensional impact on the livelihood of families. Distinguishing these traits will provide children and families with CP better modus to achieve optimal health.

In summary, motor deficiencies associated with CP contribute to gross limitations in a child's ability to perform activities of daily living, namely self-care functions such as maintaining adequate oral hygiene. Improving OHRQoL should be the goal for all children with dental disease including children with CP. Understanding the impact of factors contributing to OHRQoL will help to inform management in this population. Although often segmented from the physical diagnosis of motor and orofacial impairments, OHRQoL emphasizes the importance of defining appropriate treatment goals and outcomes in order to provide care that focuses on a person's social, emotional, and physical experience. A child simply cannot experience these factors separately. Therefore, they must function in unity for proper medical and dental treatment measures to be obtained. With this in mind, good quality of life can be provided for all CP patients.

4. Saliva, diet, and nutrition

Motor and orofacial impairments significantly impact the capability of children with CP to smell, taste, and chew their food. Children with increased motor impairments of GMFCS IV-V have worse outcomes in difficulty eating, drinking, and chewing firm foods, thereby subjecting parents and guardians to administer alternative food consistencies and frequent snacking between meals for nourishment. However, several studies have reported that these factors

contribute to the high incidence of caries and periodontal disease in those with CP [13]. Thus, elements of dietary control and feeding habits will be investigated to deduce the cause of the high dental caries incidence, in order to determine which oral hygiene practices and nutrition should be suggested for this population to obtain an optimal level of oral health.

4.1. Saliva and sensory function in CP

To subject to a higher standard of oral health, it is important to understand the specific roles of sensory and saliva functions in food consumption. Deficiencies in high-density sensory nerve endings in the craniofacial tissues affect the sensory functions of children with CP. The impact of these craniofacial tissues thereby restricts the movement of the tongue, jaws, and oral-facial muscles [12]. The modulation of these muscles thus affects the salivary glands. The production of saliva in these salivary glands is an essential guard against tooth decay. Saliva flushes out sugars and remaining food particles from the oral cavity and by eliminating these bacterial food sources, the oral cavity will host limited acid diffusion and tooth erosion [19]. In patients with CP, saliva production can sometimes be the only factor contributing to an easier way of chewing and swallowing food. Thus, saliva production within CP patients, especially those with more severe motor dysfunctions, must be monitored in order to create an easier pathway for food to be consumed. To increase saliva production, a child must drink water frequently, chew on sugar-free gum (if capable), and decrease active mouth breathing.

Studies have shown that dental caries incidence within this population can be attributed to food impaction, cariogenic foods and drinks, and sweetened medications [20]. Impaction of food indicates that nominal salivary production is not sufficient enough to keep the oral cavity clean of tooth demineralization. Commonly in CP children, food impaction can be due to "poor masticatory muscular control, which encourages food stagnation in the buccal and labial sulci and poor manual dexterity" [21]. Affirming that oral hygiene efforts including daily tooth brushing and flossing must be used in order to remove any food particles that can harbor within teeth. Removal of these food particles can prevent food from degrading and fostering acidic compounds, which could then lead to acid production. If foods and liquids are composed of acidic compounds, such as foods with high sugars and carbohydrates, cariogenicity is more likely. Therefore, a decreased intake of foods and liquids prevalent in saccharides could provide children with CP a lower plaque count. Additionally, sweeten medications referred for controlling seizures and other medical problems often contain saccharides and artificial flavors. These medications like the anticonvulsant, carbamazepine, are highly viscous and used at night thereby setting the perfect environment for dental caries to form [22]. Digesting these medications at night without the subsequent oral practice of tooth brushing enables the acidic compounds to form around teeth. As a result, parents must take into account that night medication must be considered after brushing and before going to bed, in order to maintain a proper oral hygiene routine.

4.2. Diet and nutrition

Diet and nutrition is essential in the regulation of good oral health and the promotion of overall systemic health. Unfortunately, in children with CP, malnutrition is often encountered due to a child's frequent pain in the teeth and mouth, difficulty in eating and drinking.

Malnutrition alters homeostasis, which can lead to the dental disease progression, reduce the resistance to the microbial biofilm, and reduce the capacity of tissue healing [21]. Deficiencies of vitamin A, vitamin D, vitamin B, iron, and protein can be responsible for enamel hypoplasia, hypomineralization, salivary gland hypofunction, delayed tooth eruption, and dental caries. Consuming foods that are rich in these nutrients are consequently essential in order to defend the oral cavity against infection and its ability to buffer plaque acids. Appropriate nutrition for children with CP should be considered depending on their personalized health deficiencies. Being that a majority of children with CP are dependent on nonsolid food intake, parents must be aware that the physical consistency, sequence, and frequent feedings are associated to the development of dental caries. The high and frequent sugar intake constructs this population to be highly susceptible to food cariogenicity. Thus, parents should be able to associate that a frequency in snacking of more than one time/day increases the dental caries experience [13]. If the child is dependent on nonsolid food intake, these products must have minimal refined sugars. Snacking in between meals should be minimized to decrease the anaerobic metabolism of sugars. Nevertheless, snacking should be used as an additional source of nutritional intake, not as a primary source. If a child possesses signs of nutritional deficiencies and eating disorders, early clinical signs can be noted with inflammation of the lining of the oral cavity, oral lesions, or sore throat [21]. In summary, a substantial diet filled with a variety of vitamins, minerals, and proteins should be consumed regularly in order to prevent a delay in tooth development, which could later be responsible for an increased caries experience.

The incidence of dental caries in this population can be attributed to the direct relationship between motor impairment and poor feeding habits. Children classified with CP are more prone to have trouble drinking, eating, or chewing firm foods, thus leaving food to be caught in between teeth more frequently. To diminish dental caries susceptibility, improvements must be made in the nutrient intake and oral hygiene practices in this population. By changing this behavior, CP children can reduce frequent dental pains and improve their OHRQoL.

5. Psychological and social behaviors

5.1. Effect on CP children's psychological and social behaviors

The World Health Organization has indicated that an individual who is "cured" cannot be categorized as one who is doing "well" [12]. As a child with CP, quality of life is significantly impacted by an inability to eat, be independent, or socialize. These qualities are often exacerbated if the child is at high risk for dental caries, due to the concerns of one's smile and appearance. These elements thus relate the child's emotional reaction to their oral condition and in particular reflect on their social and emotional well-being and self-esteem. Having difficulty in drinking, eating, or chewing firm foods reflects upon the domain of physical functioning, while feeling upset and shy reflect upon the individual's social and emotional experience, thereby leaving a negative impact on the OHRQoL of children with CP. As children with CP who have more severe functional mobility limitations (GMFCS IV and V) have

greater caries experience, these children are more likely to be at high risk for poor OHRQoL [11]. Concurring studies in Brazil address these issues in a population as early as preschool children [11]. As a result, children with CP with more severely impacted OHRQoL are consequently subjected to a poorer well-being. Suggesting that inclusion of OHRQoL measures can provide a more comprehensive assessment of the impact on overall health status.

5.2. Effects on CP parent's psychological and social behaviors

Parents and caregivers are indispensable members of the medical team as they provide daily support for children with CP. On the other hand, this indispensability of caregivers comes at health cost. The need for subsequent care in regard to hygiene, clothing, food, and rehabilitation leads caregivers to be physically and mentally tired 8. Studies have found that the quality of life within the parental population of children with CP is in fact worse than those of non-CP children [12]. Data suggest that parents of children with CP demonstrate higher levels of distress due to their children's oral health status than parents of children without CP. Additional studies indicate that parents of children with CP had greater uneasiness regarding their child's oral health than those parents of children without CP, and a study in Hong Kong found the same association with parents of preschool children with CP [1, 23, 24]. Parents and caregivers of children with CP may be more likely to experience frustration or difficulties supporting their children's daily oral hygiene activities due to complications related to intraoral sensibility, presence of involuntary physical movements and/or oral pathological reflexes, spasticity in masticatory muscles, and the presence of residual food common to many children with CP [12].

Individuals with CP and their families whom have a poor OHRQoL are subjective to a poorer quality of life. The deficiency of neurological and motor development in children places a dependent responsibility among parental figures. This dependent responsibility can consequently lead to an irritable and counterproductive environment for the promotion of oral health. Efforts should be made to develop an effective oral health promotion program for children with CP. Health programs should abide by the significant relationship between health care professionals, caregivers, and the child with the disability. In turn, the prioritization of this relationship can motivate the caregivers to modify their oral health experience, improve family dynamics, and subsequently improve their overall quality of health.

6. Caries prevention and restorative treatment

General rehabilitative efforts among the CP population are often used in order to improve children's health, education, and future employment. Yet, the severity of oral conditions in this population demonstrates the need for interventional dental therapy for a holistic rehabilitation effort to be performed. Involvement of evidence-based techniques such as risk assessments, preventative, and restorative treatment thus can provide a beneficial provision in the incidence of dental caries within this population. Utilizing a combination of these factors can then create a favorable oral environment and substantially reduce caries risk and progression.

6.1. Risk assessment

An assessment of risk factors associated with caries activity is necessary in order to explore and understand the oral capacity of children with CP. Being that the prevalence among dental caries has declined, but not specifically in the CP population, has lead researchers to investigate which risk assessments should more often be considered 15. Studies have shown that no singular oral examination can be indicative of dental caries status, thus a multifactorial analysis must use combining laboratory examination and observations for a cohesive diagnosis. Characteristics that place a child at high caries risk includes consumption of sugary food or drinks, poor oral hygiene, caries experience of the caregiver, poor resource settings, cavitated or noncavitated carious lesions, missing teeth due to caries, and inadequate salivary flow [25]. Since children with CP often experience frequent consumption of cariogenic nonsolid foods, inadequate practice of oral hygiene in the household, severe motor disabilities (GMFCS level IV-V), and low-quality dental care, it is subsistent for this population to face a high risk for dental caries [12, 13, 26]. Although the susceptibility for this population is high, preventative and restorative measures can still be announced and evaluated in the means of reducing the patient's risk in developing an advanced disease or arresting the disease process.

6.2. Preventative treatment, monitoring and rehabilitation, and CP

6.2.1. Modifying oral hygiene behavior

Children with CP and their caregivers must be willing to participate in daily tooth brushing and flossing. Tooth brushing twice a day can provide an effective maintenance of the oral cavity [13]. Through removal of plaque daily should markedly reduce the increment of new carious lesions. Improving oral measures at home can also provide a change in the presence of tooth erosion, plaque, malocclusions, dmft, and DMFT in this population [15]. An intensive oral hygiene instruction followed by periodic reinforcement will need to be provided to the caregivers and CP children. If a child is incapable of performing this action, it is up to the parents/caregivers to supervise this practice into completion.

6.2.2. Fluorides

Topical fluoride preventive agents such as mouth rinses, varnishes, gels, foams, and paste have been systematically reviewed by the Australian Dental Association (ADA) as a safe clinical means to reduce or arrest the development of caries. These treatments can be provided at home or professionally in accordance to the ADA clinical recommendation and practitioner's professional judgment [25]. Integration of fluoride in the oral hygiene of children with CP can provide an effective barrier to the demineralization process often caused by food deposits and harboring bacteria.

6.2.3. Modify the diet

Feeding conditions for children with CP are impaired due to the lack of neurological and muscular development. Eating efficiency is thus represented to be poor since aspects of oral skills are also impaired. Difficulty to perform normal deglutition in the tongue, lips, and cheeks prevent food to be consumed properly, leaving residual food to inhabit the mouth [27]. To minimize

food cariogenicity, parents are advised to eliminate frequent snacking and nonsolid foods rich in carbohydrates. Future evaluations should be considered in the eating efficiency in this population to provide a better nonsolid supplement for standard nutrition. Several sugar substitutes may be required to provide a broad range for stability, taste onset, and sweetness intensity. Such changes could potentially have a major public health impact in reducing dental caries in CP children.

6.2.4. Improving OHRQoL

The use of dental questionnaires can provide primary caregivers a means of interpreting their children's pain and discomfort, if the child has a limited capacity to self-report. Behaviors can be annotated with questionnaires such as the oral health-related quality of life (OHRQoL), early childhood impact scale (ECIS), family impact scale (FIS), and the child perception questionnaire (CPQ) [11, 13, 28, 29]. Although these questionnaires have been used as an additional means in their prospective studies, their singular results have repeatedly coincided with identifying the nominal risk or presence of dental caries in the CP population. Consequently, making it a functional and easy-to-use instrument to alert parents and physicians alike of the child's dental discomfort or well-being [30].

6.2.5. Restorative treatment

If the progression of dental caries is not controlled, lesions can be formed. In this event, "anatomical grooves, or pits and fissures on occlusal surfaces of permanent molars can trap food particles and promote the presence of bacterial biofilm" [25]. As a result, secondary preventative measures should be taken in order to inhibit the progression of these carious lesions. This management may include topical applications of fluoride varnish, excavation of undermined enamel, dentine conditioning, or temporary fill glass ionomer cement. The aim of lesion management will prepare the oral environment for caries arrest, bacterial infection reduction, and prevent food impaction in open cavities.

6.2.6. Patient monitoring

Physicians can educate and motivate patients by monitoring them on a regularly basis. Frequent evaluations can so be utilized to cease, prevent, and reverse dental caries from occurring. Oral hygiene instruction and coaching can also be used to train children with CP how and why it is important to have an oral hygiene routine, in the case that the caregiver is unenthusiastic.

6.2.7. Rehabilitation program

Dental therapy for the physically and mentally impaired should be a part of the normal rehabilitation process. Specifically, in children with CP, their extensive sensitivity for dental caries emulates the level importance of clinical dental evaluations in a rehabilitative program [15]. Programs must consider that oral health in this specific population is a major determinant of their physical, social, and mental well-being. If it is impacted, it can secondarily affect their motivations to integrate into society as a whole. For these reasons, rehabilitation programs should consider the efficacy and economic cost of comprehensive

care, as it must be accessible to all families. Ignorance to this measure would thus extend the gap of hosting an equal opportunity for quality oral and general health for children and families with CP.

7. Conclusion

In summary, efforts should be made to develop oral health initiatives for children with CP. The rudimentary neurological and muscular impairments default this population to be highly susceptible candidates for oral health diseases like dental caries. Children with more severe functional motor impairment might have a higher risk of experiencing dental caries, which could be attributed to difficulties in performing adequate oral hygiene. Therefore, the role of oral hygiene must be emphasized in the household of these families in order to treat the prevalent risk factors. To reduce dental caries susceptibility, improvements such as minimal snacking and carbohydrate intake must be made to mend OHRQoL and frequent dental pain. Prioritization should be given by oral health rehabilitation programs to abide the relationship between the physician, caregiver, and the child with the disability to recuperate family dynamics and subsequently improve their overall quality of health. By pinpointing these improvements, a prospective outlook can be set on the impact training and reorganization of preventative and restorative dental care can provide for this challenged population.

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Conflict of interest

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Section 4

Therapeutic Aspects of Cerebral Palsy

Chapter 6

Use of Botulinum Toxin A in Cerebral Palsy

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Additional information is available at the end of the chapter

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Abstract

Botulinum toxin A (BTX-A) is widely used worldwide to overcome the significant problem in spastic cerebral palsy (CP). In the past three decades, botulinum toxin serotype A (BTX-A) has been introduced as a selective treatment option for spasticity in children with cerebral palsy. BTX-A is an acetylcholine-blocking agent that causes presynaptic neuromuscular blocking when injected into the muscle. Its action of decreasing or normalization of tone prevent the development of contractures and deformities and avoid or postponed surgical intervention particularly when combined with other treatment modalities such as physiotherapy, casting, orthosis, etc. Equinus deformity, scissoring and crouch gait in the lower limbs, and different spastic deformities like pronation of forearm, elbow flexion, wrist flexion, fisting, or abnormal dystonic posture of upper limb deformities were the main indications wherein botulinum toxin injection is needed in spastic cerebral palsy; moreover, its benefit of relieving pain that are associated with muscular hypertonia and palpation of the muscle, particularly the large one, remains the cornerstone for injection of BTX in CP patient for most experts worldwide, but it needs a well of knowledge in anatomy and its landmark. Invasive procedure like electromyography (EMG) is more difficult to be applied successfully in children than in adults. Spasticity is considered a positive phase of muscle function. Therefore, when relaxing the muscle, the patient's condition might get worse functionally in some instance. So, the first question clinician put in his account before injecting BTX is whether hypertonia is impeding or improving function; therefore, injection is tailored individually by an expert physician. Generally, the adverse side effects of BTX-A are seldom to occur providing that the physician strictly adheres to the dose ranges and reinjection period. The interinjection period must be at least 12 weeks to avoid antibodies ands. So far, BTX-A is considered to be safe to some extent if used professionally; however, long-term adverse effect particularly with multilevel therapy are still not clear.

Keywords: cerebral palsy, botulinum toxin, spasticity, muscle function, children

1. Introduction

Cerebral palsy (CP) is a nonprogressive encephalopathy that primarily affects motor system; in consequence, there is a defect in motor milestone development with a variable degree of severity and locomotor deformities. Therefore, CP is a complex entity with known and unknown causes [1].

Cerebral palsy (CP) is the most frequent cause of spasticity in children [2]. In the last 25 years, injecting botulinum toxin type A (BTX-A) has been proven as an effective medicine strategy to decrease hypertonia in CP child. Now used in most countries of five continents, it is a green light after 2 years of age adopted by most expertise; however, there is big difference in licensing from one country to another. Therefore, most of BTX-A use is labeled according to its trademark. Nowadays, BTX-A has a major role of the multidisciplinary treatment in spastic CP, in addition to physiotherapy, occupational therapy, speech therapy, casting, ankle-foot orthoses (AFO), and knee-ankle-foot orthosis (KAFO) surgical application of intrathecal baclofen; selective dorsal rhizotomy (SDR); and different orthopedic interventions, with varying simple to complex intervention to achieve optimal reconstructive [3].

Within the current clinical management of CP in children, the use of BTX-A is recommended to improve function and to support motor development [4]. Botulinum toxin injection has an additional role on the decrease of pain associated with focal spasticity [5]. Actually, in muscular hypertonia, sever muscle contraction produces compromising vessel resulting in ischemia, ultimately agonizing nociceptive pain (ischemic muscular pain). Nevertheless, decrease of spasm by BTX injection improved blood flow, the ischemia markedly decreased, and pain subsided by muscular relaxation effect of BTX [6].

BTX had been discovered at the beginning of the nineteenth century as a poison. This poison is a protein, which is a product of *Clostridium botulinum* bacterium, a Gram-positive anaerobe. Meat is considered the primary source of this bacterium, from the name "botulus" which mean sausage, though it is present in different food types. The German physician Justinus Kerner in 1818 first wrote about poison that food-borne diseases who was described confidently in the middle-aged patient. The features of botulism have been known since ancient times around the time of Christ [7]. He then published a monograph on poisoning in 1820 in which he described the features, made many original observations, and commented on the possible causation, diagnosis, and treatment [8]. He concluded that a toxin produced by an infective agent was responsible for the features of paralysis of skeletal and smooth muscles. He published a second monograph in 1822, in which he laid out his hypotheses on BTX and described clinical evaluation of the problem through case histories of his patients and through post-mortem examination of patients with botulism [9].

1.1. Physiology of neuromuscular transmission

When we take neuromuscular junction (NMJ) in focus, it consists of the terminal branch of the motor neuron and the muscle fiber that innervates and synaptic cleft between. Acetylcholine is synthesized and stored in the synaptic vesicles that are released into the synaptic cleft by fusion with the presynaptic membrane, through the process called exocytosis. The process of

exocytosis is a result of a nerve action potential arriving at the terminal membrane causing an influx of calcium ions through voltage-dependent channel and binding to the receptors on the postsynaptic neuron, causing a change in the electrical properties of that membrane, which finally results in the contraction of the muscle fiber. Calcium regulated the process of exocytosis which is considered a complicated process that involves the actions of proteins located on the vesicles in the cytosol and on the presynaptic membrane. The protein known as synapsin I binds to the synaptic vesicle to the cytoskeleton. Calcium-dependent process known as synapsin I phosphorylation leads to the release of the vesicle from the cytoskeleton and then is transported into the active zone, where it binds to the presynaptic membrane [10]. The synaptic vesicle contains other important proteins; synaptobrevin and syntaxin on the presynaptic membrane act as shelter that pulls the membranes together. On the other hand, synaptosome-associated protein 25, which is attached to the presynaptic membrane, binds to two molecules of syntaxin, which forms a complex [11]. Synaptobrevin binds to this complex and displaces one of the syntaxin molecules from the complex, which brings the synaptic vesicle and the presynaptic membrane into the proximity that is necessary for fusion and exocytosis to take place [10].

From the above, we conclude that exocytosis is considered the primary mechanism for the release of acetylcholine, and this process is complicated and not fully investigated; however, it involved a lot of specific proteins. Therefore, any intervention with these proteins impaired acetylcholine release by exocytosis which results in presynaptic blocking, and this is what happens with BTX.

2. Mechanism of action of botulinum toxin

Botulinum neurotoxin is indeed a remarkable protein produced by *Clostridium botulinum* [12]; there are at least seven serotypes of neurotoxin discovered till now: botulinum toxin A (BTX-A), botulinum toxin B (BTX-B), botulinum toxin C (BTX-C), botulinum toxin D (BTX-D), botulinum toxin E (BTX-E), botulinum toxin F (BTX-F), and botulinum toxin G (BTX-G), only first two are medically used. Neurotoxins share with same target to inhibit presynaptic acetylcholine release to synaptic cleft, but they are different in targeting protein, their duration of effect, and their potency [13, 14]. BTX-A displays their effect in relaxing the muscle proportionally related to doses [15, 16].

The effect of BTX lasts for about 12–16 weeks; however, within 4 weeks soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex of protein has its turnover. Exocytosis resumes and new axonal sprouting is at the end plate to reestablish conduction [17].

2.1. Pharmacological aspects of botulinum toxin therapy

Botulinum toxin drugs currently available (BTX drugs) are Botox (Allergan Inc., Irvine, CA, USA), Dysport® (Ipsen Ltd., Slough, Berkshire, UK), NeuroBloc/Myobloc (Solstice Neurosciences Inc., Malvern, PA, USA), and Xeomin (Merz Pharmaceuticals, Frankfurt/M, Germany). From 1989 to 1992, Botox's trade name was Oculinum®. In the USA and in some

other countries, NeuroBloc is distributed as Myobloc. Additional BTX drugs include Hengli (Lanzhou Institute of Biological Products, Lanzhou, Gansu Province, China), which is based upon BTX type A and which is distributed in some other Asian and South American markets as CBTX-A or Prosigne®, and Neuronox® (Medy-Tox, Ochang-eup, South Korea), which is sold in South Korea and in some other Asian countries. New BTX drugs are underdevelopment at Tokushima University, Tokushima City, Japan, and at the Mentor Corporation, Santa Barbara, CA, USA. Botox was the first BTX drug to be registered in 1989, while Dysport was registered in 1991, Hengli in 1993, NeuroBloc/Myobloc in 2000, and Xeomin in 2005.

Most of the currently available BTX drugs are shown in **Figure 1**. All BTX-A drugs are powders which need to be reconstituted with 0.9% NaCl/H2O prior to application. Only NeuroBloc/Myobloc is a ready-to-use solution. For all BTX drugs, special storage temperatures are required. Xeomin is the only drug which can be stored at room temperature. The shelf lives of all BTX drugs are similar. The long shelf life of Xeomin is remarkable, since it was originally believed that the lack of complexing proteins would destabilize its BTX. Since NeuroBloc/Myobloc is stabilized by a reduced pH value, about half of the patients receiving NeuroBloc/Myobloc report intensified application pain.

2.2. Patient selection

The selection of CP patient who is a candidate for BTX-A application is based on clinical evaluation of spasticity, power, posture, gait, and other motions, rang of motion, and joint assessment whether dynamic or limited by contracture. Nevertheless, an accurate choice of the CP child for BTX-A might be difficult and need more complex assessment because of the dynamic character of spastic CP and must include motion [18].

Many studies adopted the relation between gait analysis assessment and clinical assessment; they found that both are complementary to each other in providing important information for planning the strategy of CP management. Therefore, observation of movement specially if combined with gait analysis data provides important information in selection of target muscles [19]. Assessment of motion at each joint with identification of spastic muscle that needs to be injected by BTX could be achieved by motion/gait analysis [20].

From these assessments, we conclude that motion analysis in the different anatomical posture for children while walking, crawling, sitting, rolling by physician, and videotaping is considered important in optimizing the benefits of BTX injection.

In nonambulatory CP child with Gross Motor Function Classification System [GMFCS] IV and V, x-rays are indicated in their regular follow-up, to rule out and develop hip dysplasia and scoliosis/kyphosis.

2.3. The use of botulinum toxin in cerebral palsy

There are many causes of cerebral palsy (CP) that make normal development of the limb without deformity and difficulty, but spasticity remains the most important cause as spastic muscle interferes with the neighboring bone and soft tissue growth, resulting in discrepancy

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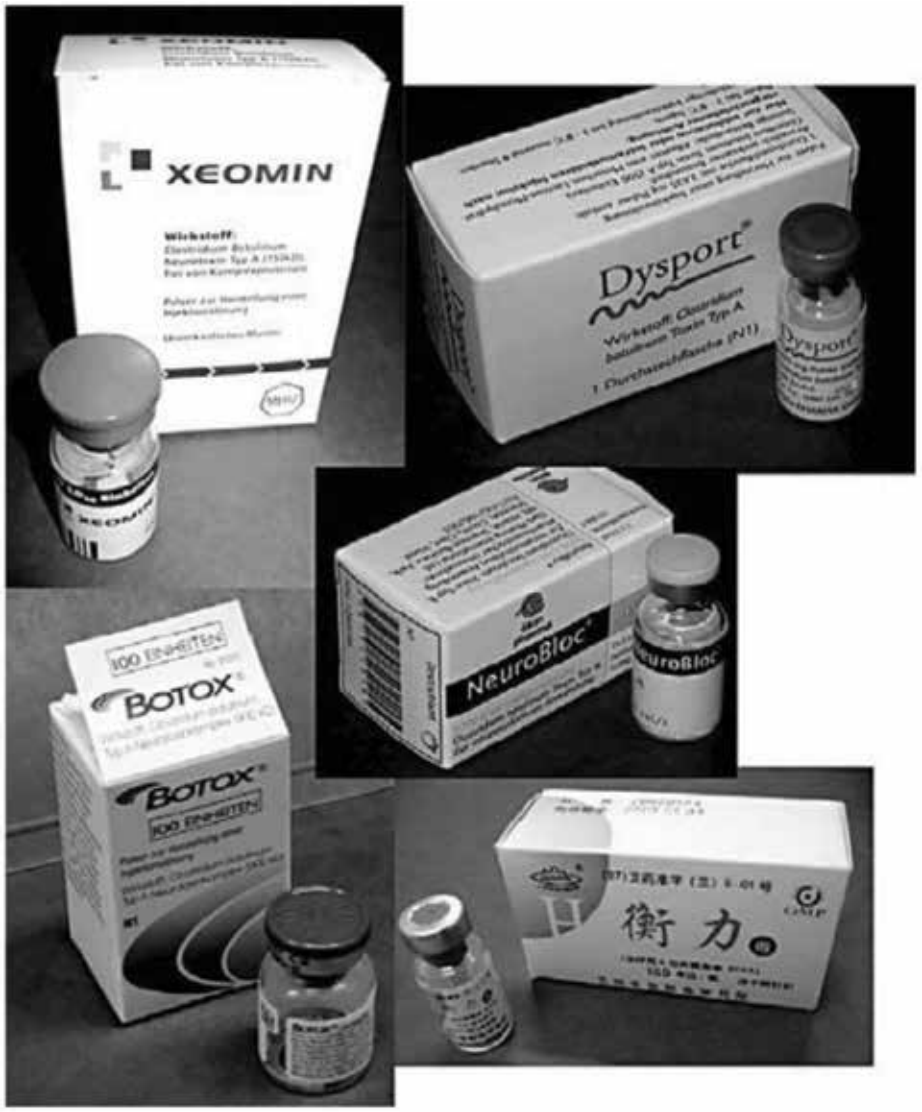

Figure 1. Some of the commercially available botulinum toxin drugs.

in growth between spastic muscle and other structures, with time of growing child dysmorphism and contracture of limb occurring with consequent loss of normal function with shortening of both the muscle and the limb if the tone is constantly remained hypertonic [21]. Such evidence of impairment of growth and deformity is also noted in animals with spasticity, for instance, spastic mouse [22]. Fortunately, stretching of the relaxed muscle may ensure no deformity and contracture with normal growth [23]. According to this hypothesis, it has been supposed that great benefit could be gotten from BTX from its action of relaxing the muscle in spastic CP, and this premise has been tested in mice with significant result regarding restoring the muscle length to normal [24].

Additional benefit from BTX injection to the hypertonic muscle enhances the reciprocal antagonist muscle to become stronger, with subsequent decrement of bone deformity as a result of decrease in discrepancy of impaired growth of spastic muscle and neighboring structure. Indeed, there is clear evidence of delay or decrease of the need for surgical intervention with injection of BTX specially if combined with other models of management such as physiotherapy, casting, and orthotics. However, to achieve optimum goal of BTX injection, many factors are required, but the appropriate selection of the patient is the most important domain for the success of BTX injection. The patient should not have fixed contracture, and spastic patient with dynamic joint is considered typical for injection, whereas the patient with dyskinesia has mild to moderate effect. Athetoid types of CP usually do not get benefit [25].

Anyhow, management target is to progress normal sequence of milestone and attain the next motor development. The goal of treatment in ambulatory patient is to improve and optimize ambulation and walking [16]. **Table 1** shows special indication.

2.4. Muscles of upper extremities

Many muscles in the upper limb are targeted by BTX injection. Again, selection of spastic muscle depends upon the patient's state. Therefore, evaluation and assessment of the patient of proposed benefit functionally avoiding bone deformity are individualized according to the patient [26].

In the upper limb, the injection depends upon the spasticity pattern. For instance, spastic flexion of the elbow usually is in the brachioradialis muscle with or without biceps brachii muscle. For spastic forearm pronation injection will be in the pronator teres, while for spastic wrist flexion, the muscles involved with injections are flexor carpi radialis and flexor carpi ulnaris. Moreover, spastic flexion of the finger needs injection to flexor digitorum profundus and superficialis, while adductor pollicis for the thumb commonly injected if the spastic thumb in the hand posture. The most common muscles injected for spastic shoulder deformity are triceps brachii, pectoralis muscles, teres major, and deltoid [27].

Of note there is some time clinical modification which is individualized according to the patient. For instance, in elbow flexion maximum dose to brachioradialis muscle and minimum or no injection of biceps brachii muscle to maintain function of arm in bearing things and in wrist spastic flexion maximum dose to flexor carpi ulnaris muscle if ulnar deviation of hand present. The injection of BTX should be done by an expert with well surface anatomical knowledge and choice large bulk of muscle with injection to near neural plate which is expected near to the mid-belly. **Table 2** shows BTX injection of upper extremities.

2.5. Muscles of lower extremities

The lower limb muscle injection is considered the most important in spastic cerebral palsy via its benefit to decrease deformity and improve gait. The gastrocsoleus complex is considered the most common site of injection in dynamic toe-walking spastic CP patient, combined with injection to tibialis posterior for dynamic equinovarus deformity. These injections are considered typical in spastic diplegic CP and spastic hemiplegic CP. Other important lower

Indication/clinical pattern	Goals	Muscles involved	Dose (U/kg) of Botox®	Number of sites
Externally rotated shoulder	Ease shoulder adduction	Infraspinatus	1–2	1–2
	Improving gait	Teres minor	1	1
	Enhance dressing	Long head of triceps	2–3	2–3
	Ease reaching	Latissimus dorsi	1–4	2
Adducted/internally rotated shoulder	Ease shoulder abduction	Pectoralis major	2	2–3
	Improving gait	Subscapularis	1	1–2
	Enhance dressing	(Teres major)	1	1
		(Latissimus dorsi)	1–4	2
Flexed elbow	Allow extension of the elbow	Biceps brachii	2–3	2–4
	Enhance reaching	Brachialis	2	1–2
		Brachioradialis	1–2	1
Pronated forearm	Allow supination	Pronator teres	1	1
	Improve dexterity	Pronator quadratus	1	1
Flexed wrist	Ease wrist extension	Flexor carpi radialis	1–2	1
	Ease wearing orthoses	Flexor carpi ulnaris	1–2	1
Clenched fist/hand	Improve hand opening	Interosseous muscles	0.5–1	1
	Improve wearing orthosis	Lumbricalis muscles	0.5–1	1
	Ease cleaning of the palm	Flexor digitorum superficialis	1–2	1–4
		Flexor digitorum profundus	1–2	1–4
		Flexor pollicis longus	1–2	1–2
Thumb in the palm	Enhance thumb abduction	Adductor pollicis brevis	0.5–1	1
	Help pinch and opposing	Flexor pollicis brevis	0.5–1	1
	Improve wearing orthosis	Flexor pollicis longus	0.5–1	1
	Ease hand opening	Interosseous dorsalis I	0.5–1	1
Flexed hip	Improving gait	Iliacus/psoas	2–4	1–2
Crouch gait	Enhance hip extension	Rectus femoris	1–3	2
Stiff knee	Improving swing phase by easing knee flexion	Rectus femoris	1–3	2
Scissoring gait, adducted thighs	Improve abduction and decrease scissoring gait	Adductor longus	1–4	1–2
	Better perineal hygiene	Adductor brevis	1–4	1–2
	Ease wearing abductor braces	Adductor magnus	1–4	1–2
	Improving sitting	Gracilis	1–2	1–2

Indication/clinical pattern	Goals	Muscles involved	Dose (U/kg) of Botox®	Number of sites
Flexed knee	Improving balance and gait	Semitendinosus	1–3	1–2
Crouch gait	Enhance heel strike in stance	Semimembranosus	1–3	1–2
	Ease sitting	Biceps femoris	1–3	1–2
		Gastrocnemius mediale/ laterale	3–6	1–4
Striatal toe	Ease footwear	Extensor hallucis longus	1–2	1
Toe clawing	Improve balance and gait	Flexor digitorum longus/ brevis	1–2	1
	Prevent toe-turn	Flexor hallucis longus	1–2	1
Equinovarus foot	Improve plantar flexion	Gastrocnemius mediale	1–3	1–2
	Enhance heel strike in stance	Gastrocnemius laterale	1–3	1–2
	Improving balance and gait	Soleus	1–3	1–2
	Ease wearing orthosis	Tibialis posterior	1–2	1–2

Table 1. Indication, dose, target muscle, and number of injection [16, 30, 31].

Muscles injected	Dose range (IU/kg of bw)	Number of sites
Adductor pollicis	0.5–1	1
Flexor pollicis longus	0.5–1	1
Flexor digitorum profundus	2	1–2
Flexor digitorum superficialis	2	1–2
Flexor carpi ulnaris	2	1
Flexor carpi radialis	2	1
Pronator teres	1	1
Biceps	2	2–3

Table 2. Muscle injected, dose, and number of injection of upper extremities [30].

limb BTX injections are semitendinosus and semimembranosus of hamstring muscles in order to decrease hypertonia of these muscles in dynamic knee joint with subsequent improvement of the gait. Scissoring posture is one of the important problems in CP which also can markedly be decreased by BTX injection of adductor groups. Another muscle also injected in lower extremities is iliopsoas for spastic hip flexor; unfortunately, later on, it is difficult to be injected by palpation and needs technical equipment like ultrasound guidance for accurate injection [28, 29].

Although the primary goal of BTX injection to the lower limb is to improve ambulation in CP, BTX has an additional benefit; for example, injection of adductor and hamstring muscles may prevent progressive hip subluxation with positional improvement and decrease pain and stiffness, particularly when combined with bracing of the hip in abduction. Moreover, the benefits in nonambulatory patients may have improved pain and stiffness after injection and easy caring by relaxing adductor group. **Table 3** shows BTX injection of lower extremities.

For optimizing relaxing effect of BTX-A, proposed high dose evolved. A lot of debate in last decade about safety of high dose of BTX-A. Generally, high doses adopted per injected muscle and multiple injections to many muscles in the same session have been used. The dosage of BTX-A per muscle depends on many factors including muscle bulk, degree of spasticity, and pathological pattern of the involved muscle. High dose of BTX-A is restricted to large muscle volume with sever spasticity. Many of spastic CP patients need multiple injections in same session to obtain maximum result [32].

The concept of high safe dose of BTX-A had been grown since the use of toxin. Initially, the toxin restricted for treatment of patient with focal spastic deformity is now widely used in multilevel therapy as the spastic CP patients have abnormal posture on multilevel of the musculoskeletal system; in consequence high dose is needed.

It is recommended to start with the lowest effective dose and increase with consequence injection depending on the previous session response and side effect. A wide range of total doses are found in review of literature, ranging from 2 to 29 U/kg/bw. As the initial use of BTX-A for equinus correction, the commonly referred dose range from 4 to 8 U/kg/bw can be found, while in the multilevel use of BTX-A, adopted higher dose with maximum doses ranged from 10 to 29 U/kg/bw. A dose up to 40 U/kg/bw was used within multilevel injection of BTX-A. In one study [33]. Subsequent studies stated that high dose of BTX-A is safe to some extent. In review of literature with the multilevel use of BTX-A and multisite injection on monkeys, [34] conclude that there were no observable systematic effects at doses below 40 U/kg/bw (**Table 4**) [34].

Muscles injected	Dose range (IU/kg of bw)	Number of sites
Tibialis posterior	1–3	1
Soleus	2–3	1
Gastrocnemius	3–6	1–2
Adductors	3–6	2
Lateral hamstrings	2–3	2
Medial hamstrings	3–6	3–4
Quadriceps	3–6	4
Iliopsoas	2	2

Table 3. Muscle injected, dose, and number of injection of lower extremities [30].

	Botox	Dysport	NeuroBloc/Myobloc
Range maximum dose/site (U)	10–50	50–250	Not established
Maximum total dose (U)	400 (−600)	500–1000	Not established
Range (U/kg bw)	1–20 (25)	1–20 (25)	Not established

Table 4. Usual maximal dose of botulinum toxin preparation.

Of note, one has to put in his mind that the muscle like sponge principle pattern when exceed maximum contains fluid, leak from muscle could occur, and toxin enters the general blood circulation causing distant side effect which might be serious and life-threatening. That's why we advise to use multisite theory, in which the dose has to be divided between more sites, with an up to a maximum of 25–50 U per site and not exceed in a volume of 1 ml per site, in addition to an inter-site distance of a minimum of 4–5 cm. As an interesting issue, for those who are obese, adjust the dose to the reference of their typical pairs with same age.

3. Postinjection BTX period

Although its maximum effect appears at 10 days to 4 weeks, the relaxing effect might start within 1–3 days and usually last for 3–6 months with exception of some patient for over a year called golden responder. Proper multidisciplinary team in terms of splinting, physiotherapy, and casting improve the outcome and increase golden responder patient numbers. Many centers adopt serial casting after significant relaxing effect of BTX that started and lasted for 2–3 weeks after injections may optimize the benefit of injection [35].

3.1. How to localize muscles for botulinum toxin injection?

The child is not a small adult, generally uncooperative and sensitive to pain, and doesn't like any technique that involves restriction of his movement for a long while. Therefore, invasive procedure like EMG is more difficult to be applied successfully in children than in adults.

3.2. Palpation

Palpation of the muscle, particularly for the large one, remains the cornerstone for injection of BTX in CP patient for most experts worldwide, but it needs a well of knowledge in anatomy and its landmark. If possible after injecting the needle to the target muscle belly by using anatomic landmarks, palpation of the muscle, movement of distal joints that involve the target muscle, and then movement of injecting the needle confirm correct needle position.

In a study comparing manual needle injection and needle injection guided by electrical stimulation, 226 spastic CP children are involved with 1372 separate injections for upper and lower extremity spasticity. A 27-gauge insulated Teflon-coated needle was used to stimulate the muscle and deliver BTX-A contraction of the target muscle without contraction of the neighboring muscle. Then, needle position must be considered correct. The study concludes that

needle placement guided by electrical stimulation is highly recommended for injections into small, slender, and deep-seated muscles, but dropout of such procedure needs cooperation which is difficult in children, so it is usually done by general anesthesia which could cause relaxing muscles and palpation of the target muscle become difficult [31].

BTX-A injections into 15 different muscles of 100 outpatients in cross-sectional study treatment sessions were performed. All patients received combined analgesia and sedation with chloral hydrate prior to their BTX-A injections. Target muscles included small muscles of the forearm as well as large muscles of the lower extremity. Target muscles were identified based on anatomical palpation, and after the use of different tools, we conclude that injection of BTX with palpation results from significant improvement in ambulation [36].

3.3. EMG

There are two electrophysiological techniques to localize muscles: electromyography (EMG) and electrical stimulation [5, 37]. In a randomized, controlled clinical study, 28 patients with cervical dystonia received EMG-guided BTX-A compared with other patients using manual palpation-guided BTX injection. The study concludes that significant improvement to those patients that are guided by EMG for their BTX injection, specially patients with retrocollis, laterocollis, and shoulder elevation suggests great benefit from EMG-guided injection for deep cervical muscles [38] but unfortunately is inapplicable in spastic CP because EMG needs active and/or passive muscle stimulation for targeting muscles from neighboring muscles as long as spastic CP had difficulty to perform specific movements [39]. In addition needle EMG painful procedure limited its use in children; moreover, there is inaccurate correlation between the extent of spasticity in dystonia and the muscle activity detected by the EMG.

3.4. Electrical stimulation

Although electrical stimulation is considered an excellent procedure to localize the needle in the muscles [40], its use in children is imitated due to the localizing target muscle that needs multiple reposition of the needle which needs time and cause significant pain. Therefore, if electrical stimulation is necessary, we need good analgesia with sedation; moreover, the effective use of electrical stimulation needs expert personal in neurophysiology and clinical anatomy.

3.5. Ultrasound

As an alternative to the above procedure, ultrasound is considered applicable and can directly visualize the muscle for injection. This procedure has been considered a successful method for anatomical muscle imaging, and there are many literatures concluding the use of ultrasound as a reliable technique for botulinum injection [41–43].

3.6. Evaluation and assessment of botulinum toxin injection in spastic cerebral palsy

The use of any parameter for assessment of post BTX-A injection based on the patient clinical situation for whom BTX-A indicated and what expected gain and accordingly appropriate

parameter tailored to patient, for instance, in nonambulatory patient, the usual goal to improve his care is by decreasing spasticity. Therefore, the choice measure to assess tone, while ambulatory patient we choice parameter that related to gait as our goal to improve his gait, etc. Therefore, the setting of evaluation, including pre- and postinjection of BTX-A is individualized according to the goal of intervention; in addition to clinical examination, there are many tools used for this purpose, including the range of motion of the joints passively and actively; assessment of contractures by many tests, e.g., Thomas test, popliteal angle test, Silverskiöld test, and Duncan-Ely test; assessment of muscle power and imbalance, e.g., MRC, Janda, and Oxford scale; assessment of gait by gait analysis equipped by videotaping [44]; and goal attainment scale (GAS) [45, 46]. Modified Ashworth Scale (MAS) is simple and reproducible in the assessment of muscle spasticity but is probably of limited validity [47, 48]. Modified Tardieu Rating Scale is more reliable and is focused on most clinically relevant parts of the Tardieu Scale [49, 50]. Gross Motor Function Measure (GMFM) is a validated tool for the measurement of motor function in children with CP [51, 52]. It may, however, not be sensitive enough to detect the minimal changes that occur following relatively minor interventions. Upper limb assessment tools, e.g., SHUEE and AHA scores or PEDI [53, 54], Activities Scale for Kids (ASK), only applicable to children aged 5–15 years [55], and gait analysis with three-dimensional assessment are extremely useful tools with objective analysis of gait before and after toxin injection and also useful in surgery intervention. Moreover, nowadays, the three-dimensional gait analysis became indispensable in clinical studies of gait [48, 56]. However, application of these assessment tools in everyday clinical practice may be limited by cost and availability.

Full detailed checklist for every child planned for BTX-A injection includes identity, goal of injection, last session date, side effect of the previous injection, muscles injected, doses, and assessment tools used.

3.7. Clinical decision of botulism toxin injection and its limitation

Spasticity is considered a positive phase of muscle function. Therefore, when relaxing the muscle, the patient might get worse functionally in some instance. So, the first question clinician put in his account before injecting BTX is whether hypertonia is impeding or improving function. Another thing is that spasticity itself is associated with weakness and its high muscle tone may be a consequence to avoid involuntarily weakened muscle movement. For the time being no tools like EMG and gait analysis accurately provide obvious data related to hypertonia, and the clinical decision remains the cornerstone [57, 58]. Therefore, general functional and development assessment are considered the most important, while individual muscle assessment and using parameter, e.g., the Modified Ashworth Scale, Modified Tardieu Scale, or range of motion, are less important than general functional impairment assessment. As it is well known that spastic CP management needs a multidisciplinary team, hence it is crucial to determine the goal of management with periodic assessment for outcome with frequent modification of treatment in order to tailor appropriate management to every patient.

Although there is general consensus that recovery from BTX-A injection is always complete and seems effective and safe, nevertheless there is no data till now about long-term effect and dropout. For that reason long-term studies are mandatory.

BTX-A is a neurotoxin spread or injected to nontarget muscle that might cause further suffering to the patients and therefore should be done by a well-trained personnel who familiar with BTX and muscle anatomy.

Many causes for inadequate outcome like false indication, incorrect injection, and lack of complementary treatment (physiotherapy, occupational therapy, orthosis, etc.) are most common.

3.8. Adverse side effects of botulinum toxin

Generally, the adverse side effects of BTX-A are seldom to occur providing that the physician strictly adheres to the dose ranges and reinjection period [16]. The side effect may be local or distant from the injection site regarding local side effects, as with any intramuscular injection can cause pain, cause hematoma at the site of injection but usually not severe, and rarely cause significant problems. However, diffusion of BTX from the target injected muscle might cause weakness of neighboring muscles [28]. This is proportionally related to the volume of dilution; nevertheless, this diffusion is useful in injection of large muscle to optimize bulky muscle relaxation. Systemic side effects distant from injection site are rare and include double vision, dysphagia, generalized weakness of muscles, fluelike illness, constipation, and impaired bladder function, in CP patient with preexisting dysphagia. Further deterioration of bulbar muscle function might lead to aspiration pneumonia [28] which may be seriously life-threatening in such patient. Antibodies to botulinum toxin are found in some patients after several injections. The antibodies may be responsible for the tolerance to BTX developed by some patients [59, 60].

4. Conclusion

Botulinum toxin had established its significant role in management of spastic CP combined with other modalities of treatment. Most experts recommended it for use after 2 years of age for spasticity; in contrast untreated spasticity might lead to joint contracture, and the management may become difficult with multiple surgical interventions. Multilevel injection therapy is indicated to improve gait as most of spastic CP patients have multiple malposition of musculoskeletal system. The inter-injection period must be at least 12 weeks to avoid antibodies and ensure subsequent effect. So far, BTX-A is considered to be safe to some extent if used professionally; however, long-term adverse effect particularly with multilevel therapy is still not clear.

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Chapter 7

Baclofen Pump Implantation for Cerebral Palsy

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Additional information is available at the end of the chapter

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Abstract

Programmable baclofen pump implantation is used to provide the patient with minimal intrathecal dose of baclofen to provide relaxation when the oral permitted doses are no longer withstand able by the patient. We discussed the efficiency of programmable baclofen pump implantation in treating spasticity by reviewing several international papers. Satisfactory relaxation was noticed in most of the patients. The complications following intrathecal baclofen (ITB) surgeries are not uncommon. ITB is an advised method for treating spasticity whether due to cerebral or spinal causes. It has significant improvements with minor complications. It needs special trained multidisciplinary team to manage it.

Keywords: spasticity, baclofen, drug infusion pump, treatment, cerebral palsy

1. Introduction

Spasticity is defined as a velocity-dependent resistance to the passive movement of a joint and its musculature [1]. It usually occurs with hyper-excitability of the stretch limb reflexes. It is related to the loss of inhibition from descending supra spinal neurons.

The contraction of the skeletal muscles can cause involuntary jerky like movements with difficulty in relaxation, coordination and movement control. It is often seen with ordinary activities like changing positions, stretching or by just touch. The severity of the spasticity is quite variable from patient to another and even with the same level or type of insult.

Spasticity is not always treated, because, in many conditions, it compensates for the loss of motor power helping the patient to mobilize. However, treatment indicated when the hypertonicity causes significant functional impairment or limb and spine deformities.

Modified Ashworth rating scale	
0	Normal muscle tone
1	Slight increase in resistance, catch with movement
1+	Catch plus minimal resistance through a range of motion
2	More marked increase but limb easily flexed
3	Considerable increase in the tone throughout the range of motion
4	Affected part rigid

Table 1. Modified Ashworth rating scale of spasticity [1].

Spasticity may result from either cerebral lesion (e.g., dystonia and cerebral palsy) or spinal cord lesion (e.g., spinal cord tumors, injury and syrinx).

The degree of spasticity is usually assessed using the Modified Ashworth rating scale (**Table 1**). Those with grade 3 and above are regarded as disabled persons.

2. Treatment modalities

2.1. Non-pharmacologic methods

A variety of physiotherapeutic modes are applied in order to stretch the muscles and increase their range of motion:

1. Splints (orthotics) or braces and taping.
2. Electrical or vibratory stimulation to the opposing muscle to attempt to relax the spastic muscle.
3. Physical and occupational therapy.
4. Massage, ice or heat
5. Serial or inhibitory casting – by this process we cast the limb repeatedly and progressively closer to the desired position so as to "reset" the muscle stretch reflexes and to lengthen muscles/tendons.

The advantage to these non-pharmacologic measures is that they have minimal side effects and can be used in addition to medications. However, in many patients, these measures are not sufficient to control the muscle tightness or spasms to the desired extent.

2.2. Pharmacologic methods (medications)

2.2.1. Regional (in situ) treatments

Injections of anesthetics, nerve blocks or neurotoxins such as botulinum toxin (Botox) are used if spasticity that requires treatment is limited to one or a small area of the body.

2.2.2. Oral medications

Patients with more profound spasticity need oral medications. They include baclofen, tizanidine, clonidine, clonazepam, gabapentin and dantrolene.

Although these oral medications are very effective in treating spasticity, they have several disadvantages. Among them sedation (sleepiness) and fatigue. They may need periodic blood monitoring for some of these drugs that can have potential side effects on liver function or blood counts and some may interact with other medications.

2.3. Surgical methods

The surgical treatment can be either ablative procedures, such as dorsal entry zone rhizotomy or augmented therapy such as baclofen pump implantation. The augmented therapy is a neuromodulation technique which modulates the function of the nerves without creating irreversible damage to any neuronal element. All these surgical options are provided only when other modes of treatment fail to relax the patient.

Baclofen pump implantation is a surgical procedure performed to permanently implant a pump that delivers baclofen to the spinal fluid to treat severe to moderate-severe spasticity that is refractory to oral medications.

As compared to baclofen taken by mouth, the direct infusion into the intrathecal space will reduce the amount needed to provide the same degree of relaxation. We can give even higher doses that cannot be tolerated by the patient when taken orally. It will limit or eliminate the undesirable side effects associated with taking oral baclofen. The pumps can provide a consistent and precise dosage throughout the day. It will avoid the peaks and valleys of taking oral baclofen. The dosing is very flexible and can be programmed in many ways, for example, we can give continuously the same dose for the whole day or administer on an hourly basis for 24 h a day, to different doses at different times of the day or the week.

There are two types of drug infusion pumps:

2.4. Fixed-rate pumps

This is now historical, and no one is manufacturing it any more. They operate mechanically, no battery is required. It operates with a butane gas pressure chamber surrounding a flexible inner reservoir. There are either 20 or 40 mm drug reservoir to minimize refilling while keeping overall dimensions as compact as possible.

Gas in the pressure chamber is warmed by body heat and expands, squeezing the inner chamber to drive the drug through a filter then to the catheter ending to the site of action in the body. The device designed to provide highly accurate flow rate.

Depending on treatment needs, the dose of spasticity medication is adjusted to individual needs, making the device operation simple and safe.

The pump is designed for life long. The purely mechanical pump operates without a battery.

Changes in pressure or temperature have influence on the flow rate, especially in hot countries. A baclofen overdose reported in some cases during summer time in several hot countries.

2.5. Variable-rate pumps

These are now widely used nowadays. These pumps have a drug reservoir from which they automatically dispense a programmed amount of medication through a catheter. These pumps have a small, on-board battery and integrated microelectronic circuits to control the drug delivery.

In this chapter we will discuss the rationale for the use of this mode of treatment in spasticity.

3. Indications for ITB

Baclofen pump implantation is indicated if patients have:

1. Sever spasticity grade 3 and above (equal or more than 12 months duration). This spasticity significantly interfere with voluntary movement, causing difficulty in maintaining range of motion or position. It even affects safety, contributing to pain or skin breakdown and making personal care difficult for you or your caregiver.
2. Spasticity refractory to oral medications (baclofen) or having unacceptable side effects.
3. Positive response to ITB at test dose 100 μg with no response to placebo.
4. No hypersensitivity to baclofen.
5. No medical comorbidity to surgical intervention.

Patients with profound pain are preferred to have morphine pumps rather than baclofen.

4. Screening test before implantation

All candidates for intrathecal baclofen (ITB) therapy were planned to perform screening trials before pumps implanted. The patient receives 25 μg of baclofen through lumbar puncture. The resulting hypotonia is measured using the Modified Ashworth score. Pulse rate, blood pressure, respiratory rate and any adverse effects (including seizures) should be recognized. A test is successful if the Ashworth score is reduced by at least two points from 4 to 8 h following administration. If this reduction is not achieved, a bolus dose is given the next day, with an increment of 25 μg up to a maximum bolus of 75 μg. The drug amount that reached a satisfactory test result is also used to guide us to give the initial dose after pump implantation. If the response obtained with 25 μg for 24 h or more, then the initial dose of the implanted pump will be 25 μg/day; if the duration of relaxation were less than 24 h, the initial dose of the implanted pump would be 50 μg/day.

5. Operation of pump implantation

The pump is inserted under the covering of the abdominal muscles, while the patient is under a general anesthetic. A small catheter is then inserted through a Touhy needle into the thecal sac. When spinal fluid appeared, a spinal catheter threaded upward to a site depends on the distribution of the patient's spasticity (i.e., to the T10-11 spinal segment level for patients with spastic paraplegia and the C7-T4 spinal segment level for those with spastic quadriparesis. The catheter is then tunneled under the skin to the abdomen and is connected to the pump. The incision is closed with suture material or surgical staples. The procedure usually lasts 1–2 h.

6. Dosing of intrathecal baclofen

After implantation, we will fill the pump with baclofen, the pump is then programmed with certain external programmer, for example, N-vision. In all the cases, we prefer to use the "simple continuous infusion". ITB doses are titrated over the next few months. Initially, the infusion often begins at 25–50 μg/day and the dose is titrated gradually by 10–20%, a week incensement until the patient's spasticity significantly reduced. The dose then adjusted with less frequent periods on an outpatient basis. In most of the patients, the satisfactory dose is usually achieved within 2 months.

Refills are generally done every 3–9 months, a refill kit is provided with a sterile needle and syringe. The filling is done in the outpatient just by passing the needle to the pump through the skin of the abdomen. Pumps hold 20 or 40 ml and will signal with a beeping noise if the amount gets below 2 ml. The devices also sound alarms if there is a malfunction, or if the battery runs low (generally between 3 and 7 years of use). When the battery runs low, the implant will be replaced under local anesthesia.

7. Prognosis

We conducted a study of 55 patients with spasticity, who had baclofen pump implantation in Neuroscience Hospital, Baghdad, from October 2011 to December 2016 [2]. The spasticity decreased, significantly in the lower extremities and remained so during the 2.9 years of infusion. In 55 patients (41 patients with a spinal cause of spasticity and 14 patients with spasticity caused by cerebral palsy), the results were remarkable.

Comparing our data with other international studies (**Table 2**) [3–10], the 2.9 years follow-up quite objectively concluded the efficiency of use of the pump to treat spasticity.

Many review papers were published to assess the efficiency of the baclofen pump. Butler and Campbell [11] in 2000 reviewed 12 published studies on ITB. They concluded that spasticity improved and that limb functions probably improved with ITB.

Reference	Country	Patient no.	Type of study	Result
Kvascevicius et al. [5]	Lithuania	5	Prospective	Very good
Baker et al. [6]	United States	117	Prospective	Excellent
Penn [7]	United States	18	Double blind	Excellent
Coffey et al. [8]	United States	75	Double blind	Excellent
Muller [9]	Germany	211	Prospective, multicenter	Excellent
Lazorthes et al. [10]	Belgium/Holland	18	Prospective	Excellent
Jierski et al. [11]	Germany/Sweden	28	Prospective, multicenter	Excellent
Penn et al. [12]	United States	62	Prospective	Excellent

Table 2. Comparison of the outcomes from international data.

In our study, we concluded that spasticity decreased significantly in the lower limbs and to a lesser extent in the upper extremities. The Ashwarth scale remains low during the years of infusion. Westbom et al. in 2003 reported in a multicenter study a sustained decline in the Ashworth scores in both lower and upper extremities during a 6-year follow-up [12].

The reduction of upper limbs spasticity is usually less than that noticed in the lower extremities; if the catheter tip was at the mid-thoracic level or lower. Motta et al. [13] evaluated ITB's effect on the upper extremities of 20 patients with quadriplegic cerebral palsy with a mean age of 11.4 years. The spasticity of the upper extremity decreased (P b 0.05), and the range of movement improved remarkably.

The range of motion in the lower limbs increased following ITB therapy due to the reduction of spasticity. Further, this accompanied by an improvement in the gait. In our study, improvement in gait noticed in 10 patients (4 with multiple sclerosis, 3 with cerebral palsy and 3 with partial spinal cord injury). Gerstzen et al. [14] studied the effect of ITB on gait. They classified gait functionality into four types (community, household, non-functional and non-ambulatory). In their study, 24 patients had some ambulation before ITB therapy. The level of ambulation was improved by one level in nine patients, worsened in three and unchanged for the remaining patients.

8. Complications

1. Pain, numbness, weakness or paralysis due to nerve damage (rare)
2. Cerebrospinal fluid leak
3. Bleeding/injury to blood vessels
4. Infections
5. General anesthetic complications
6. Hardware-related complications during surgery are rare, but can include catheter migration. After surgery though, the potential hardware complications include catheter fracture or migration and infection or pump malfunction.

The most frequent complication was catheter malfunction (e.g., disconnection of the catheter tip from the pump, drug leakage from the catheter and migration of the catheter outside the thecal sac).

8.1. Baclofen withdrawal

Sudden cessation of ITB infusion can occur when the pump running empty; programming error; incorrect baclofen concentration; a problem with the catheter system and a problem with the battery. Some of these problems will activate the alarm. It is followed within a few hours by symptoms of generalized pruritus, increased spasticity and agitation. The symptoms may range in severity from mild to severe [15, 16]. The Classic symptoms of baclofen withdrawal are a sudden increase or return of your spasticity or tone, profuse sweating and itching without an associated rash. Fever, tachycardia, tachypnea, hypotension or hypertension or even confusion. Severe withdrawal symptoms include hallucinations or delirium, seizures, rhabdomyolysis, organ failure and even death. We noticed some patients might not recognize the mild withdrawal symptoms; consequently, the interruption in therapy may not detect. Severe withdrawal symptoms are severe complications and must manage urgently. Moderate withdrawal symptoms are managed by high doses of oral baclofen (e.g., 10–20 mg every 4 h), intravenous benzodiazepines (diazepam, 2–5 mg every 6 h) or bolus baclofen injections can be given too [17]. Despite the complications reported in many papers, almost 90% of patients with baclofen pump implantation at the end of the battery life prefer to have a new pump exchanged and to continue ITB therapy [18].

8.2. Baclofen overdose

This is far less common than withdrawal. The overdose could be a human error in dosing, programming or filling the pump; system malfunction or unsafe combination of intrathecal and oral medications. Most of the time, mild overdose symptoms can be easily managed by turning the pump rate of infusion down. The mild symptoms are characterized with low muscle tone, low attention, lightheadedness and sleepiness. Moderate symptoms are bradycardia, respiratory depression and difficulty awakening. When sever symptoms developed the hypotonia spreads to the trunk, arms, face and neck. Stupor, coma, seizures, severely slowed breathing that needs mechanical ventilation and eventually death. Some papers recommend an intravenous injection of 1–2 mg of physostigmine to treat overdoses, but their therapeutic effects are minimal and brief [21, 22]. Severe overdoses may necessitate assisted ventilation. CSF aspiration may also help with severe overdoses: 20 ml of CSF is withdrawn and replaced with 20 ml of a 5% dextrose to 0.25% normal saline solution 2 or 3 times [22].

8.3. Infections

Infection occurs in 5–10% of patients mostly caused by *Staphylococcus aureus* [19].

Most infections that start in the first 3 weeks after surgery are due to bacterial contamination at the time of pump insertion. Those related to future pump refills are extremely rare. Infections can occur either at the site of pump implantation, that is, anterior abdominal wall. This will result in erythema, swelling, tenderness and fever. It is treated with intravenous antibiotics and surgical cleaning of the pump wound. In severe cases, the infection may affect the whole

system, including the catheter and cerebrospinal fluid (CSF). It requires removal of the entire pump with postoperative parenteral antibiotics for 3 weeks [19].

8.4. CSF leaks

Leak may appear due to insertion of Tuohy needle with a catheter. The incidence is from 5 to 15% in patients with CP (most of whom are children), in contrast to the 3% leak rate reported in adults. The difference explained by malnutrition of chronically disabled children, thinner tissue masses, the smaller body size and the presence of higher CSF pressures associated with occult hydrocephalus [20].

9. Regular checkup and replacement

This process is quick. It involves "interrogating" or analyzing the pump using the handheld programmer, for example, N-Vision Programmer. We have to check whether the pump is working correctly and looking for any trauma at the pump site. If the patient has an MRI appointment, we must stop the pump before examination, then the pump is checked within 2 h after MRI to make sure the pump rotor has restarted itself after an expected stall because of the magnetic effect on the rotor.

Replacement is needed usually after 5–7 years. It is replaced with surgery. Unless there is a problem with the catheter system, the catheter will not require replacement, and the section near the pump will be simply reconnected to the new pump.

10. Conclusions

ITB is a good method for managing spastic cerebral palsy, especially in patients with some potentially useful extremities. Performing ITB requires a well-trained multidisciplinary team that can deal with patient education, pump refills and dose adjustments.

However, it is expensive and associated with some complications; yet, it is one of the best therapeutic options available for patients with spasticity.

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Chapter 8

Plasma Growth Factors in Cerebral Palsy

Jesús Alcaraz Rubio and Juana María Sánchez López

Additional information is available at the end of the chapter

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Abstract

The use of plasma growth factors is opening a new field of clinical application in medicine, developing a new discipline called regenerative medicine. In many fields such as traumatology, dental implantology or anesthesia, the use of this biotechnology is improving the quality of life of patients, through techniques that are not invasive but with extraordinary functional results. A discipline where this type of procedure opens an interesting field of application is undoubtedly neurology, especially those processes of ischemic or hypoanoxic origin such as cerebral palsy, where recent studies point to an improvement of cognitive abilities in patients, together with specific neurorehabilitation therapies.

Keywords: cerebral palsy, growth factors, neuronal plasticity, intravenous infusion

1. Introduction

The use of plasma rich in growth factors in various fields of medicine especially orthopedics, dentistry, and general surgery has experienced an extraordinary development given the enormous capacity for regeneration, differentiation and chemotaxis that produce so-called growth factors, modulating angiogenesis, and cellular plasticity of injured tissues. Among them the best known are: insulin-like growth factor (IGF-1), transforming growth factor A or B (TGF-A B), vasculo-endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) [1, 2].

Through complex biochemical regulatory feedback-type mechanism that involves numerous cytokines, the injured cell f has specific receptors for these proteins which have shown great power to intervene in apoptotic and antiapoptotic mechanisms that regulate both their own life cycle and as cell differentiation. Also recent studies have objectified the possibility

of improve levels of certain plasma growth factors depending on the platelet or mononuclear predominance of the product finally obtained [3, 4].

An emerging medical field of application is undoubtedly neurology, especially those processes of anoxic or hypoxic ischemic origin, including cerebral palsy. The immunomodulatory and proangiogenic effect that plasma growth factors have on neurogenesis opens up a surprising range of treatment possibilities together with neurorehabilitation with the aim of improving functional capacity in these patient with the aim of improving functional capacity in these patients, especially in the cognitive area: language, memory, ability to perform complex tasks, etc., using a technique that is minimally invasive, easy to reproduce and with a very low economic cost [4–6] (**Figure 1**).

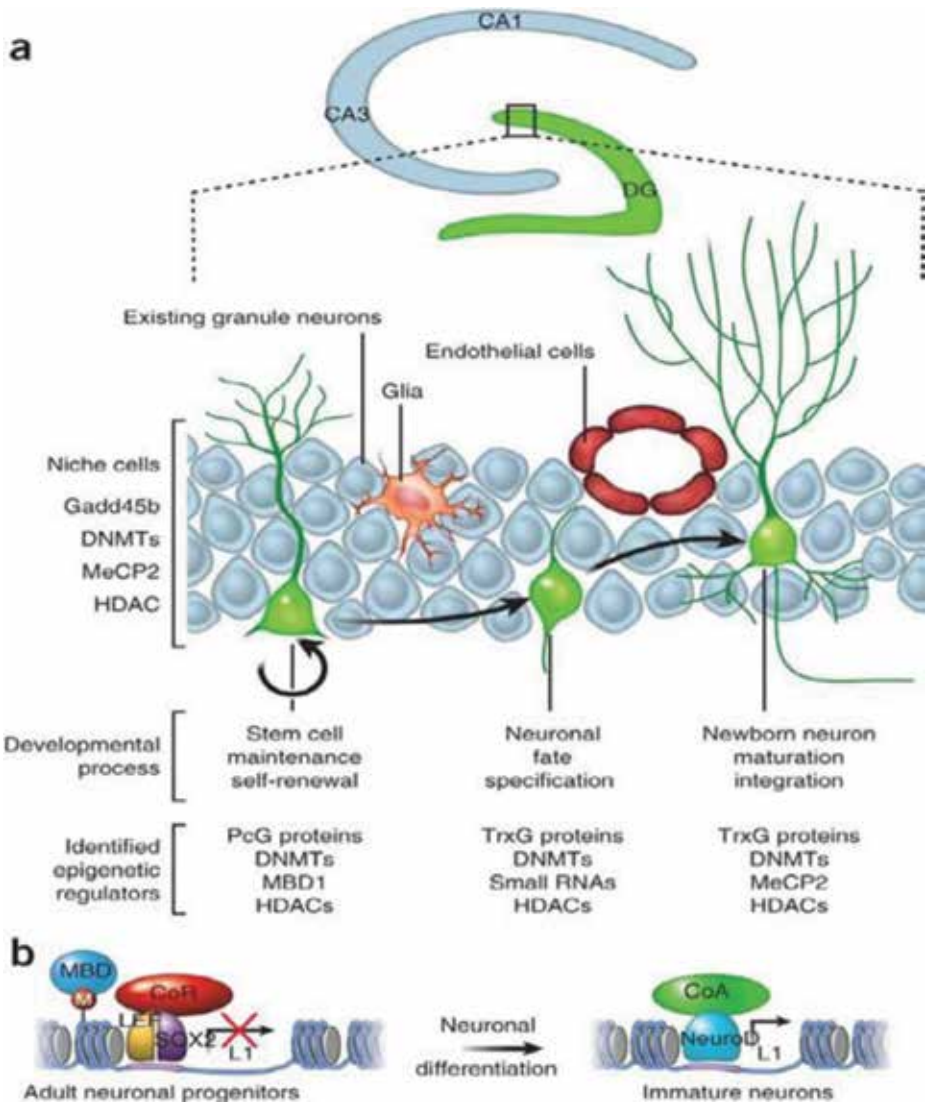

Figure 1. Effects of growth factors in neural tissue.

2. Plasma growth factor functions

PDGF (*platelet-derived growth factor origin*): promotes angiogenesis via macrophages by a mechanism of chemotaxis, having a significant mitogenic activity on neurons, microglia cells, making both proliferation and remyelination and facilitates the formation of type 1 collagen [5, 7].

TGF-beta (*transforming growth factor-beta*): induces differentiation of neural stem cells.

FGF (*fibroblast growth factor*): enables the proliferation and differentiation of neural stem cells.

IGF-1 (*insulin-like growth factor 1*): it induces a potent mitotic effect on neural progenitor stem cellularity.

VEGF (*vasculo-endothelial growth factor*): enables chemotaxis and differentiation neural cells promoting blood vessel air permeability.

Ectodermal growth factor (*EGF*): great proapoptotical capacity, chemotaxis on neural and glial cells.

BDNF (*brain-derived neurotrophic factor*): produces proliferation, differentiation and neuronal chemotaxis on microglial and oligodendrocitarial cellularity and remyelination thereof.

HGF (*hepatocyte growth factor*): induces cell proliferation and differentiation, chemotaxis, angiogenesis and extracellular matrix synthesis (**Table 1**).

Content	Feature
Chemokines, cytokines	Regulation of inflammation, chemotaxis
Platelet factor 4	
B-tromboglobina	
RANTES*	
Macrophage inflammatory protein 1-alpha	
Interleukin 1 and 8	
Adhesive proteins	Cell interactions and coagulation
1 and 2 thrombosin	
Fibrinogen	
Fibronectin	
Growth	Cell proliferation and differentiation, chemotaxis, angiogenesis, extracellular matrix synthesis
Platelet-derived growth factor (PDGF)	
Transforming growth factor b (TGF-B)	
Epidermal or epithelial growth factor (EDGF)	
Vasculo-endothelial growth factor (VEGF)	
Insulin-like growth factor-1 (IGF-1)	
Hepatocyte growth factor (HGF)	
Brain-derived neurotrophic factor (BDNF)	

Content	Feature
Immunoglobulins G	Immunological
Ig-A, Ig-E, Ig-M and Ig-G	
Clotting factors V and VIII	Thrombin production
Von-Willebrand factor	Platelet adhesion to subendothelial collagen
plasminogen activator inhibitor	Inhibition of fibrinolysis
P-selectin	Leukocyte-platelet interaction

*Rantes: regulated on activation normal T cell expressed and secreted.

Table 1. Summary of the proteins in the platelet alpha granules.

3. Definition of plasma growth factors

Growth factors are obtained in an autologous way from the whole blood of the same patient with the aim of reducing the possibility of producing hypersensitivity effects or transmission of infectious diseases during their application. It is called leukocyte-rich plasma or (PRL) to the suspension of the mononuclear fraction or buffy coat in a quantity of patient's serum with a count higher than 20,000/ mm^3; while platelet-rich plasma (PRP) would be that platelet concentrate suspension in a small amount of patient serum whose count exceeds 1000,000/mm^3 of platelets. The optimum pH to obtain both cellular fractions is estimated between 6.5 and 6.7 at a temperature of 22°C. Recent studies, such as the one led by the group of Dr. Alcaraz et al., have observed the predominance of PDGF and IGF-like plasma growth factors in platelet-rich suspensions, while other growth factors such as VEGF or TGF would predominate in those final concentrates rich in leukocyte-mononuclear cells [4–6] (**Table 2**).

Peripheral blood	PRP	
PDGF-AB (10–50 pg/ml)	45 pg/ml	360 pg/ml
TGF-B1 (10–70 pg/ml)	35 pg/ml	320 pg/ml
VEGF (15–85 pg/ml)	55 pg/ml	560 pg/ml
IGF-1 (0.5–19.5 pg/ml)	13 pg/ml	175 pg/ml
Platelets (150,000–350,000/mm^3)	265,000/mm^3	1,250,000/mm^3
Leucocytes (3200–9000/mm^3)	5600/mm^3	20,000/mm^3
Granulocytes	60% (3330/mm^3)	24% (480/mm^3)
Mononuclears	35% (1960/mm^3)	70% (14,000/mm^3)
CD 34+	0.5/mm^3	175/mm^3

Table 2. Levels of growth factors and cell count in peripheral blood and PRP.

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4. Plasma growth factors (PRP) in cerebral palsy

PRP produces a release of cellular signaling molecules only or in combination that have been shown to produce both neuroprotective and anti apoptotic effect on the neuron and adult neural stem cells repairing neural tissue. Plasma growth factors constitute support that facilitates the survival and neuronal differentiation [2, 3, 7].

It has been shown that application of autologous plasma growth factors had a neuroprotective and antifibrotic effect, improving nerve regeneration probably induced by the activation of the PI3K/Akt anti apoptotic signaling pathway [2].

We do not yet have enough studies to evaluate effect of angiogenesis in the nerve repair. Administration of autologous PRP rich in VEGF and IGF-1 accelerates the regeneration of the neuromuscular junction owing to the increase of angiogenesis. Intramuscular injections of PRP would increase the angiogenesis and produces reperfusion after the induction of a severe skeletal muscle ischemia [2, 3, 7].

The main function of PRP has been showed in a rat brain sample, where application of plasma growth factors induced both the increase in the number and the growth of axons. The PRP has been used in a model of acute cerebral nerve injury in rabbits, as a culture medium to neurological stem cells reporting beneficial effects on axonal count, myelination and electrophysiological functionality. PRP could increase both the thickness of the myelin and amount of axons, producing an increase in functional activity at the date of latency associated with improvement in the thickness of the myelin. PPR could contribute significantly to the two key events for a proper axonal regeneration: angiogenesis and the establishment of an optimal microenvironment for the differentiation, immunomodulation and cell division [1–3, 5, 6].

It has been objectified an anti-inflammatory activity of PRP, aiming that b-amyloid expresses cytokines inhibited when astrocytes are cultivated with autologous growth factors, that could be explained by suppression of NFkB in astrocytes with the activation of the Cyclooxygenase and the expression of tumor necrosis factor in the brain. Several studies have reported that plasma growth factors like IGF-1, PDGF and TGF-B, could inhibit the NFkB on the tenocytes, synovial cells, fibroblasts, chondrocytes and change the macrophages from phenotype M1 to M2 [2, 6, 7].

The growth factors would produce neurogenesis phenomena through 3 ways: first inhibiting the inflammatory process that would difficult the anatomical and physiological neuronal recovery; secondly improving the migration and proliferation of stem neuronal cells at the site of the lesion and finally stimulating its differentiation toward mature neuronal mass reestablishing the normal functional circuit of the same.

The lesion of a neuron actives macrophages and mononuclear cells like Monocytes that phagocyte the myelin residues, stimulating by autocrine way the nerve growth factor (NGF), that facilitates the recruitment of Schwann cells to the area of the lesion, their differentiation and proliferation join to the vasculo-endothelial growth factor producing remyelination and final reconnection of the affected axon.

5. Discussion

The evolution of regenerative medicine in various clinical areas revolutionizes the field of tissue repair, providing an instrument for treatment which is economical, easy to use, no side effects, and less invasive [1, 3]. However, scientific and social requirements make it necessary to design appropriate clinical trials to establish treatment protocols for each particular medical application [1, 2]. Today, medical areas with stronger scientific evidence to use plasma growth factors are dentistry (to repair the dental alveolar bed) and traumatology (arthropathy, tendinopathy, ligament injuries, and meniscopathy), with proper design randomized clinical trials in phase I-II [1, 4]. But the empirical use in many diseases and medical specialties sometimes exceeds the capacity to produce sufficient scientific evidence power for use. An important fact to comment, as previously demonstrated by other authors is the great capacity of these proteins to spread through the tissues and the short half-life objectified once achieved therapeutic plasma levels that do not usually exceed 48–72 h [8, 9], which shows that the actuation mechanism is complex, it is believed that activating pathways or biochemical cascades through numerous chemokines or cytokines that involve in the inflammatory processes both specific tissue, such as migration, proliferation and differentiation of precursors cell maturation in different states and angiogenesis phenomena would produce increased tissue oxygenation with the consequent increase in cell survival and protection thereof. Some more promising medical fields for the use of this biotechnology are neurology, neuroendocrinology and neurorehabilitation. A few months ago was published the first clinical case of cognitive improvement supported by cerebral PET in a 5 years old child with severe cerebral palsy who was applied by intravenous infusion a plasma concentrate growth factors-enriched with buffy-coat mononuclear fraction. Several authors hypothesized neuroregenerative phenomena, antiapoptotic, immunomodulatory and neurotrophic effects that would produce these autologous plasma growth factors on neuronal tissue, making this a feasible therapy from a medical point of view, to be applied in neurological diseases with neurodegenerative profile or hypoxic-anoxic, such as Alzheimer's disease, brain-stroke, spinal cord injury, and cerebral palsy [5, 6]. Spontaneous remission of the signs and symptoms of cerebral palsy is rare due to the large number of neuronal glial mass and degenerate secondary to the effects of hypoxia in the evolution of the disease [9]. Effects of neurostimulation, neurodegeneration and neuroprotection have been observed in these patients treated with synthetic growth hormone (HGF), which causes functional improvement, especially in the cognitive domain (e.g., memory, language, ability to perform complex tasks, and acquisition of new skills). In these patients, the neuronal degenerative effect has been accompanied by a qualitative and quantitative marked decrease in plasma growth factors such as HGF-IGF-1-VEGD, PDGF, and TGF-B [7–9], regulated by the hypothalamic axis pituitary, which produce a neuroprotective effect, due to neurotropic and chemotaxis phenomena, cell differentiation, and neuroplasticity in neuronal tissue. Furthermore, these substances have the ability to stimulate the so-called gray areas corresponding to those neural tissues found in hibernation as a result of lesional hypoxic or anoxic effect. However, treatment with synthetic growth hormone is costly, not only from the economic standpoint but also from the clinical point of view.

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Chapter 9

Hip Surgery in Cerebral Palsy

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Additional information is available at the end of the chapter

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Abstract

Hip pathology is one of the main orthopedic concerns in cerebral palsy (CP) patients. It has been demonstrated that correctly applied hip screening programs could significantly diminish the incidence of hip pathology. Unfortunately, in several countries, hip dislocation is significantly prevalent and is still a major concern in these patients. Depending on the age, the disability grade, the rehabilitation support, and the surgical strategies, results of hip treatment are variable. The ideal outcome of a stable, reduced, and long-lasting pain-free hip are not always achieved. In this chapter, we discuss theoretical and practical strategies used to treat specific CP hip dislocation. In younger children, simple femoral reorientation procedures (tenotomies with or without femoral osteotomies) promote correct acetabular remodeling. Later, surgical hip reduction can be an option even in late adolescents, and the use of capsuloplasty can lead to greater hip stability, in spite of eventual pelvis obliquity caused by associated spine pathology. Several technical tips for hip surgery are presented. It is essential that patients with CP hip problems receive proper follow-up, including rehabilitation medicine, physiotherapy, anti-spastic medication, on-time orthosis availability, and real teamwork concerned with this kind of pathology.

Keywords: cerebral palsy, hip, surgery, technical tips, children, adolescents

1. Introduction

In recent years, the cerebral palsy (CP) definition has evolved from Bobath's concept [1] of a group of non-progressive disorders of movement and posture caused by abnormal development of, or damage to, motor control centers of the brain. Nowadays, CP is also considered "a disorder of the development of movement and posture, causing activity limitations attributed to non-progressive disturbances of the fetal or infant brain that may also affect sensation,

perception, cognition, communication, and behavior. Motor control during reaching, grasping, and walking are disturbed by spasticity, dyskinesia, hyperreflexia, excessive coactivation of antagonist muscles, retained developmental reactions, and secondary musculo-skeletal malformations, together with paresis and defective programing" [2]. This concept expands the definition significantly: weakness and hypo-extensibility of the muscles are due not only to inadequate recruitment of motor units, but also to changes in mechanical stresses and hormonal factors. The notion of functional classification has become a major criterion in diagnosis, prognosis, and therapeutic strategy, particularly, the Gross Motor Function Measure (GMFM), has made it possible to evaluate the change over time and the effects of clinical interventions.

This means that a multi-disability, and not only a motor one, is present in CP patients in most cases. All of these factors must be taken into account to reach better clinical/functional results. The goals for each patient must be clear, "reachable" (technique, clinical team, drug therapy, and orthosis), and shared between the patient/family and the respective supporting team.

Several studies show that a correct screening program (Australia, Scandinavia, WHO [3–6]) can almost "eradicate" hip dislocation in CP patients, but the reality is that a large number of patients still have hip symptoms and disability, all around the world.

In this chapter, hip problems and their surgical treatment are discussed.

Most of the clinical studies that support our treatment options are widely documented in CP manuals and papers; some are cited in the "References" chapter.

Combining methods for hip evaluation and treatment with remarks and surgical tips, this chapter aims to enhance the efficacy and duration of positive results in CP patients.

2. Evaluation

The question of evaluation concerns more than just the patient. We must consider several factors:

- Type of CP and GMFCS grade
- Co-morbidities
- Health support
- Clinical exam and complementary diagnosis exams

2.1. Type of CP and GMFCS grade

Nowadays, the GMFCS grade is a fundamental tool in CP patient evaluation and treatment planning:

Milder forms have fewer hip problems—hemiplegic type is less prone to hip dislocation than either diplegic type or quadriplegic type.

Lesser GMFCS grades are also less prone to hip dislocation; walking patients can also have hip problems but it is relatively rare. Most hip dislocations are observed, crescently, in GMFCS Type III, IV, or V.

Spastic types are more prone to hip dislocation than athetotic and dyskinetic types, with involuntary movements; however, when these kinds of patients have hip symptomatology, they are much more difficult to treat (post-surgery care is very difficult; there are more cases of pressure sores within plasters, casts, or splints, and patient agitation tends to be greater).

Clinical evaluation is fluctuant in these patients. Even with careful and systematic observation and testing, there are some incongruities between different observations (consecutive or by different observers), due to the level of momentaneous spasticity, possibility of relaxation, expertise of the medical staff, or even imaging interpretation. For this reason, it is critical to take into account all of the data for each patient because clinical evolution is one of the key factors in the treatment strategy. In rare cases, the condition does not deteriorate as anticipated and abnormal findings can be surprisingly stable over time. This may permit the postponement of an initially planned surgery.

2.2. Co-morbidities

There is some association between GMFCS grade and the amount of co-morbidities: mental retardation, impaired deglutition, drooling, gastro-intestinal hernia, seizures, respiratory, bowel or bladder problems, deafness, and others [7]. All of these co-morbidities influence not only the health status of patients, but also treatment strategies and patient compliance, and increase the risks of the different interventions. The problem of low weight in more disabled patients is a major concern for anesthetic and surgical teams. Sometimes a period of "fattening" is needed, and a gastric button for feeding may be considered.

2.3. Health support

It is important to be aware of the scarcity of sufficient CP reference centers that address the needs of these kinds of patients. Another common shortfall is in the follow-up in the period of child to adult transition. Depending on where in the world treatment is taking place, the quality of the health care system and related organizational problems can vary dramatically. Unfortunately, these are issues without short-term solutions. It can be very frustrating for patients, respective family, and medical and social staff, to know that the most successful expected results will not be reached for a certain kind of patient, due to the lack of sufficient support.

There are a number of critical links in the treatment process, all of which impact the success of the outcome, among them are: correct patient screening and diagnosis; adequate medical and physical therapy (sometimes psychological and learning therapies); adequate and on-time adapted orthoses, social support to caregivers, transportation to and from medical/physical departments, access to movement quantitative analysis, and so on.

In many countries and/or regions (even in developed countries), all of the optimal needs are not available simultaneously. So, the reality is that patients are usually treated in sub-optimal or, sometimes, in incomplete conditions. Adaptations must be made and patients and family expectations should be adjusted accordingly.

That said, we must have the courage to refuse some interventions when the conditions to assure the possibility of a positive result are inadequate and pain and suffering outweigh the potential benefits.

2.4. Clinical exam and complementary diagnosis exams

Most of the data needed for treatment decisions is provided by a good history and a correct clinical exam, and by a succession of observations that demonstrate the progression of the disability.

After clinical evaluation, radiographic parameters become the key points for therapeutic decisions. Primary among these are the anteroposterior (AP) and frog lateral images. Obtaining standardized radiographs can be challenging. Pelvic obliquity, lumbar lordosis, and contractures interfere with proper positioning and measurements. The hips should be flexed to overcome the lumbar lordosis. We can observe evident asymmetry and femoral head coverage insufficiency (**Figure 1a**).

Several radiographic measurements have been reported, but the most widely used are the acetabular index and Reimer's migration index. The acetabular index is a helpful predictor of instability. It corresponds to the angle between a line uniting the two triradiate cartilages (horizontal, when the pelvis is leveled) and the line between medial and lateral edges of acetabulum (**Figure 1b**). Cooke and colleagues [8] identified an acetabular index of greater than 30° as a predictor of future instability in children more than the 4-year-old. The acetabular index varies with pelvic orientation. It decreases with lordosis and increases with flexion, and also varies with rotational malposition. The Reimer's migration index measures the degree of subluxation on the AP view. It is a simple, reliable, and reproducible measurement, comparing width of femoral head and percentage of head not covered by acetabulum (see **Figure 1c**). In a healthy child, the 90th percentile for migration percentile is 10%. The upper limit of normal is 25% in a 4-year-old. A migration index of 30% is considered abnormal. In a normal child, the spontaneous progression is less than 1%. In children with cerebral palsy, an annual increase of 7.7% was observed in those unlikely to walk, and 4% in those with walking potential. Spontaneous stabilization and correction without treatment were observed in some children with a migration index of 33% [8].

We can separate walkers and non-walkers in our exam.

For the first group, generally, the major concern is the asymmetry of the child, when walking, or the so-called femoral anteversion with a marked "in-toeing", or the progressive "crouch-gait" (primary or "iatrogenic"). These are the usual clinical figures we have to evaluate, and are often candidates for a movement analysis.

We can describe the highlights in *ambulatory/walking patients*:

- The incidence of hip abnormalities is of 7% in independent ambulators [8].
- The presence of asymmetry of range of motion (ROM) of both hips is common; tests for distinguishing adductors or ischio tibialis (Phelps' test), to detect rectus femoris shortening (Duncan-Ely's test), to detect retraction of hip flexors (Thomas' test), are important in

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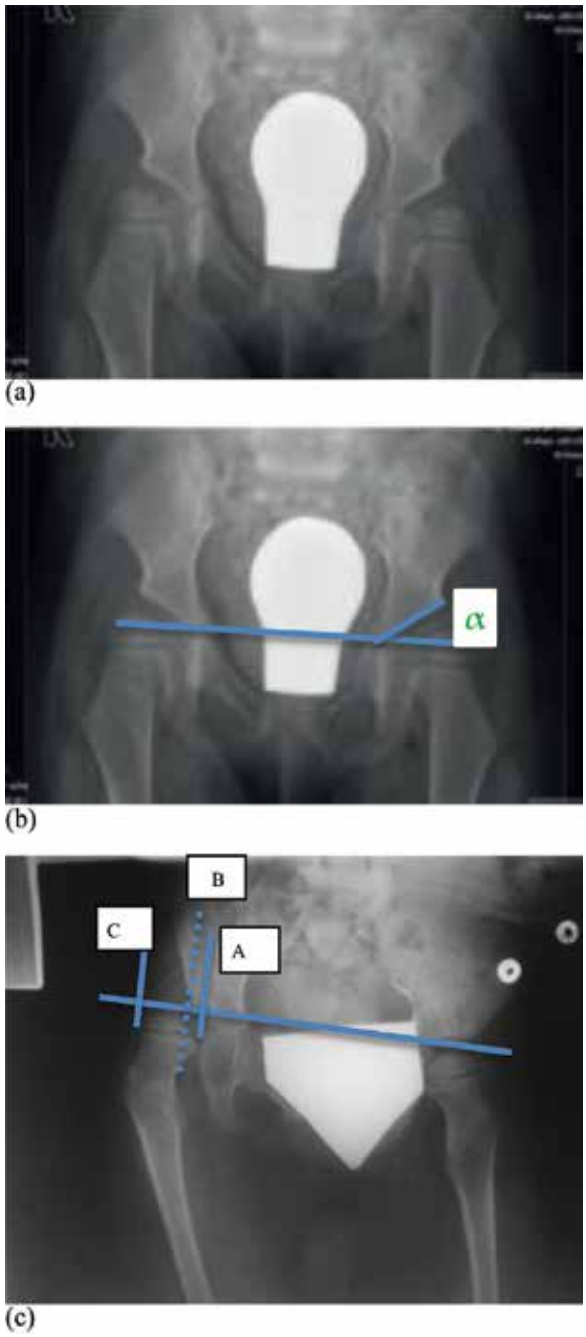

Figure 1. (a) Bilateral head coverage insufficiency, (b) acetabular index—α, (c) Reimer's Index: $\frac{BC}{AC} \times 100 = X\ \%$.

these patients; some knowledge is needed to make tests at different speeds, countering the spasticity of the limb, and trying to evaluate real articular ROM or making a differential diagnosis between muscle contracture and muscle shortening.

- Diagnosis of a true anatomic anteversion can be prone to confusion; there are two major clinical tests to evaluate the femoral anteversion (1) palpation of great trochanter in prone position—the angle between vertical plane and plane of tibia when trochanter is more palpable, gives us the anteversion of femoral neck (**Figure 2**); (2) difference between hip internal rotation and external rotation angles), but some errors occur because of muscle shortening/retraction, or anomalies of acetabular orientation, or unusual pelvis positioning can give a "false" clinical diagnose of anatomic anteversion; there are studies with 3D CT scan and more recently with EOS® imaging ("this system takes simultaneous anteroposterior and lateral 2D images of the whole body and can be utilized to perform 3D reconstruction based on statistical models") [9], which confirm some cases of incongruity between clinical exam and true anatomy. A final exam under anesthesia can confirm (or modify) our pre-determined strategy and surgical planning for each case
- Dealing with patient and family expectations is generally more difficult with walkers. Among the factors that may affect this are: greater awareness of the concept of self-esteem and social difference among less disabled patients; an unrealistic focus on minor, "almost esthetical" details; or "border" cases. Additionally, expectations change dramatically in some type III GMFCS cases where the patient may lose the ability to walk when they reach adolescence (because of a gain of body weight and loss of relative strength, and simultaneously, because a wheelchair can free their hands when they abandon crutches). It is important to distinguish between anatomic bony deformities (femoral anteversion, tibial torsion, and foot equinus versus cavus and/or adductus) and major muscle imbalance, which can be reducible clinically by slow counteracting of affected muscles, or even under anesthesia. It is critical to locate precisely the true causes of clinical status, because of child/family expectations and also for surgical reasons (correct indications). Despite the best intentions, an incomplete and incautious evaluation can be responsible for severe unplanned complications.

For the group of *non-ambulatory/non-walking patients*, the orthopedic goals are simpler: it must be clear that the main purposes are to treat pain, to permit hygiene and sitting in the best conditions and, sometimes, to permit positioning in a standing-frame. A proper screening program and adapted interventions should avoid hip dislocation and subluxation, but,

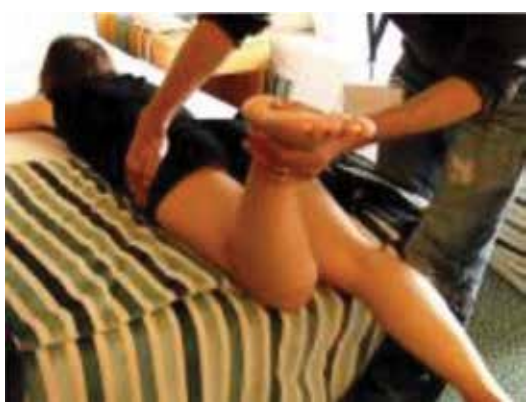

Figure 2. Palpation of greater trochanter, to evaluate femoral anteversion.

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unfortunately, these diagnoses are still usual, at different degrees. So, evaluation must be directed, with the cited clear goals in mind:

- The incidence of hip abnormalities is of up to 60% in non-independent sitters [8].
- Passive abduction of less than 40° with the hips in flexion should raise a suspicion of hip instability. Dislocation can be suspected by leg-length discrepancy, but early subluxation is difficult to assess by physical examination [10].
- The clinical exam follows the usual steps; in these very disabled patients, there is an association between hip dislocation, spine deformities, and pelvic obliquity. We have particularly challenging clinical tests to try to understand the main concerns of each situation and their close interrelationship warrants continuing analysis [10]. Sometimes, the pelvis obliquity is so important (due to spine deformity) that it promotes hip hyper adduction and, then, dislocation. Sometimes the problem begins in hip hyper adduction that promotes pelvic obliquity and scoliosis that turns structural, with progressive aggravation. There is some discussion about this concern [10, 11] but we do not have clear guidelines to predict the evolution for each case, even though we know that about 75% grade IV-V GMFCS patients will develop a scoliosis during their lives [7].
- The discussion still remains about whether or not to treat a contralateral hip apparently normal at the time of the dislocated hip reduction. So, much care should be taken during exam: once more, relations between both hips, pelvis and spine are evaluated and noted, muscular tests are also done, and close follow-up is mandatory to have a clear sense of the progression/evolution of the clinical status over time.
- The information provided by caregivers is fundamental. It can help to decide the priority between spine and hip treatment.
- In certain cases solving pelvic obliquity does not mean a sure hip protection [7], as demonstrated by cases of secondary hip dislocation after spine surgery.
- Clinically, cases that cause the greatest concern present a frank hip asymmetry (with cases of a "wind-swept "appearance of lower limbs); there are also a number of cases of "scissors" positioning of lower limbs (with a simultaneous adductus of hips, which obliges a crossing of legs). The malpositioning for sitting becomes disabling and pain becomes a major concern, as well as difficulties in carrying out hygiene tasks because of a "lack of space". We must try to relax the patient and, with gentle but firm testing, we should try to understand if spasticity is the greater problem, or if the hip is stiff, with reduced ROM, and if there are bony deformities that are insurmountable.

3. Planning—treatment strategy

When we plan our therapeutic approach, a wide range of data must be present: clinical (orthopedic concerns and also globally medical ones), radiographical, eventual gait laboratory analysis data, if available, time progression, and patient care (feeding, medication, orthoses, transports, and physiotherapy).

In this particular field of CP patients, one of the primary challenges for surgeons is the uniqueness of each case. There are very tiny nuances that can change the expected outcomes for a certain kind of disability or abnormality. Therefore, we must be very systematic and cautious in our analysis and treatment decisions.

There is generally a crescent therapeutical approach to these patients: first non-surgical (physiotherapy, occupational therapy, splints, orthoses, positioning, botulinum injections, and oral anti-spastic medication), and later surgical (orthopedic, neuro-surgical, and oro-gastro-intestinal). Several times, the interventions are mixed to optimize results.

When a hip surgery is indicated (unbearable pain, progressive subluxation with Reimer's Index >40%, or dislocation), we differentiate three levels of intervention, depending on age and anatomical structures to correct. The first level consists of soft tissue releases intended to prevent or halt subluxation. The second level incorporates bony osteotomies and is addressed to advanced hip subluxation or dislocation, associated with acetabular and/or femoral dysplasia. In the last level, palliative measures ("salvage procedures") are indicated for the treatment of painful, arthritic, and/or dislocated hips [8].

In the first level, and in children younger than 6 years-old (Y-O), it is astonishing how acetabulum can remodel some months/years after surgery in which femoral heads were "pointed" correctly into the central acetabulum in the end of procedure. The same occurs in second level of surgery, with simple varus proximal femoral osteotomies, when optimal reduction and abduction is obtained, in younger ages (before 6–7 Y-O).

In older children, soft tissues releases have, unfortunately, inconsistent results. Sometimes, after a short period of pain relief, there are, paradoxically, cases of increasing pain; this is observed more frequently when additional treatments are not correctly followed. In rare cases, where hips are on external rotation, even wide external rotators tenotomies have a high rate of recurrence, and are very difficult to deal with. Positioning, orthosis, and anti-spastic medication are fundamental, in association with physiotherapy to obtain better results.

In walking patients, incidence of hip subluxation or luxation is very low but, when it happens, reduction should be "perfect" with acetabular and femoral osteotomies and concentric reduction, with a good global pelvic balance.

In non-ambulatory patients, generally with huge asymmetry of pelvis, we can discuss what kind of intervention should be done in children between 6 and 12 years (sometimes older, if really immature).

It is generally accepted that, when it is not reducible under anesthesia with simple procedures (tenotomies), we have to reduce the hip with "heavier" techniques; the standard procedure is the so-called varus derotation osteotomy (VDRO) of the proximal femur; it consists in varus osteotomy (nowadays we try to reach a final cervico-diaphyseal angle of ~120°) combined to a derotation of excessive femoral anteversion (the final angle depends on the grade of GMFCS; in very disabled children, we can hyper-rotate externally distal femur, so that the weight of the lower limb counteract the internal rotational spasticity torque).

But, of critical importance is the simultaneous shortening of femur, allowing a hip reduction in abduction without any stress, during the procedure; if this criterion is not fulfilled, the risk of recurrence is much higher and a rather early clinical deterioration can occur.

There is also some discussion about simultaneously performing acetabuloplasty to correct the usual and particular development hip dysplasia in this neuro-muscular context.

There are several anatomic situations: sometimes you find a long shallow acetabulum, with a high acetabular index (>30%), without any depth to stably receive the reduced femoral head; sometimes, there is a" neo-acetabulum" separated from the original by a kind of smooth crest, but the original acetabulum has enough depth to achieve a certain intrinsic stability, after reduction. In this last situation, the acetabuloplasty is not necessarily required.

We must remember that the addition of one more invasive intervention (pelvic osteotomy) with its immediate and late complications should be established for solid reasons. Complications of the combined single-stage reconstruction include infection, avascular necrosis, femoral fractures, and premature closure of the triradiate cartilage. The avascular necrosis can occur from injury to the femoral head circulation during the open reduction, injury to the medial circumflex artery with iliopsoas release, or increased pressure between femoral head and acetabulum [8]. Theoretically, the acetabuloplasty is meant to "normalize" acetabular index and only can be done while the triradiate cartilage is still open (<11–12 Y-O maximum, for some authors). Some authors advocate adding this procedure in a one-stage procedure with VDRO, to achieve better hip stability. According to these authors, from patients who had VDRO alone, 25% needed revision procedures and none of the combined group needed other procedures [11], and they conclude that "the clinical and radiologic results obtained by the one-stage procedure were far better than doing VDRO alone justifying a more extensive approach".

One type of associated procedure is rarely discussed in literature: it is the shortening capsuloplasty. This technical point could make a significant difference in the hip stability outcome in severe patients with highly dysplastic acetabula. The technique consists of, after totally freeing the acetabulum (transverse ligament, ligamentum teres, inferior excision of joint capsule and of pulvinar) and confirming that the femoral head can be lowered completely in anatomic position, shortening of the superior joint capsule with a matrass Mayo type suture, sometimes through the labrum or even the superior bony acetabulum, in order to make an obstacle to head re-dislocation (**Figure 3**) [12]. The inferior flap will occupy space inside the articulation, lowering the femoral head more; the hip capsule is used as the interposition material between the femoral head and the deformed acetabulum. In time, the capsule undergoes metaplasia and fibrocartilage mimics the function of articular cartilage. Intrinsic stability can be confirmed with an intra-operatory hip radiograph in full adduction.

This is an important matter; in practice, the purpose is to correctly reduce the hip so that it will remain stable and painless throughout the years, with a minimum of complications.

In our practice, if we can avoid acetabular gesture with capsulorrhaphy and a VDRO with enough shortening, that is our preference; but if the stability is not sufficient and the triradiate is still open, we join a Dega osteotomy.

It is important to level both hips as best we can, and, sometimes, we have to perform tenotomies (or even reorientation osteotomies) of the contralateral side.

Another associated procedure is the neurectomy of the obturator nerve. Although we do not perform this technique, Valencia describes the technique: "the anterior branch of the obturator nerve lies on the anterior surface of the adductor brevis. Historically, division of the nerve

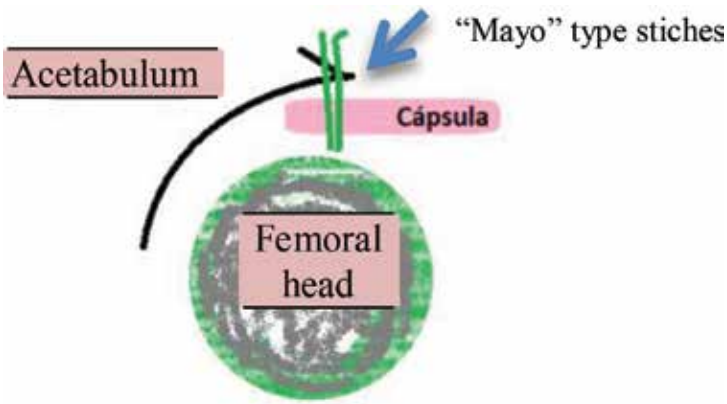

Figure 3. Mayo type capsulorrhaphy double "matress" stiches; capsula is shortened and occupies the "void" of deformed superior acetabulum.

had been used as an adjunct to reduce the recurrence of an adduction contracture, but has been associated with creation of an abduction contracture after surgery. It is difficult to delineate whether the neurectomy, overly aggressive tenotomies, or prolonged abduction splinting is the cause of this complication. Although a neurectomy is no longer advocated, the author has used temporary interruption of the signal with a crush neurectomy in non-ambulatory settings without leading to an abduction-posture complication. Phenol can also be placed directly on the nerve at the time of surgery" [7].

Discussing treatment options for children with major disabilities at the end of their growth, the primary criterion is pain; only ~50% of dislocated hips will be painful, and those should be treated. In these older children (>12 Y-O, with closed triradiate cartilage), we have to face several arthritic changes of the femoral head, an almost absent remodeling ability, and frequent low weight and skin problems. At times, we must choose between a hip reduction strategy and a "salvage procedure".

In the first option, hip reduction (our preferred course of treatment), we use the procedures described previously (VDRO with femoral shortening, with or without acetabuloplasty, capsuloraphy, adductor, iliopsoas, and hamstrings tenotomies), and, sometimes, we have to burr osteophytes of the severely deformed femoral head (queilectomy). Robb and Brunner have shown that it is feasible to perform a peri-acetabular osteotomy (Dega type) after triradiate cartilage closure in this type of patient using the same surgical principle as when the cartilage is open [13].

Unfortunately, we usually have to face 6–12 months of a difficult post-operative period that is sometimes still painful, until a steady-state is reached where daily activities can be achieved, such as sitting and hygiene.

The second option is the "salvage procedure": the options available are valgus redirectional osteotomy, hip arthrodesis, femoral head resection, interposition arthroplasty, and total joint arthroplasty [8]. These options may be recommended after a failed attempt of hip reduction with uncontrolled pain.

The advantage of the first option is to avoid an uncertain evolution of "salvage procedures" that can evolve to an almost fixed adduction and non-wished femur uprising, with a painful and "unfunctional" outcome. Alternatively, we have to accept the risks and difficulties of a total hip prosthesis in a spastic and "uncontrollable" patient. But, sometimes, this can be the last solution.

In summary, a fluxogram is proposed, trying to integrate some different nuances of these complex questions.

3.1. Proposed algorithm

1. For hip subluxation, dislocation

- <6 Y-O sub-luxated hip(s) Reimer's Index between **40** and **60%**, **reducible** after adductor tenotomy alone → adductor tenotomy alone + > 1 month abduction cast/splint.
- <6 Y-O sub-luxated hip(s) Reimer's Index between **40** and **60%**, **NOT reducible** after adductor tenotomy alone → adductor tenotomy + medial harmstrings tenotomy + varus proximal femoral osteotomy (centralizing head in acetabulum) + > 1 month abduction cast/splint.
- <6 Y-O sub-luxated hip(s) Reimer's Index >**70%**, **NOT reducible** after adductor tenotomy alone → adductor tenotomy + varus and shortening proximal femoral osteotomy (centralizing head in acetabulum or, if not possible, open reduction + capsuloplasty) + > 1 month abduction cast/splint.
- 6 Y-O sub-luxated hip(s) Reimer's Index between **40** and **60%**, **reducible** (rare cases) after adductor tenotomy alone → adductor tenotomy alone + (thinking about shrinking capsuloplasty) + > 1 month abduction cast/splint.
- 6 Y-O sub-luxated hip(s) Reimer's Index between **40** and **60%**, **NOT reducible** after adductor tenotomy alone → adductor tenotomy + iliopsoas tenotomy + medial harmstrings tenotomy + varus, derotation proximal femoral osteotomy (centralizing head in acetabulum) + Dega Osteotomy if triradiate cartilage open and very shallow acetabulum + > 1 month abduction cast/splint (try to operate at 8 Y-O or more, to reduce recurrence rate).
- 6 Y-O sub-luxated/dislocated hip(s) Reimer's Index >**70%**, **NOT reducible** after adductor tenotomy alone → adductor tenotomy + medial harmstrings tenotomy + iliopsoas tenotomy + open reduction + varus, derotation and shortening proximal femoral osteotomy + Dega Osteotomy if open triradiate cartilage and very shallow acetabulum + reduction capsuloplasty + > 1 month abduction cast/splint (try to operate at 8 Y-O or more, to reduce recurrence rate).
- 10 Y-O sub-luxated/dislocated hip(s) Reimer's Index >**70%**, **NOT reducible** after adductor tenotomy alone and sometimes with arthritic deformity → adductor tenotomy + medial hamstrings tenotomy + open reduction (queiloplasty) + varus, derotation and shortening proximal femoral osteotomy + reduction capsuloplasty + > 1 month abduction

cast/splint—NB—Dega Osteotomy is to consider, even with closed triradiate cartilage [14], if very shallow acetabulum and reduction is not enough after capsuloplasty, when you accept higher risk of complications.

- 12–14 Y-O (completely mature) sub-luxated/dislocated hip(s), with Reimer's Index **>70%**, **NOT reducible** after adductor tenotomy alone and with arthritic deformity.
  - (First option) adductor tenotomy + medial hamstrings tenotomy + iliopsoas tenotomy + open reduction (queiloplasty) + varus and shortening proximal femoral osteotomy + reduction capsuloplasty + > 1 month abduction cast/splint—NB—you can also consider Dega Osteotomy even with closed triradiate cartilage if very shallow acetabulum and reduction is not enough after capsuloplasty OR
  - (Second option, after painful failure of previous attempt of hip reduction) "salvage procedure", per example, Mc Hale procedure: it is a 90° proximal femoral valgus osteotomy with suture of distal ligamentum teres to lesser trochanter to avoid subsequent femoral uprising.

2. For hip internal rotation (sometimes associated to knee flexed and foot equinus varus, in diplegic patients)

- Concerning only the hip, in this chapter: sub-trochanteric external rotation osteotomy with plate (leaving ~30° passive internal rotation) in children or diaphyseal external rotation osteotomy with a nail in adolescents, in order to permit early standing. Usually, intertrochanteric osteotomy is proposed [7, 8], but, in walking patients, there is a risk of an further femoral head subluxation because of the continuous action of hip rotators muscles, and namely iliopsoas; after post-operative healing, its spastic action continues, forcing hip internal rotation, contributing for further dislocation. I believe that immediate sub-trochanter osteotomy (instead of intertrochanteric) is safer in the long-term evolution.

4. Technical tips

The purpose of this chapter is to summarize tips used to face some technical challenges in CP hip surgery.

First, we cannot plan a procedure correctly without an accurate previous evaluation. There are several moments (in CP cases) where we can easily have a false perception of reality, and some of those points are discussed below.

Second, the surgery planning is the moment where we try to imagine the surgical approaches and the technical steps we will have to fulfill and what eventual orthopedic materials and respective ancillary equipment we will need to achieve our osteosynthesis. Sometimes, even the enterprises who sell orthopedic material have their own technique manuals not adapted to the specificity of this kind of "extreme" deformities. This is also the reason for the following explanations.

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Third, the main goal in hip surgery, is a correct and, if possible, concentric hip reduction; as so, a good femoral osteosynthesis is not, *per se*, enough if final hip reduction is not satisfying. Taking care to shorten femur and to stabilize the femoral head in correct position (acetabulum "cleansing", iliopsoas distal section, acetabuloplasty, and/or capsulorrhaphy), without any residual stress in abduction, are mandatory to have a successful procedure.

These are the technical highlights that usually can raise some theoretical and practical discussion.

4.1. Correct evaluation of hip deformities

After clinical evaluation, X-ray is fundamental. However, generally the patient is awake and information is biased by malposition of patient and spasticity. Or, if we do not have access to EOS® technology [9] or an eventual 3D CT scan, a correct understanding of real bony deformities, will be achieved only by X-ray evaluation under anesthesia. After this, we can have a clear idea of the real initial state, and we can adapt our planning to reach the final state desired.

A hyper-lordosis can preclude correct evaluation of acetabulum parameters, or an excessive femur rotation can increase an impression of femoral valgus (**Figure 4a** and **b**).

Another practical and important question is the real evaluation of valgus deformity when the physis have a long period of progressive deformation. Instead of being in the continuity of the femoral neck, it is deformed in valgus, sometimes adding about 10° more in evaluation (**Figure 5a** and **b**). This notion will be important for the amount of needed correction and for the correct perception of hip reduction.

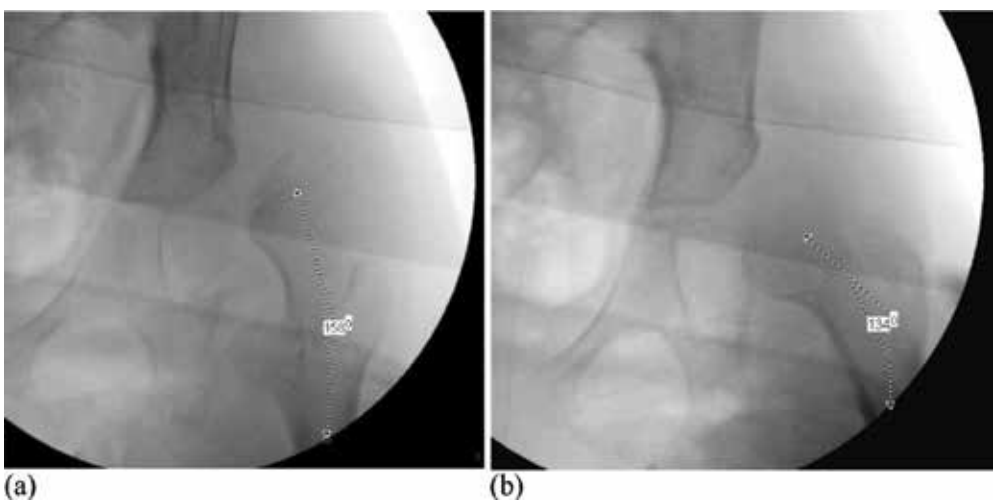

Figure 4. (a, b) In AP view, the cervico-diaphyseal angle is measured as a 158° valgus, but if we correct rotation of the thigh, achieving a true femoral neck AP view (the great trochanter physis is clearly viewed), we find a 134° real angle—the proximal femoral varization will be less important than planned.

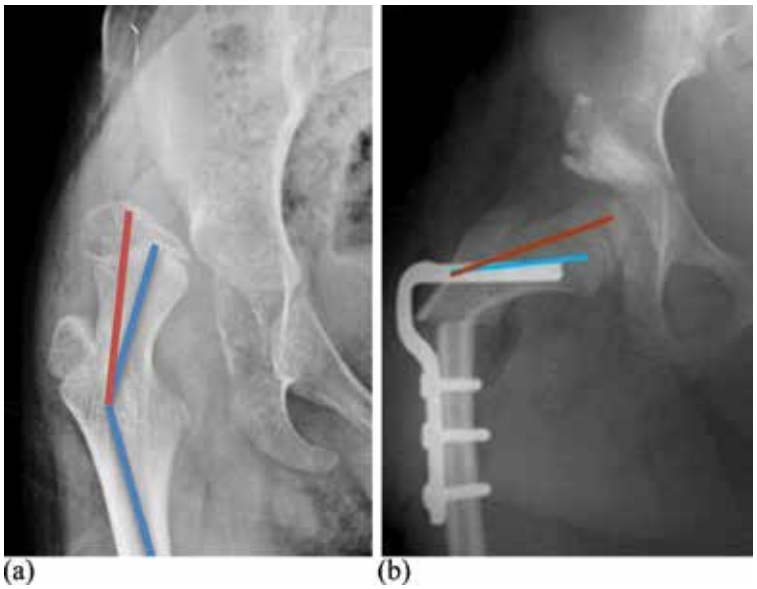

Figure 5. (a) dislocated hip; the cervical line doesn't correspond to "head cervical" line, because of head progressive deformity in valgus, (b) post-operative reduced hip; when head is correctly reduced, we observe a bigger "true" cervico-diaphyseal angle than classically measured and an "infra leveling" of the Shenton's line.

4.2. Calculation of the final angle in femoral osteotomy and bone osteosynthesis

As mentioned previously, when we plan a proximal femoral osteotomy, the goal for the inner question of the femur is to reach a final state where the cervico-diaphyseal angle (or head-cervico-diaphyseal angle, when femoral head is in valgus) is about 120° in the AP view, with a correction of rotation that permits about 30° of hip internal rotation and an eventual femur shortening, depending on the previous amount of femur uprising associated with dislocation. Sometimes, when we have a flexed hip, we can incorporate a "deflexion" procedure, adding an extension component at the osteotomy site (with a corresponding slope for the plate positioning).

There are several materials we use to achieve a correct osteosynthesis—straight plates, angled blade plates, angled screw plates, Altdorf plates, and others. Age, weight, bone density, need of external contention (splints, casts), and surgeon experience, impact the implant choice for each patient.

For the correction of femoral proximal valgus, we have to calculate the amount of varization we need. There are several ways to calculate it: we can use a goniometer and an X-ray transfer (always remembering that correction is made more accurately after evaluation under anesthesia), measuring the angle between initial valgus and final planned position, just rotating image/transfer (**Figure 6a–c**). We can also plan the angle of entrance of our guide wire (when we use an angled plate for our osteosynthesis), using the following formula:

$$\text{initial angle} - \text{final (pretended) angle} + \text{plate angle} = \text{guide wire angle}$$

In this formula, the *initial angle* is the real valgus of the patient, the *final angle* is about 120°, the *plate angle* depends on angle availability in the equipment we are using (and decision

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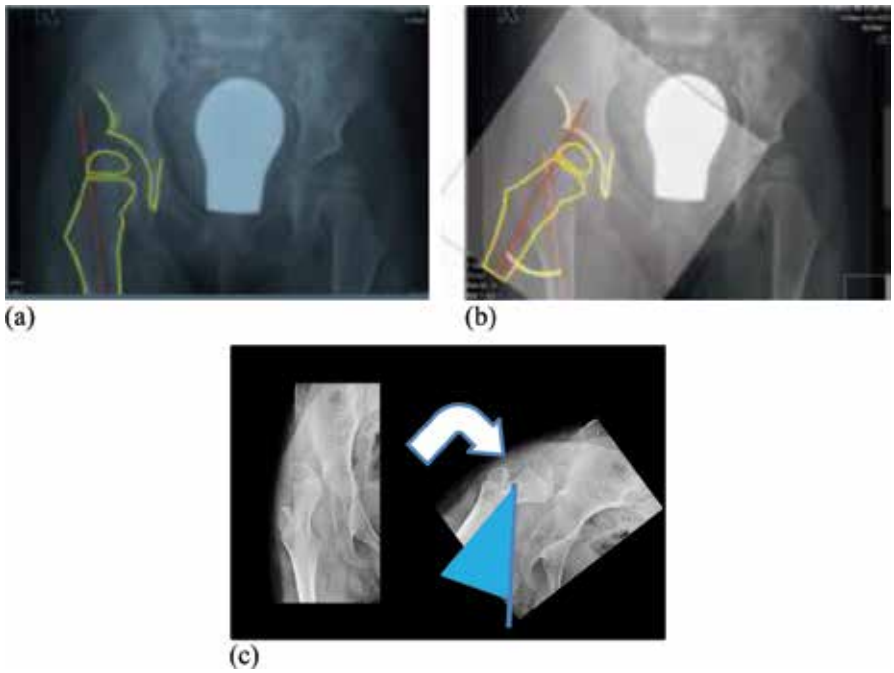

Figure 6. Planning varus osteotomy with a transfer; we measure the angle between initial (a) and the final (b) correct position we pretend, and it corresponds to the amount of varus needed, (c) planning varus osteotomy with a simple rotation of the X ray: we measure also the angle between initial and final correct position we pretend; it corresponds to the amount of varus.

regarding the point of entrance on lateral femur), and *guide wire angle* is the angle of entrance in femur which should be adjusted using the equipment pointer.

A third strategy can be employed to insert the guide wire and is based on the following technical assumptions: when we use the equipment pointer to insert the guide wire in cases of significant valgus (>140–150°), the off-set provoked by the thickness of the metal piece gives us a worse result than planned (the osteotomy will be too far, causing the plate to be too lateral); another assumption is that soft tissues can interfere in the guide wire and pointer orientation when we have very "vertical" orientation of the guide wire and a huge femoral internal rotation; even so, if we know that we want a final head-cervico-diaphyseal of about 120°, and that there is an angle of about 10° between cervical line and real head cervical line (when femoral head is deformed in valgus). So, if we insert the guide wire by free hand, parallel with the femoral neck, and if we use a 110° plate, we will reach a final angle of 120°. Given the real constraints of soft tissue during surgery, it is easier to find the correct point of entrance for the wire using this technique (**Figure 7a** and **b**).

Before we make the osteotomy, we have to make marks on the femur, so that we can have clear indicators when we achieve the final state after osteosynthesis. To avoid rotation errors, we can mark the bone, inserting Kirschner wires, above and distally to the osteotomy line (sufficiently far to not interfere with the plate placement), or marking the bone, for example, with a vertical superficial line made with a chisel or a saw, long enough, because of eventual femur shortening at the osteotomy site, once more, far from the location where the plate is

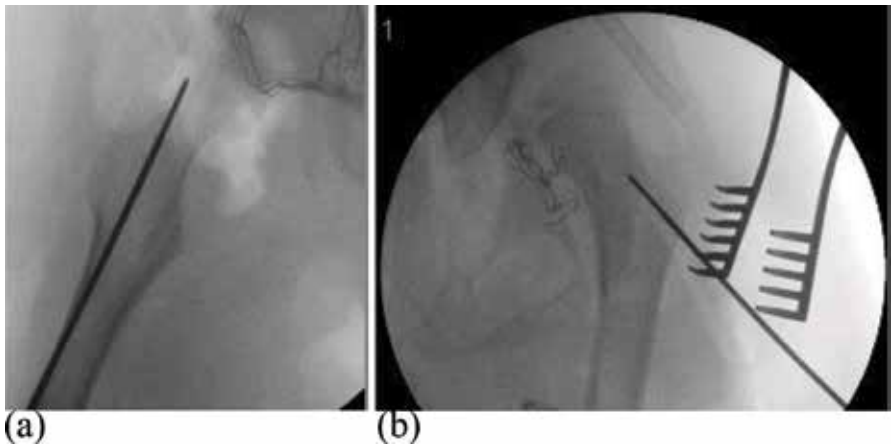

Figure 7. (a, b) Profile and front guide wire correct insertion.

going to be screwed. At the site of the osteotomy, we try to detach and preserve periosteum so that it contributes to a good consolidation, in particular when the initial valgus is very important and respective correction implies some significant off-set of the proximal femur and risk of late pseudarthrosis. In these cases, the adjunction of an auto graft seems wise.

Now we discuss the entry point for the plate; as we can see in **Figure 8a**, we can imagine different entry points in function of the angulation of the plate. For example, we have planned

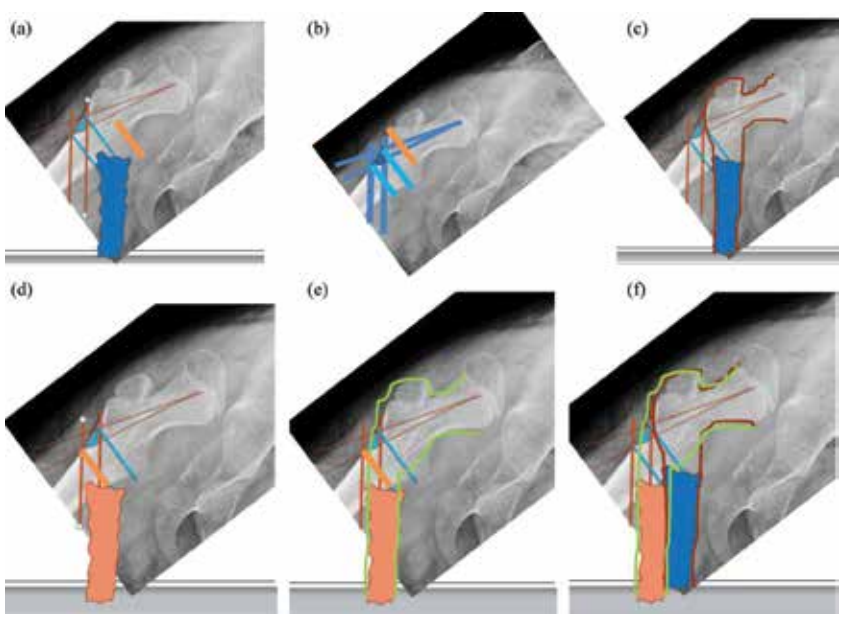

Figure 8. (a) Different entry points of the guide–wire, in function of the angulation of the plate, (b, c) more proximal femur osteotomy and achievement of a final balanced result, (d, e) slight more distal osteotomy and achievement of a final "Shepherd's crook", (f) comparison of anatomic final results in function of the osteotomy level.

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a 100° [upper line (**Figure 8a–c, f**)] or a 110° [lower line (**Figure 8a, d–f**)] angled plate. The difference of the two entry points implies an osteotomy almost 1 cm more distal in the second option. If we are not aware of this issue, it is easy to make an osteotomy that is too distal which negatively affects hip's Pauwels' balance [15]. In the latter option, we risk obtaining a "Shepherd's crook"-like femur instead of a balanced hip (**Figure 8d–f**). It is not a rule to choose plates with lower angles because, sometimes, they reach the lower femoral neck or even the calcar and that is not our goal. In consequence, it is important to choose the best angulation on a case by case basis.

When we face a situation where the proximal femur lateral cortex prevents correct apposition of the plate, provoking the cited femur "shepherd's crook"-like deformity, we can cut the lateral beak, so that the plate can join completely its osseous "bed". The problem is that we will have less bone apposition between proximal and distal fragments (**Figure 9a–c**). It is advisable to preserve periosteum and to join autograft, if possible.

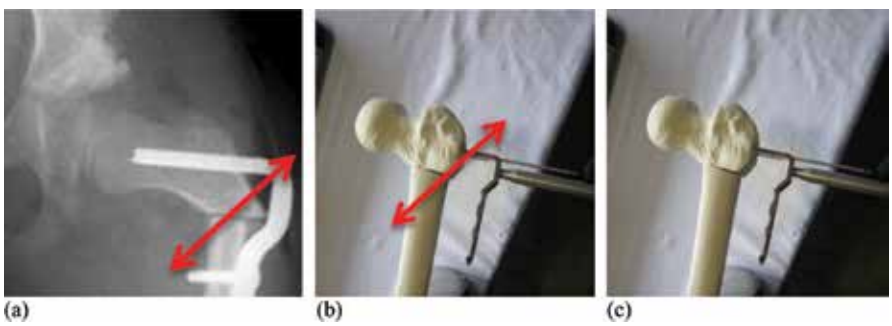

Figure 9. The proximal femur lateral cortex prevents correct apposition of the plate (a), provoking a femur "shepherd's crook"- like deformity; we can cut the lateral beak (b), so that the plate can join completely its osseous "bed" (c).

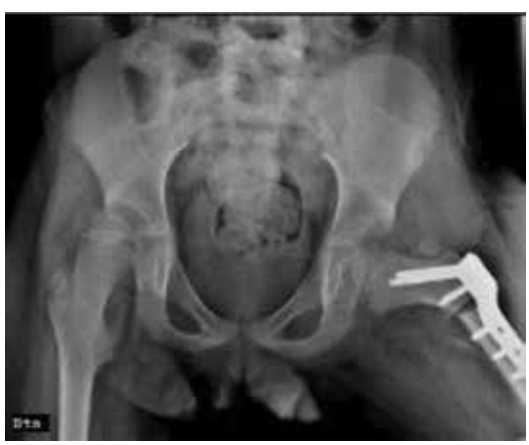

Figure 10. Femur shortening is regulated until null tension on the femoral head remains on abduction, after hip reduction; if some tension remains, the proximal femur should be more shortened.

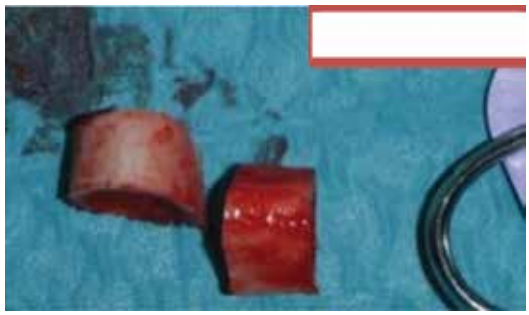

Figure 11. Femur shortening, resection pieces–They can be used as auto-graft in supra-acetabular pelvic osteotomy or in the femur osteotomy site.

Before final screwing of the plate to distal fragment, we must be sure that hip muscle tension does not stress hip reduction during abduction. The shortening is made until null tension on the femoral head remains on abduction (**Figure 10**). If some stress remains, the femoral head has a tendency to upraise in acetabulum, or even dislocate. Sometimes we can make an important shortening, as much as 2–3 cm (**Figure 11**).

4.3. Correct concentric hip reduction

The steps used for hip reduction depend on reducibility of the femoral head; in classic spastic cases, we make an adductor (and ischio tibialis) tenotomy, and after iliopsoas tenotomy we can test if the femoral head is reducible or not; if it is difficult, we begin the proximal femoral osteotomy step of the procedure, so that we can free at maximum all of the proximal femur. With forceps, we can handle the femoral neck and trochanter and we can test reducibility and eventual stability of the head in acetabulum. We must be aware of a false sensations of reducibility, for example, in cases of head valgus deformity, which can fool us (we tend to follow the neck alignment visually and not the head location in R-ray). In these situations, to be sure that reduction is achieved, we have an "infra-leveling" of Shenton's line (**Figure 12**) because the femoral head is well centered and the neck is below the head level, and not in continuity with it. If the head is not totally reduced, we have to open the joint capsule and cleanse all the obstacles to total reduction with special care to transverse ligament excision and freeing of lower joint capsule, permitting complete lowering of the femoral head.

As mentioned before, and depending on age (presence or not of the triradiate cartilage), depending also on anatomic profile of acetabulum, and of femoral head reducibility, we decide if we add an acetabular step [acetabuloplasty, (**Figure 13**)], reorientation procedure, shelf) or a capsulorrhaphy (cf. Section 3). A dynamic X-ray can be made at the end of the procedure to test the stability of hip reduction. The external immobilization depends on age and osteosynthesis stability. In younger children, we use pelvi-podalic casts and in older children and adolescents we use bi-cruro-podalic casts, for a period of 4–6 weeks.

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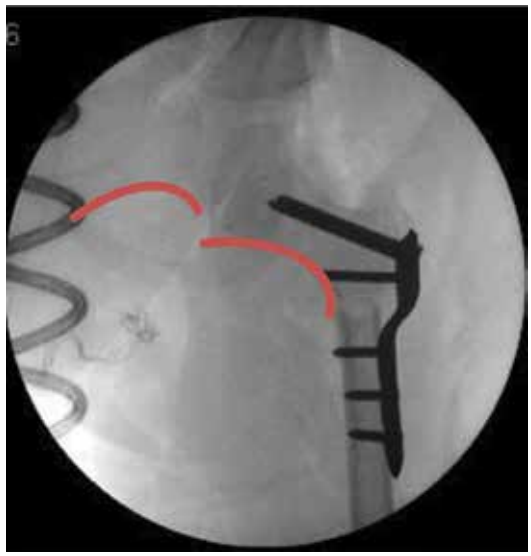

Figure 12. When femoral head is deformed in valgus, and when hip reduction is correctly achieved, we verify a discontinuity of the Shenton's line(that is "infra-leveled").

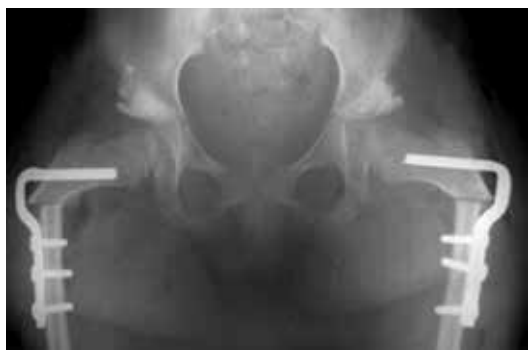

Figure 13. In this case, a bilateral Dega pelvic osteotomy was added to a femoral VDR osteotomy.

5. Conclusions

Cerebral palsy is a particularly complex field of medical knowledge, where clinical experience is probably more important than in other fields. For that reason, trying to teach and to share some "shortcuts" about CP "thinking" with new generations of health professionals is an important and challenging concern.

The goal of this chapter is to facilitate hip evaluation and decision making for surgeons who deal with these complex problems in CP patients. Practical clinical situations were presented with a wide array of comprehensive solutions.

I hope this summary of experience and reflections about the subject will be useful for interested readers.

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Conflict of interest

The author has no disclosures.

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Cerebral palsy is a common pediatric problem and is the leading cause of childhood disability. It occurs at a rate of 3.6 cases per 1000 children, and represents a major social and psychological impact on both family and society. It is a group of disorders with movement difficulties being common for all affected patients. Its severity and extent are variable from one patient to another. Additionally, the impacts of cerebral palsy on daily activities, communications, and requirements are also variable. Recent advances in clinical research increase our knowledge and understanding of causal pathways, possible preventive measures, specific intervention strategies, and the value of new treatment modalities such as botulinum toxin and intrathecal baclofen in the management of cerebral palsy.

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