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ORIGINAL ARTICLE

Cerebral Palsy

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Abstract

Cerebral palsy is a permanent and nonprogressive lesion of the developing nervous system. It affects tonus, reflexes and posture and impairs the child's motor development. It is the main cause of deficiency in childhood and has a variable presentation and many clinical and neurological comorbidities. In this review, it is related the main causes, it is described the topographic and functional diagnosis, highlighted the importance of the early diagnosis and evidence based treatment, including the need for hip supervision.

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Cerebral palsy, also known as chronic nonprogressive encephalopathy, is the most common cause of childhood motor deficit and refers to a heterogeneous group of conditions that progress with central motor dysfunction affecting tonus, posture, and movements. It results from permanent damage to the developing brain and varies in terms of anatomical distribution of the lesion, severity of motor involvement, and associated clinical symptoms. The considerable variability of this condition requires patients with cerebral palsy and their families to be approached in a systematized manner, taking a variety of healthcare aspects into account.

The estimated prevalence of cerebral palsy is approximately 2.1 cases per 1,000 live births and has remained constant for decades, according to several studies[1,2]. In countries with significant regional heterogeneity and inequality of care, such as Brazil, a range of different scenarios may coexist, with greater mean prevalence in some population groups and regions. Of note, that health conditions are greatly influenced by poverty, and 80% of differently abled individuals in the world belong to low- and middle-income countries[3]. Therefore, it is possible that the prevalence rates in European and American underestimate disability and cerebral palsy in Brazil. Pre- and perinatal care and advanced care for high-risk neonates as well as developmental supervision affect the final prevalence of the diagnosis and severity of cerebral palsy.

RISK FACTORS AND ETIOLOGY

Factors for an increased risk of cerebral palsy include negative influence on the mother's health, such as exposure to toxic and infectious agents; infant nutrition and viability conditions; parturition conditions; and the occurrence of hypoxic or traumatic events in the perinatal period. Factors that pose the highest risk of cerebral palsy are extreme prematurity (<28 weeks), low birth weight (<1,500g), and a neonatal vitality index measured by the Apgar score of <7 at 5 min [4]. In addition, multiple factors increase the extent of brain damage.

Regional structural malformations with motor deficit, such as several types of agenesis, schizencephaly, hemimegalencephaly, pachygyria, polymicrogyria, lissencephaly, and other migration and embryogenetic defects are common etiologies for cerebral palsy. These conditions can occur in children without a history of gestational or perinatal risk, are not apparent, and can only be diagnosed using suitable imaging tests, usually magnetic resonance imaging (MRI) techniques.

Perinatal strokes may occur due to focal cerebrovascular disease of the arterial or venous network, thereby promoting the outcomes of ischemia, consequent cell death, and cerebral palsy. By definition, strokes considered perinatal should occur during the fetal age of 20 weeks–28 days after birth and should be confirmed by neuroimaging or neuropathology. They are the most common cause of hemiplegic cerebral palsy, and neonates with encephalopathy or seizures of undetermined origin require diffusion-weighted MRI of the skull and magnetic resonance angiography to rule out acute stroke[5].

Perinatal strokes in full-term infants are divided into the following subtypes: neonatal arterial ischemic stroke, neonatal cerebral sinovenous thrombosis, neonatal hemorrhagic stroke, arterial presumed ischemic stroke (APPIS), and periventricular venous infarction. Although the causative factor for stroke is often not identified, it is important to investigate potentially recurring causes. The main ones to be investigated include antiphospholipid antibodies, factor V Leiden, prothrombinogen, protein S or protein C deficiency, lipoprotein, antithrombin III, factor VIIIc, and homocysteine. Children who develop manual dominance before the age of 12 months should be investigated to rule out the occurrence of a neonatal stroke, accelerating the choice of the dominant hemibody[6].

Hypoxic-ischemic encephalopathy (HIE) refers to brain symptoms following a reduction of oxygen in the blood and tissues resulting from a disruption in its supply. Changes in consciousness, tonus, reflexes, and the occurrence of seizures make up the clinical symptoms of the acute condition. The vulnerability of basal ganglia structures to hypoxic-ischemic injury makes it the main etiology of dyskinetic forms of cerebral palsy and approximately 30% of total cases[7]. Factors that sensitize the fetus to the effects of hypoxia are fever and maternofetal infection. The release of proinflammatory cytokines in these situations produces a synergic effect to that of hypoxia and causes cell injury. Genetic factors produce differences in the pattern of inflammatory response or of the activation of prothrombotic pathways, and the sex of the fetus determines different sensitivities to agents of injury owing to different apoptosis activation pathways in fetuses of different sexes[8].

The presence of intrauterine growth retardation (IUGR) and chronic intrauterine hypoxia predisposes patients to higher levels of acidosis when exposed to the same degree of hypoxia compared to events without these conditions. Clinically, HIE is classified into mild, moderate, or severe. Severe HIE involves alterations in consciousness with stupor and coma, weak sucking ability and primitive reflexes, as well as seizures that may be drug-resistant. In severe cases, bradycardia, hypotension, and apnea are common and mortality and morbidity rates are high. The presence of an isoelectric, a generally slow, or a burst-suppression electroencephalogram pattern is an unfavorable prognosis marker.

Numerous therapeutic measures aim to minimize the cascade of events that cause cell death in the process triggered by hypoxia. Adequate seizure control and the use of therapeutic hypothermia in eligible infants are some widely accepted therapies. The introduction of compounds with varying actions in the complex physiopathological arrangement of HIE, such as melatonin, epoetin solution, N-acetylcysteine, allopurinol, and xenon, may be efficient adjuvant therapies once dosing and safety issues have been solved[9,10].

Of note, bilirubin is the most common endogenous neurotoxin and causes kernicterus, a specific form of cerebral palsy due to the impregnation of the basal ganglia. Total serum

bilirubin level above 25 mg/dL is associated with an increased risk of neurological damage. Factors related to prematurity and infections increase the risk, and acute bilirubin encephalopathy includes changes in mental state, muscle tone, and crying pattern; refusal to suckle; cyanotic attacks; and oculogygiric movements. Upward gaze paralysis and sensorineural hearing loss appear at a later stage. In its chronic form, it manifests with muscle tone alterations, choreoathetoid movement disorder, and perceptual and sensorial alterations. Mild cases have been described as "bilirubin-induced neurologic dysfunction"[11].

Maternofetal infections such as chorioaminionitis, genitourinary tract infections, vaginitis, and even periodontitis, may be responsible for direct and indirect mechanisms injury to the fetal brain. Lesions caused by the inflammatory response to infection, with apoptosis, disruption of the normal neuronal migration processes, calcifications, and hydrocephaly, are some of such mechanisms. Indirect effects are related to a change in fetal inflammatory modulation, with overproduction of interleukins, particularly IL-6 and inflammatory cytokines that predispose to injury processes. In addition, protection against these processes appears to be conferred by specific gene arrangements that increase the production of factors such as IL-19 [12], and cases of cerebral palsy with genetic predisposition would have this mechanism among those possible.

In addition to routine tests related to metabolic and infection control (such as the tests that aim to determine underlying diseases and control potentially toxic metabolites), electroencephalogram, MRI, and ultrasound tests are also employed.

The electroencephalogram pinpoints unfavorable prognosis patterns, such as the aforementioned burst-suppression pattern, as well as some positive indicators, such as a return to sleep-wake patterns in the first 36 h [13].

Transfontanellar ultrasound (TFU) is a widely used method that can indicate edema and lesions at an early stage. Although not the most specific or sensitive method, it reveals malformations and bleeding and may indicate the best time to perform MRI. Increased resistance in transfontanellar Doppler imaging is useful for the assessment of the patient. Normal resistance or Pourcelot index values are around 0.7, and those with indices below 0.55 are associated with a poorer outcome [14].

In MRI of the head when basal ganglia lesions are present, the development of cerebral palsy can be expected in 75% of cases. Magnetic resonance spectroscopy and measurement of the lactate-to-aspartate ratio has been proposed as a method of major prognostic correlation (15). Abnormalities that cause the motor problems of cerebral palsy are located in the gray matter and in the subjacent white matter. In severe cases, the thalamus, basal ganglia, and brainstem are also affected. White matter lesions disrupt the sensorimotor connections as well as the modulating connections of the cortex with the basal ganglia and the cerebellum, which are important for planning and fine motor control.

EARLY DIAGNOSIS

Early diagnosis of neurological damage and its progression to a clinical presentation of cerebral palsy is one of the determinants of a better prognosis. The beginning of a systematized intervention during the period of intense neuroplasticity that occurs within the first 2 years increases the prospects for functional recovery.

Even in infants with numerous brain lesions documented by MRI and a high probability of sequelae, the functional result can be surprising. Others, with less pronounced risk factors or even no apparent factors, contrary to expectations, may develop severe conditions. Several factors, such as a genetic predisposition to cerebral palsy and factors related to the production of inflammatory cytokines, particularly IL-6 [16], are currently being studied. The quality of perinatal care and factors such as the quality of attachment to the caregiver, the stimulation environment, and the association with sensory deficits are key determinants of the final prognosis.

The mean age at diagnosis is 18–24 months. This is undoubtedly one of the major limiting factors to the effectiveness of interventions, because these initial years include the most suitable period from the point of view of neuroplasticity. Many children miss this precious window of intervention. Therefore, early signs should be actively sought in pediatric and follow-up assessments, and the inability to adequately achieve a developmental milestone should be viewed with concern and never neglected or minimized. Even before major motor milestones are expected, the child's behavior, whether overly irritable or docile, the presence of heightened primitive reflexes and inadequate postures such as opisthotonus, difficulty in feeding and in gaining weight, are early indicators of dysfunction.

Motor dysfunctions in cerebral palsy can be divided into positive and negative categories. Positive dysfunctions include signs added to the usual motor behavior and are usually easy to identify on physical examination. These are spasticity, abnormal posture, dyskinesia, heightened reflexes, and the persistence of primitive reactions. Negative dysfunctions include weakness and paresis, central coordination problems, cocontractions, and mirror movements[17].

Systematic neurological examination has been the first tool used to assess infants, and its value is indisputable. Specific items of the examination show a greater correlation with negative neurological outcome including altered or persistent Moro reflex, palmoplantar reactions and asymmetrical tonic neck reflex, and the non-appearance of the parachute reaction at approximately 8 months of age. All of these are particularly sensitive indicators of the subsequent development of cerebral palsy[18].

MRI of the head is another demonstrably sensitive and specific method for defining the prognosis of infants with neonatal risk, and its sensitivity and specificity are close to 100%. However, due to the practical difficulty and costs involved in applying this method, it is usually reserved for cases where

the definition of the immediate conduct depends on it being performed.

A systematic review study of early diagnosis methods defines the evaluation of the General Movements Assessment created by Hans Prechtl as the gold-standard method in the early diagnosis of CP, with 98% of specificity at 3 months and 95% of sensitivity[19]. These high early indicators modify the paradigm of diagnosis and treatment, transferring interventions to a more suitable and promising neuroplasticity window.

The Prechtl method is based on the qualitative analysis of the infant's spontaneous movements at three different stages: the preterm period starting from the 26th week; the full-term period at approximately the 40th week in corrected age, and of a nursing infant, that is, at 12 weeks calculated from the 40th week. Each time point presents normal patterns of spontaneous movement related to nervous system integrity, and these patterns change with the lesions without yet presenting the classic signs of motor syndromes. The patterns found are highly predictive of normality or abnormality at an age as early as 3 months or even earlier and assertively define the need for early treatment and stimulation programs. The technique is very simple and requires filming the infant's spontaneous movement for 3–5 min, which should be assessed by an observer with formal training in the method[20; 21].

Diagnostic Classification and International Classification of Functioning, Disability and Health (ICF)

The classification of cerebral palsy subtypes traditionally refers to motor subtypes related to the topographic base of the lesion, and its severity is referred to as mild, moderate, or severe. Due to the variability of concurrent factors, functional assessment in this approach is very imprecise, although it describes the predominant motor pattern in the case. Table I presents a summary of the subtypes and their main characteristics according to the topographic classification.

To better describe patient functionality, in 1997, Palisano proposed the use of the Gross Motor Function Classification (GMFCS) scale, which describes children aged 2–18 years, with function categorized in five levels of motor independence[22]. Its application is considerably useful, and other authors have produced scales related to other functions considered crucial for independence. Further, Eliasson et al, in 2006 [23], at the Karolinska Institute, devised the Manual Assessment Classification System (MACS), which classifies the use of both hands and upper limbs. The authors then proposed Mini-MACS, for children aged <4 years, also stratified into five levels.

It is estimated that approximately 88% of children with CP have communication problems. The Communication Function Classification System (CFCS) was designed to evaluate this domain[24]. Similar to the GMFCS and MACS, it analyzes the individual's proficiency at producing and receiving messages in five levels and allows all methods of communication, including vocalization, manual gestures, figures, and voice generators, taking into account the efficiency achieved with familiar people and strangers. As for eating functions, the Eating and Drinking Ability Classification System (EDACS)[25] was produced according to a similar methodology. The Function Classification System is summarized in table II.

EVIDENCE-BASED TREATMENT

Cerebral palsy is a chronic disease that requires multidisciplinary, intensive, and coordinated treatment to restore motor functions or at least adapt the individual's functionality independently. There are many existing treatments designed to positively influence or even cure cerebral palsy; however, unfortunately, many of them were not produced on scientific bases and have been employed for several decades with inconsistent results. In recent decades, along with a greater understanding of the processes involved in synaptogenesis and neuroplasticity, we have been paying more attention to the efficacy of the techniques used. In a systematic review coordinated by Novak I et al, 2013 [26], 64 different rehabilitation methods were assessed according to their outcomes and were classified as follows: 16% effective (indicated as a green light, do it), 58% probably effective, 20% probably ineffective, and 6% ineffective (red light, do not do it). Surprisingly, several techniques widely used in the rehabilitation of children with cerebral palsy have shown weak scientific evidence. In general, it is necessary to develop research protocols that bring awareness about methods of uncertain effectiveness; in addition, time and resources must be invested to offer demonstrably efficient methods.

Demonstrably effective interventions span areas of functionality according to the International Classification of Functioning, Disability and Health (ICF), and are a set of techniques including drug products and surgical or nonsurgical procedures in addition to therapeutic intervention activities. Anticonvulsants for the treatment of seizures, botulinum toxin, and benzodiazepines are certainly effective, as are dorsal rhizotomy for the treatment of spasticity and bisphosphonates for bone health. The use of orthopedic gutter splints/braces and systematic supervision for the prevention of hip dislocations, control of pressure ulcers, and aerobic training to maintain functionality are also recommended[26].

Regarding rehabilitation training, training aimed toward improving functional activities, such as bimanual function training, are recommended. The detailing of specific therapeutic recommendations does not fall within the scope of this text, but the search for evidence of efficacy must always be established in therapeutic recommendations. These recommendations should be directed with the goal of making the individual functional according to his or her means and not with a promise of cure.

OVERALL HEALTH AND COMPLEX CLINICAL ISSUES

Patients with cerebral palsy are at an increased risk

Table I. Classification of Cerebral Palsy by type of lesion and main clinical characteristics[5].

	Type of involvement	Proportion of cases	Risk group	Clinical status
Spastic diplegia	Periventricular lesion	13-25%	Prematurity	Hypotonia followed by hypertonia and pyramidal signs in lower limbs with motor retardation
Spastic hemiparesis	Neonatal stroke Prenatal circulatory disorders and malformations	21-40%	Full-term and AGA infants	Motor asymmetry, early dominance, clumsy bimanual coordination, and abnormal postures; unilateral pyramidal signs; and asymmetric protective reaction
Spastic quadriplegia	Congenital infection, cerebral dysgenesis, and perinatal events	20-43%	SGA infants, but can occur in preterm infants	Pyramidal syndrome of upper and lower limbs, severe motor retardation, poor head control, cross spasticity in the lower limbs. Do not assist in the pull-to-sit maneuver.
Dyskinetic cerebral palsy	Thalamic, basal ganglia, and hippocampal lesions, reticular formation and cerebellum. HIE. Kernicterus	12-14%	Usually full-term	Hypotonia or hypertonia, abnormal postures, grimacing, and hypersalivation. Dyskinesia is more important at 2 years.
Ataxia	Early perinatal events, malformations, and genetic causes	4-13%	Usually full-term	Hypotonia, ataxia, and slow speech; they usually improve with age.

Table II. Gross Motor Function Classification Scale (GMFCS); Manual Assessment Classification Scale (MACS); Communication Function Classification Scale (CFCS) and Eating and Drinking Classification Scale (EDACS) function classification systems[22-25,30].

Functional Level	GMFCSGross Motor	MACS Manual	CFCS Communication	EDACS Eating
I	Walks without limitations	Handles objects easily	Sends and receives messages efficiently	Eats and drinks safely and efficiently
II	Walks with limitations but without assistance	Handles objects with reduced speed/ability	Efficient but slow	Effective with some loss of quality
III	Mobility aids crutch/walker	Handles objects with difficulty, needs help	Efficient with familiar people	Limitations to safety and efficiency
IV	Limitations to mobility. Motorized wheelchair	Handles a few objects in adapted situations	Inconsistent with relatives	Significant limitations to safety
V	Transported in a manual wheelchair	Does not handle objects	Seldom effective	Unable to eat or drink safely

of clinical comorbidities and those classified as having major functional impairment, GMFCS IV and V are particularly prone to severe complications leading to hospitalization and death. Such patients should be monitored with the aim of reducing morbidity and mortality. Respiratory complications often lead to hospitalization and death. Reduced chest expansibility, associated with increased respiratory secretions caused by bronchial inflammatory processes, gastroesophageal reflux, and microaspiration of gastric contents and saliva, are factors that contribute to the recurrence of repeat respiratory infections. Therefore, interventions that reduce the occurrence of saliva aspiration, such as the application of local drugs, botulinum toxin injections into the salivary glands, or even permanent sectioning of the innervation of these glands, can be recommended[27].

Treatment of gastroesophageal reflux is necessary to combat respiratory issues and because of the discomfort the reflux causes to the patient in addition to the prevention of the rare occurrence of Barrett's esophagus. Fundoplication may be recommended when lower esophageal sphincter dysfunction or the presence of hiatal hernia is proven. Gastrostomy may be indicated, depending on a combination of factors related to safety and efficiency when eating. Constipation and sphincter dysfunctions with enuresis or urinary retention are common problems, and the management of kidney health and neurogenic bladder is also part of the care regimen[28].

One of the clinical procedures with the greatest impact on the overall health of a person with cerebral palsy is the regular and preventive supervision of hip dislocation and progression of scoliosis, which is common in GMFC IV and V functional level patients. It is estimated that without proper supervision, 10%–20% of children with CP develop hip dislocation. Although a number of risk factors are known, some children may develop the condition even without risk factors. A series of studies is currently being published on the follow-up strategies for performing this supervision, which must be clinical and radiological, throughout the growth phase[29].

The follow-up routine is defined by the functional level measured according to the GMFCS, and outlines the following recommendations. First, for people with GMFCS I, radiographs

should not be routine unless the clinical examination reveals deterioration of the hip or spine. Second, in patients with GMFCS II, radiographs should be performed at 2 and 6 years. If the physical examination is normal at 8 years and the previous radiographs are also normal, a clinical examination should be performed every 2 years until the closure of the growth plates to define the need for additional radiological assessment. Third, in patients with GMFCS III-V, radiological examination should be performed as soon as the diagnosis of cerebral palsy is confirmed or suspected and annual radiographs should be taken up to 8 years. After this age, the interval between assessments should be determined individually. Children older than 8 years with normal X-rays and no clinical deterioration should undergo radiographs every 2 years until the growth plates close. Children with pure ataxia or athetosis at GMFCS level II or III may be excluded from subsequent radiological assessments if the first assessment is normal and the child does not present with clinical deterioration. The adoption of this routine in Scandinavia during the last decade brought about a dramatic reduction in surgical cases of hip dislocation, considerably reducing morbidity and costs.

The integration of differently abled individuals and their families into independent and productive living is a quality indicator for health services and the exercise of citizenship. The education system, which should ensure school inclusion for these patients, is part of this network.

CONCLUSIONS

Patients with the diagnosis of cerebral palsy are part of a group with complex clinical issues. They should be diagnosed early and have their functional and topographic disease classification established with a focus on evidence-based rehabilitation and supervision of overall health and of complications with a high risk of morbidity. Therefore, 1) prenatal and perinatal care; 2) early assessment of signs indicative of cerebral palsy by clinical examination, imaging, and the Prechtl method guarantees early inclusion in rehabilitation treatment; 3) correct performance of the patient's etiological, topographic and functional classification; 4) indication of rehabilitation methods based on scientific evidence, optimizing resources and personal investments; 5) attention to the clinical health of the child, especially respiratory, gastrointestinal and orthopedic issues; 6) treatment of neurological and behavioral comorbidities, special attention to the treatment of epilepsy, spasticity and pain; and 7) school inclusion measures, leisure, and social participation must be actively encouraged and defended, always aiming at independent living.

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