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ADVANCES IN PEDIATRICS

Cerebral Palsy

Diagnosis, Epidemiology, Genetics, and Clinical Update

Abimbola Michael-Asalu, MBBS, MPH[a],
Genevieve Taylor, MD[b], Heather Campbell, MD[b],
Latashia-Lika Lelea, MD, MPH, MSc[c],
Russell S. Kirby, PhD, MS[d,*]

[a]Department of Community and Family Health, College of Public Health, University of South Florida, 13201 Bruce B. Downs Boulevard, MDC56, Tampa, FL 33612, USA; [b]The University of North Carolina at Chapel Hill, 260 MacNider Building, CB# 7220, Chapel Hill, NC 27599-7220, USA; [c]University of Central Florida College of Medicine, UCF/HCA Consortium – Gainesville, North Florida Regional Medical Center, 6440 West Newberry Road, Suite 508, Gainesville, FL 32605, USA; [d]Strategic Area Faculty Lead for Population Health Science, College of Public Health, University of South Florida, 13201 Bruce B. Downs Boulevard, MDC56, Tampa, FL 33612, USA

Keywords

• Cerebral palsy • Diagnosis • Epidemiology • Genetics • Clinical management

Key points

- Cerebral palsy is one of the most common physical and developmental disabilities in childhood, with a prevalence of approximately 3 per 1000 births.
- Although preterm birth accounts for approximately 35% of cases of cerebral palsy, more cases occur among term births. Antepartum risk factors figure more prominently in cerebral palsy than peripartum complications.
- Although the cause and pathophysiology of cerebral palsy remain poorly understood, advances in molecular genetics and genomic research continually add to the knowledge base.
- Clinical management of children with cerebral palsy requires a multidisciplinary, family-centered approach, focusing not only on physical health and development but also on maintaining or improving the child's quality of life.

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*Corresponding author. *E-mail address:* rkirby@health.usf.edu

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INTRODUCTION

Cerebral palsy (CP) is a common physical and developmental disability varying in severity but with common developmental features [1]. CP was originally characterized by Little in 1861, and thoughts concerning its origins and clinical features have evolved in the 150 years since then. An international panel provided a consensus definition in 2006: "Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain" [2]. As one of the most common developmental disorders, many pediatric health providers encounter patients and their families with this condition. This update reviews methods for diagnosis, data regarding prevalence and risk factors, recent research on the genetics of CP, and current approaches to clinical management.

DIAGNOSIS OF CEREBRAL PALSY

The diagnosis of CP relies on a combination of neurologic assessment, neuroimaging findings, and recognition of clinical risk factors. Diagnosis is thus often complicated and delayed, and typically occurs at the age of 1 to 2 years or beyond [3]. In recent years, earlier and accurate diagnosis of CP has become possible and highly desirable, because it allows earlier initiation of therapies that may improve long-term outcomes during the period of rapid brain growth and neuroplasticity. Moreover, contrary to concerns that attempts at earlier diagnosis may lead to false-positive screens and create unnecessary parental stress, population studies have shown that parents generally prefer to know if their child has CP or is at high risk for CP sooner rather than later, so that they can start therapies that may optimize their child's development [4,5].

The pathways to diagnosis of CP differ depending on whether a child has identifiable risk factors for CP in the neonatal period, which result in earlier screening and closer developmental surveillance. A wide array of developmental screening tools and neurologic assessments have been used to aid in the diagnosis of CP among high-risk newborns. A recent review by a multidisciplinary, international group of CP experts focused on the following tools with the best predictive validity for detection of CP before 5 months of age: neonatal magnetic resonance imaging (MRI) (86%–89% sensitivity), the Prechtl Qualitative Assessment of General Movements (GMA) (98% sensitivity), and the Hammersmith Infant Neurologic Examination (HINE) (90% sensitivity) [6]. These investigators recommend that infants with newborn-detectable risk factors for CP undergo a standardized neurologic examination, motor assessment, and neuroimaging to help make the diagnosis, ideally before 5 months of age. The diagnosis of CP is made when an infant has evidence of motor dysfunction as well as either abnormal neuroimaging or a clinical history suggestive of risk. If a clinician suspects CP but is unsure of the diagnosis, Novak and colleagues (2017) recommend the use of the label "high risk for CP" in place of more general terms like "high risk for developmental delay" so that children can be appropriately referred for CP-specific early intervention therapies.

The diagnosis of CP in children who lack risk factors often occurs later in life, when parents or general pediatricians realize that they are not achieving their expected motor milestones. Signs that warrant specific evaluation for CP include the inability to sit independently by 9 months of age, the presence of asymmetric movements or limb preference, or the inability of an infant to bear weight on the plantar surface of the feet [6]. This evaluation should consist of a standard neurologic examination (eg, the HINE); a neuromotor assessment; and, if possible, neuroimaging by MRI to identify brain lesions that may corroborate the diagnosis. Useful standardized neuromotor assessment tools in this population include the Developmental Assessment of Young Children, the Alberta Infant Motor Scale, the Motor Assessment of Infants, the Neuro Sensory Motor Development Assessment, and the Test of Infant Motor Performance [6].

Neuroimaging

Numerous studies have reported on the predictive validity of MRI and cranial ultrasonography for the diagnosis of CP, with MRI generally accepted as the more sensitive imaging modality [7–9]. Neonatal MRI findings that are particularly suggestive of high risk for CP include white matter injury (eg, cystic periventricular leukomalacia [CPVL], periventricular hemorrhagic infarction, progressive ventriculomegaly, neonatal stroke), injury to deep gray matter structures such as the basal ganglia, cerebellar hemorrhage, and developmental brain malformations (eg, lissencephaly, microgyria, cortical dysplasia) [5,6,10]. Some children with CP have normal MRI or cranial ultrasonography in the neonatal period. Clinicians may consider repeating the MRI closer to 2 years of age to detect more subtle signs of white matter injury that may have been missed on earlier neuroimaging. Consideration should also be given to underlying genetic or metabolic causes of CP for children with normal neuroimaging but persistent neurologic abnormality [8].

Imaging for patients with CP can be important not only in differentiating between various forms of brain injury leading to CP but also as a prognostic assessment to determine the risk of neurodevelopmental disability [11]. Using MRI at the time of diagnosis of CP can determine the type and extent of brain damage [11]. Vossough's [11] 2017 analysis of several studies reported that 50% to 94% of infants who had changes in the basal ganglia seen on MRI developed CP, intellectual disability, and seizures at 1 to 2 years of age. The morphology of the brain damage is strongly associated with the stage of brain development at which the injury or insult occurred (Jacobsson and Hagberg [12], 2004). Cerebral malformations occur during the first 20 weeks of pregnancy, periventricular leukomalacia (PVL) occurs between 24 and 34 weeks, and the damage to gray matter occurs after 34 weeks [12].

Neuromotor assessment

Although many neuromotor assessment tools exist and have been shown to have varying abilities to accurately identify children with CP, this article focuses on the 2 assessments that have been identified as having the highest

predictive value for CP detection in early infancy [6]: the GMA and the HINE examinations. The accuracy of these motor assessment tools improves with serial examinations, which allow clinicians to establish an overall developmental trajectory for a given child, as opposed to relying on an assessment performed at a single point in time.

General movements assessment

The patterns of spontaneous movements in infants have long been studied as a way of identifying children with motor dysfunction [13]. Heinz Prechtl, an Austrian neurologist, developed the GMA, a tool that uses specific descriptions of the spontaneous movements of infants which change in a predictable way during normal development. A recent systematic review of the GMA identified 2 specific movement patterns that are highly sensitive and specific for the diagnosis of CP: cramped synchronous general movements (70% sensitivity, 90% specificity), characterized by rigid contraction and relaxation of the infant's trunk and extremities; and absent fidgety movements (97% sensitivity, 89% specificity), characterized by a lack of the normal small-amplitude fidgety movements that should be present in newborns from 10 to 20 weeks corrected age [14]. Other systematic reviews have also reported a high sensitivity and specificity of abnormalities on the GMA for the prediction of CP among high-risk newborns [7]. The GMA should be performed by providers who have completed standardized training to ensure accuracy and high interrater reliability [15].

Hammersmith infant neurologic examination

This examination has also been evaluated for its ability to aid in the diagnosis of CP. This tool, originally developed as a standardized neurologic examination to help detect movement disorders in infants aged 2 to 24 months, consists of 26 scored items that assess an infant's cranial nerve function, posture, movements, tone, and reflexes. A recent literature review found that a global HINE score less than 56 at 3 months and less than 65 at 12 months was highly sensitive and specific for the development of CP. Moreover, scores less than 40 were invariably associated with later severe nonambulatory CP [16]. Hay and colleagues [17] found that adding an asymmetry score, a tally of items on the neurologic examination that are different between right and left sides, to the overall HINE score allowed a reliable diagnosis of hemiplegia with a sensitivity and specificity of 91.8% and 100% respectively.

Differential diagnosis

A range of neurologic abnormalities from a variety of causes may contribute to the clinical diagnosis of CP. A small subset of children diagnosed with CP may have motor dysfunction related to an underlying neurogenetic or metabolic disorder. Some clinicians recommend genetic testing for children who have normal neuroimaging, a concerning family history, progressive symptoms, a lack of identified clinical risk factors for CP, or who otherwise do not fit the typical pattern of CP [8,18]. Testing may include chromosomal microarray,

targeted gene sequencing, whole-exome, and/or whole-genome sequencing depending on the clinical scenario [18,19]. A recently published study by Takezawa and colleagues [20] found that 9 out of 17 cases (52.9%) of full-term children with a diagnosis of CP and nonspecific MRI findings had a pathogenic or likely pathogenic candidate gene variant found on whole-exome sequencing. Decisions concerning genetic testing should be made in conjunction with a pediatric geneticist.

Pediatricians should also be aware of another diagnosis that is being recognized with increasing frequency, particularly among preterm and very-low-birthweight survivors: developmental coordination disorder (DCD). This disorder is characterized by problems with coordination, balance, gross and fine motor skills, and visual-motor integration [21–23] without the neurologic abnormalities seen in children with CP. Although children with DCD generally have more mild motor impairment compared with children with CP, this disorder can have a significant impact on a child's functional abilities and quality of life. Children with DCD should be referred to physical and occupational therapy to address motor skill development.

CLASSIFICATION OF CEREBRAL PALSY

CP is a heterogeneous disorder encompassing a range of clinical phenotypes and types of motor impairments. Traditionally, CP has been classified by motor type, topography of motor impairment, or by degree of functional impairment. Four main motor types of CP have been described in the literature: spastic (by far the most common form, characterized by hypertonicity and muscular resistance to movement), dyskinetic (presents with athetosis or dystonia), ataxic (primarily presents with difficulties with coordination), and hypotonic (decreased muscle tone) CP [24]. Because of low interrater reliability and the tendency for the type of motor impairment to evolve over time or involve features of multiple subtypes, some CP registers simplify designation to spastic versus nonspastic CP [21]. In terms of topography, the term hemiplegia generally refers to involvement of 1 side of the body. Diplegia refers to involvement of the lower extremities to a greater extent than the upper extremities, and quadriplegia refers to involvement of all 4 extremities (although there may be differences in severity of involvement). It is important to distinguish between unilateral and bilateral neuromotor involvement because treatment strategies may differ.

The gold standard for describing motor function is the Gross Motor Function Classification System (GMFCS) [25], with motor classification descriptions that change slightly based on the age of the patient. The GMFCS uses an ordinal scale to provide clinicians with an assessment of the child's level of motor function at present, as well as what mobility aids or equipment the child may need in the future. It is generally thought that the GMFCS is not reliable until after age 2 to 5 years, so clinicians should be cautious about using children's GMFCS levels in early childhood to prognosticate their long-term functional outcome [6,26].

EPIDEMIOLOGY OF CEREBRAL PALSY

Because CP is often diagnosed in infancy or early childhood, it is difficult to obtain reliable prevalence estimates. Data from birth certificates or newborn hospital discharges underenumerate cases of CP. Birth certificates must be filed within 3 to 5 days after birth, before most diagnoses, and many diagnoses occur in specialty clinics or outpatient settings and are not captured in hospital discharge databases. Population surveillance using registries, active case-finding, or representative sample surveys is required to obtain population-based estimates. In the United States, the Autism and Developmental Disabilities Monitoring (ADDM) Network estimates the prevalence of CP among children 8 years of age in several catchment areas. Overall prevalence declined from 3.5 per 1000 8-year-old children in 2006 to 2.9 per 1000 in 2010 [27]. This incidence compares with estimates of 2.6 to 2.9 per 1000 children 2 to 17 years old from the 2011 to 2012 National Survey of Children's Health and the 2011 to 2013 National Health Interview Survey, respectively [28].

Risk factors

Although numerous risk factors for CP have been identified, many children with these risk factors (for example, premature birth) do not go on to develop CP, and nearly 50% of children who are ultimately diagnosed with CP are term-born children who have no identified risk factors in the neonatal period [24].

A 2013 systematic review described the following risk factors as significantly associated with CP in term infants: neonatal respiratory distress syndrome, meconium aspiration, instrumental or emergency cesarean section, birth asphyxia, neonatal seizures, hypoglycemia, and neonatal infections [29]. For many risk factors identified through epidemiologic investigation, direct causal relationships are not clear. For example, respiratory distress syndrome is caused by surfactant deficiency or dysfunction, which is overwhelmingly caused by prematurity. Term infants with respiratory distress syndrome may have inaccurately estimated gestational age and their underlying relative prematurity may be the true risk factor for CP, therefore this article does not discuss respiratory distress syndrome separately from prematurity. Similarly, instrumental or emergency cesarean section are likely associated with birth asphyxia and may not represent independent risk factors for development of CP. Hypoglycemia has not been definitively linked to CP and is not discussed further.

Maternal risk factors

Maternal sociodemographic characteristics and reproductive history are associated with CP. Maternal age less than 20 years or greater than 34 years, low maternal educational attainment, numerous pregnancies, nulliparity, short or long interpregnancy interval, and previous history of intrauterine fetal demise are risk factors for CP [12,30]. Although the crude odds for CP are higher among black non-Hispanic births compared with white non-Hispanic births,

after controlling for gestational age as well as other maternal characteristics and socioeconomic factors black non-Hispanic infants were at slightly reduced risk for CP (adjusted odds ratio, 0.87; 95% confidence interval, 0.77–0.99) [30]. Mothers who have a child with CP have a higher risk of having another child with CP [12].

Antenatal risk factors

Assisted reproductive technology. Neonates conceived by in vitro fertilization (IVF) have an increased risk of CP because of the high frequency of twins, low birth weight, and prematurity [12]. Although the increased risk of CP in children born after IVF is most likely secondary to the increased risk of preterm birth and low birth weight, this is not entirely the case. The incidence of CP is higher in monozygous twins than it is in heterozygous twins, and this is thought to be caused by the anastomosis of the vasculature in the placenta in monozygotic twins [31]. If 1 twin dies in utero, the surviving twin may develop brain injury because of the release of thromboplastic substances or shifts in hemodynamics [31]. The death of that twin can also affect the neurologic development of the surviving twin, and the surviving twin has a 20% overall risk of cerebral impairment [12].

Intrauterine growth restriction. Intrauterine growth restriction (IUGR) is thought to be associated with CP because it affects brain development, causes restriction in gray matter development, and increases neonatal morbidity and mortality [12]. IUGR has various causes, some known and some unknown. IUGR is most commonly caused by poor implantation of the placenta to the uterine wall leading to placental insufficiency, causing poor fetal growth and potentially leading to abnormal brain development [32]. In term neonates, IUGR is associated with up to a 10-fold to 30-fold increase in the risk of developing CP [32]. Studies in growth-restricted animal models have shown a reduction in oxygen delivery to the brain and delayed growth of the forebrain and cerebellum [12].

Intrauterine infection. Maternal fever and infection are associated with a significantly increased risk of CP [32]. Maternal infection during pregnancy can affect the fetal brain, causing white matter damage and thus increasing the risk of CP [32]. It is possible that some children with CP who do not have any recognized risk factors for CP development may have experienced an intrauterine infection. Many viral and bacterial infections have mild or nonspecific maternal signs and symptoms and go undiagnosed, therefore not giving any indication for the need to send the placenta to pathology after delivery for further inspection that may indicate an inflammatory disorder [32]. Similarly, infections in neonates may show no clinically detectable signs at birth but may present as CP, developmental delay, or sensorineural hearing loss later in life [12]. TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) infections are well-known infections that can occur in utero and are associated with long-term neurodevelopmental disabilities, including CP [12]. These infections account for about 5% or less of CP cases in industrialized countries [12].

Chorioamnionitis is an independent risk factor for CP and is associated with a 4-fold increased risk of CP in term infants [33]. It is thought that placental infection may cause or exacerbate brain injury because of hypoxia-ischemia, which leads to an increase in inflammatory cytokine levels in the fetus [33]. High levels of inflammatory cytokines have been implicated in the pathogenesis of preterm birth, as well as in the development of intraventricular hemorrhage and PVL in preterm children [12]. In children born with CP, an increased prevalence of abnormalities in the placenta and cord has been observed, highlighting the importance of obtaining placental histology as well as arterial cord gases in those infants that are delivered in poor condition [32].

Peripartum risk factors

Premature birth. Preterm birth (<37 weeks' gestation) is one of the most important risk factors for CP [12]. Children born prematurely account for about 35% of cases of CP, with higher prevalence of CP at earlier gestational ages [32]. With advancements in neonatal care, babies born very premature are more likely to survive; however, extreme prematurity puts them at an increased risk for CP because of underdevelopment of the brain as well as lack of lung maturity increasing their risk of postnatal hypoxia [9]. PVL and intraventricular hemorrhage (IVH) are the two major disorders affecting very preterm infants that are associated with CP [31].

Meconium aspiration. Meconium aspiration may occur when the fetus has its first bowel movement, referred to as meconium, while in utero; when the neonate is born and starts breathing there is increased risk of aspiration caused by fluid and secretions present in the mouth at birth. If the neonate aspirates the meconium-stained amniotic fluid, this can lead to respiratory distress and aspiration pneumonia, which can lead to hypoxia, pulmonary hypertension, and cardiorespiratory failure in severe cases [31]. Among term infants experiencing severe meconium aspiration, 41% may develop mild deficits such as speech delay or mild hypotonicity without motor or cognitive deficits, 7% may develop CP, and 14% may develop other severe long-term developmental disabilities [34].

Hypoxic-ischemic encephalopathy. Birth asphyxia is a much less frequent cause of CP than was previously thought. Birth asphyxia may account for less than 3% to greater than 50% of cases of CP depending on how birth asphyxia is defined [35]. The definition of asphyxia was previously less rigorous and often referred only to the need for oxygen after birth [36]. The term hypoxic-ischemic encephalopathy (HIE) refers more specifically to neonatal encephalopathy resulting from an acute intrapartum hypoxic event. The diagnosis of HIE is made through a combination of neurologic examination findings and biochemical evidence of metabolic acidosis on cord blood gas or arterial blood gas obtained within an hour of birth. Other supporting evidence for HIE may include low Apgar scores, seizures, and brain MRI findings suggestive of an ischemic insult to the watershed areas of the brain or to the deep structures,

such as germinal matrix hemorrhage, which is caused by reperfusion of ischemic brain tissue leading to increased venous pressure and rupture of weak capillaries, PVL, passive ventriculomegaly, and thinning of the corpus callosum [37]. Other findings include electroencephalogram findings, or evidence of multisystem organ failure [38]. An Australian study of a cohort of 235 neonates with CP found that in only 1% could CP be associated with birth asphyxia when criteria from the American College of Obstetricians and Gynecologists (ACOG) and the international CP task force were used in a cohort of 213 infants of the 235 cases [39]. Although other studies report slightly higher risk, this risk may be mitigated by the use of therapeutic hypothermia [40]. Davidson and colleagues [41] found that recent hypothermia treatment protocols showed a significant improvement in outcomes; however, it is only partially effective, and more research is needed to further reduce the burden of injury. The hypothermia protocols advise systemically cooling patients with HIE within the first 6 hours of life to 34.5° ± 0.5°C for cooling the head, or 33.5° ± 0.5°C for whole-body cooling with continued treatment for 48 to 72 hours [41].

Neonatal seizures. Neonatal seizures may occur in infants with HIE but also may be a presenting sign of perinatal stroke or central nervous system (CNS) infection, both of which are associated with increased risk of CP. About 30% of infants with perinatal arterial ischemic strokes develop CP, with unilateral spastic CP as the most common subtype. A 2018 analysis of 188 infants with perinatal arterial ischemic stroke suggests the middle cerebral artery is most commonly involved, and findings on initial MRI correlate with later neurodevelopment [42].

Risk factors for postneonatally acquired cerebral palsy

Postneonatal CP is often described as injury outside of the neonatal period and before 5 years of age, accounting for fewer than 10% of CP cases [39,43]. Almost all cases of postneonatal CP are caused by head trauma, near-drowning events, or meningitis [39,44]. In the United States, CP cases with documented postneonatal causes accounted for 6% to 10% of all cases in the ADDM Network data [27]. Many postneonatally acquired cases of CP could be prevented through public health programs designed to reduce likelihood of child injury.

PREVENTION

Although many neonatal measures to prevent CP have been studied, very few have been shown to be effective [43]. Of 96 randomized controlled trials reviewed in a 2018 Cochrane Review, therapeutic hypothermia and caffeine were the only effective interventions. This article briefly reviews several of the more commonly used interventions.

Therapeutic hypothermia

Therapeutic hypothermia initiated within 6 hours of birth and lasting 72 hours decreases the risks of CP in term and late preterm infants with moderate to

severe HIE by approximately one-third. Hypoxic-ischemic brain injury is characterized by several cellular-based events, which include failure of the Na+/K+ ATP-dependent pump from deranged metabolism; accretion of excitatory amino acids (EAAs); production of cytotoxic oxygen free radicals; and generation of the reactive oxygen species nitric oxide, which leads to cell membrane and cytosol organelle damage. The cumulative effects of these events is neuronal depolarization and cerebral edema. Further complicating brain swelling is the disruption of the blood-brain barrier with associated leaks. Hypothermia has been shown to reduce cerebral metabolism, accumulation of EAAs, suppression of nitric oxide, and the leakiness of the blood-brain barrier [45]. This neuroprotective effect is likely caused by the inhibition of a variety of inflammatory and apoptotic cellular processes that occur following an ischemic insult. It has been estimated that for every 8 infants treated with therapeutic hypothermia, 1 case of CP is prevented. Whole-body cooling and selective head cooling with mild systemic hypothermia seem to be equally effective [40].

Recent studies have sought to refine therapeutic hypothermia practices. An attempt to optimize therapeutic hypothermia suggested cooling for longer than 72 hours, and cooling to lower than 33.5°C did not reduce death or moderate to severe disability at age 18 months [46]. Another study supported late initiation of therapeutic hypothermia from 6 to 24 hours after birth, reporting 76% probability of any reduction in death or disability [47]. The investigation of potential adjuvant therapies is a subject of active research with ongoing studies evaluating the used of xenon, erythropoietin, antiepileptic drugs (such as topiramate), melatonin, magnesium sulfate, and umbilical cord stem cells [43]. Another current clinical trial is investigating therapeutic hypothermia in preterm infants from gestational age 33 to 35 weeks with moderate to severe HIE [48].

Caffeine

Preterm infants are often treated with caffeine for apnea of prematurity or to facilitate extubation. Caffeine, like other methylxanthines, increases respiratory drive and decreases the number of apneic events. The Caffeine for Apnea of Prematurity Trial compared caffeine versus placebo in very-low-birth-weight infants initiated during the first 10 days of life [49]. Post hoc analysis of the study suggests caffeine reduces the incidence of CP in very-low-birth-weight infants treated with caffeine specifically to facilitate extubation (relative risk, 0.54) [50]. However, post hoc analysis of the same study suggested no clear differences in CP following overall treatment or prophylaxis with caffeine for apnea of prematurity [43].

Avoidance of early postnatal corticosteroids

Postnatal corticosteroids are used to decrease inflammation in order to decrease rates of bronchopulmonary dysplasia and facilitate extubation. Despite the pulmonary benefits, early (<8 days) use of dexamethasone after birth has been associated with increased rates of CP [43,51]. The 2010 American Academy of Pediatrics policy statement on postnatal corticosteroid use for

bronchopulmonary dysplasia recommends the avoidance of early high-dose dexamethasone because of the association with CP [52].

The risks and benefits of postnatal corticosteroids must be balanced for individual patients. A 2005 meta-analysis notes that among infants with less than 35% risk of bronchopulmonary dysplasia, corticosteroid treatment significantly increased the chance of death or CP, but among infants with more than 65% risk of bronchopulmonary dysplasia, treatment decreased the chance of death or CP [53]. In a recent randomized controlled trial, early low-dose hydrocortisone decreased survival without bronchopulmonary dysplasia and no association with CP was noted [54]. The risks and benefits of hydrocortisone remain unclear in meta-analyses and is an area of ongoing research [43,55].

Antenatal steroids

In a population-based case-control study by Jacobsson and colleagues [56], antenatal corticosteroids were associated with a decrease in the risk of CP. Betamethasone has been shown to reduce PVL in preterm infants; however, dexamethasone has not shown the same outcome [56]. Betamethasone helps to reduce the severity of respiratory distress syndrome as well as decrease the risk of IVH [57].

Magnesium

Administration of magnesium sulfate during the antenatal period is important for neuroprotection in preterm infants [58]. Magnesium given before preterm delivery is associated with a significant reduction in the risk of CP at 2 years of age [58]. Magnesium sulfate reduces inflammatory effects by reducing oxidative stress as well as proinflammatory cytokines [58]. Based on Chollat and Marret's [58] (2018) findings, the use of magnesium sulfate antenatally did not result in adverse neonatal outcomes, including respiratory distress, the need for mechanical ventilation, and necrotizing enterocolitis. However, reduction in CP with antenatal use of magnesium sulfate occurred only in infants of nonobese women, which suggests that adjustment of magnesium dosage based on maternal weight may be required for adequate neuroprotection.

PATHOGENESIS

The cause of CP is multifactorial and remains incompletely understood. CP can be a result of a brain insult or injury that occurs during the prenatal, perinatal, or postnatal periods. The old views of CP being caused by asphyxial injury during delivery are not supported by evidence [31]. Platt and colleagues [31] (2017) found that a prenatal cause was most likely to be responsible for about 50% to 55% of quadriplegic CP, a perinatal cause in 30%, and a postnatal cause in 15% to 20%. Different brain structures show varying levels of susceptibility to insult or injury at different gestational ages, which further supports the idea that CP can develop at any point through pregnancy caused by multiple injuries throughout development. Despite advances in diagnostic techniques, a specific cause is found for no more than 50% to 75% of CP cases.

Many pathways can lead to development of CP. Intrauterine hypoxia affecting the fetal brain is one of the most common prenatal risk factors associated with CP [31]. Hypoxia in utero typically occurs because of placental insufficiency toward the end of pregnancy or because of anomalies in the placenta and cord, or placental abruption leading to decrease in oxygen delivery to the fetus [31]. During the second and third trimesters of pregnancy, the main causes of CP are placental problems or other problems that can cause chronic endometrial hypoxia [31]. Chronic hypoxia of the fetus over a long period of time can lead to an abnormal head circumference in the fetus, indicating abnormal brain development [31]. Fetal hypoxia can occur during labor as well; however, it requires severe hypoxia or prolonged anoxia to cause deterioration in the CNS because of the protective mechanisms the fetus has that protect it from repeated episodes of mild hypoxia during contractions and the process of labor [31].

Another hypothesis regarding the pathogenesis of CP is the inflammatory/cytokine hypothesis. It suggests that when maternal infection or fever occurs it causes an increase in cytokine levels in the fetal blood and brain and these cytokines can cause periventricular white matter damage as well as preterm birth [12]. Interleukin (IL)-6 and IL-8, as well as other proinflammatory cytokines, have been found to have an association with CP in preterm children [12]. IL-6 in the amniotic fluid has been shown to be related to intraventricular hemorrhage and increased levels of IL-6, IL-1 alpha, and TNF-alpha are related to PVL [12].

THE GENETICS OF CEREBRAL PALSY

CP is considered a complex disease because of the convoluted interactions between environmental and genetic factors. Although the diagnosis and classification of CP are mainly clinical, and its cause varies greatly, there is considerable evidence that many cases of CP have genetic underpinnings [59]. The prevalence of congenital anomalies in children with CP is about 11% to 32%, significantly higher than the general population prevalence of 2% to 3% [60]. Higher rates of CP have been observed in monozygotic than in dizygotic twins, and there is a 2 to 5 times higher risk of CP in consanguineous compared with outbred families [60].

Genomic insights are a gateway to understanding the neurogenetic routes that cause CP and have the potential to influence patient care. Suspicion of CP's genetic basis stems from its syndromic presentations and its association with twinning (especially the monozygotic variant), consanguinity, and congenital anomalies [61–63]. Human genome sequencing, including whole-exome sequencing, X-chromosome exome sequencing, and chromosomal analysis in population studies, has led to the identification of various gene mutations that are linked to the development of CP, indicating that no single CP gene exists but that multiple genes are involved [64,65]. This genetic heterogeneity underscores the complexity of the contribution of genes to the development of CP.

Numerous Mendelian disorders inherited as autosomal dominant, recessive, as well as X-linked can present with characteristics that are distinct to CP. Some of these conditions are rare as individual disorders, but others are not all that uncommon as a group and should be taken into account when assessing children with CP [60]. Several known single-gene causes of CP were discovered through studying families with 2 or more individuals with CP; these include mutations in the KANK1, AP4M1, and GAD1 genes [32].

Plausible genetic variants associated with CP can be grouped into several categories, which are discussed later.

Single-gene mutations

The many genes that have been identified as being related to CP encode proteins with a variety of functions [66]. KANK1 controls actin polymerization and its heterozygous deletion often leads to a spastic CP phenotype [62]. Also linked to spastic CP are mutations in subunits of the Adaptor protein 4 complex (subunits B1, E1, M1, and S1), which are responsible for vesicle formation and selection of inclusion molecules to be transported across cells [67]. ADD3 mutation has also been linked to spastic CP and its function is related to that of KANK1 [64]. The GAD1 gene is responsible for cytogenetic production of the gamma-aminobutyric acid neurotransmitter and its homozygous mutation causes CP [61,62]. ITPR1, KCNC3, and SPTBN2 all code specific ion channels in body cells and their mutations are linked to ataxic CP [64,68].

Candidate cerebral palsy genes

According to McMichael and colleagues [69], gene mutations thought to be associated with CP together with numerous newly identified associated genes were found in 14% of unselected CP cohorts using whole-exome sequencing. De novo candidate CP genes identified were AGAP1, JHDM1D, MAST1, NAA35, RFX2, and WIPI2, whereas known hemizygous X-linked variants were L1CAM and PAK3 and, in novel genes, CD99L2 and TENM1, inherited from an unaffected mother. This diverseness implies that newer and less familiar mutations can potentially contribute to the development of CP, further emphasizing the complexity of the genetics in CP etiopathogenesis.

Copy number variants

Copy number variants (CNVs) are variations in the structure of DNA sequences, which can be duplications or deletions greater than 1000 base pairs. CNVs can either occur de novo (observed in an affected individual and not in the parents of the individual) or inherited from either parent, who can be affected or not affected. This variability in expressivity makes it difficult to determine the link between a single gene and CP. Various CNVs have been associated with specific subclasses of CP, of which several percentages in different studies have either occurred de novo or been inherited. CNVs that have been associated with the development of CP include: GRIK2, LAMA1, DMD, PTPRM, and DIP2C, associated with hemiplegic CP [70]; SPAST, MEF2C, WDR45, KANK1, NKX2-1, and tripXq28 [62,64]; PARK2, PACRG

and HSPA4, WNT4, RAPGEF1 [59,64]; MC2R, CTNND2, SPG6/NIPA1, associated with spastic paraplegia; and DAAM1, MCPH1, NIPA2 [71].

Single nucleotide polymorphisms

Single nucleotide polymorphisms refer to a substitution of nucleotide base pairs on specific positions in a gene and has been implicated in heterogeneity seen in different populations. It is also responsible for occurrence of some diseases (cystic fibrosis, sickle cell disease) and differences observed in susceptibility to diseases processes and responses to illnesses and medications. Although several studies have tried to find associations between CP and several single nucleotide polymorphs, no strong associations were found, and conflicting results abound across studies [64]. The link between mutations in genes causing hereditary thrombophilia (eg, antithrombin, proteins C and S) and CP as a result of its tendency to cause hypercoagulative states and therefore perinatal stroke and CP was small [72]. A case-control study of more than 1400 Chinese participants found that IL-6 gene polymorphisms on IL-6 synthesis and the risk of CP was related to sex and gestational age [73].

As study into the neurobiology of CP continues, the use of lower eukaryotes, as opposed to current large-animal models, seems to be the way forward. These lower eukaryotes have a high percentage of gene/protein analogues to humans, are less costly, and are more genetically pliable in nature, providing potent insights into how CP-associated variations in human gene/proteins affect normal physiology and cause disorders [64]. Overall, a thorough understanding of the interplay between genes and environmental risk factors on the clinical manifestations of CP will require more studies of larger populations. This research should be accompanied by comprehensive evaluations of their applicability in prenatal diagnosis and prevention, as well as for clinical diagnosis and management.

MANAGEMENT OF CEREBRAL PALSY

Historically, many interventions, ranging from activity-based rehabilitation interventions to use of antispasticity medications, have been used to ameliorate symptoms and improve motor outcomes in children with CP. However, high-quality evidence about the efficacy of these interventions is largely lacking, because few interventions have been rigorously studied [74,75]. Novak and colleagues [74] conducted a systematic review in which they deemed the following interventions effective: botulinum toxin, diazepam, or selective dorsal rhizotomy for muscle spasticity; casting to improve ankle function; hip surveillance to maintain hip joint integrity; goal-directed therapies based in the home; bisphosphonates to improve bone density; pressure care to reduce risk of pressure ulcers; and anticonvulsants if needed for seizure disorders. Goals Activity Motor Enrichment (GAME) is a specific early intervention program that involves goal-directed activities and parental coaching and has been shown in a randomized trial to improve motor and cognitive skills of children with CP at 1 year of age compared with usual care [76]. There is robust evidence that

infants with hemiplegia who receive early constraint-induced movement therapy, which encourages use of the affected extremity by restraining the unaffected one, improves hand functioning, at least in the short term [77]. Evidence for other intervention strategies continues to evolve, but experts advocate early initiation of therapies as soon as signs of CP are recognized in order to optimize motor development during the period of neuroplasticity in early childhood.

The management of CP requires a multidisciplinary approach and clinicians must also address other comorbidities that may coexist with motor impairment. Children with CP may be followed by a range of specialists, including orthopedic surgeons, urologists, neurologists, physiatrists, gastroenterologists, sleep medicine specialists, and developmental pediatricians, in addition to physical therapists, occupational therapists, developmental therapists, speech therapists, and feeding specialists.

Addressing quality of life in patients with cerebral palsy

Much of CP management has focused on improving motor function, but an understanding of what affects quality of life most is important when devising care plans. Quality of life is often evaluated using the framework of the World Health Organization's International Classification of Functioning, Disability and Health, which includes the following domains: body structure and function, activity limitation, participation, environmental factors, and personal factors [36]. Many of these topics were addressed by a recent systematic review describing comorbidities in children with CP. Common comorbidities, in declining level of frequency, included pain, inability to walk, hip displacement, bladder control problems, sleep disorders, dribbling, and dependence on tube feeding [78]. The high percentage of children with pain is especially striking, because pain is often associated with poor quality of life across domains [79]. Associated developmental and behavior impairments included intellectual disability (1 in 2), inability to talk (1 in 4), epilepsy (1 in 4), behavior disorder (1 in 4), blindness (1 in 10), and deafness (1 in 25) [78].

Some clinicians assume children with CP have worse quality of life than their typically developing peers. Quality-of-life assessments done in 500 children with CP aged 8 to 12 years across Europe evaluated self-reported quality-of-life measures in domains of physical well-being, psychological well-being, moods and emotions, self-perception, autonomy, relationships with parents, social support, school environment, financial resources, and social acceptance. Self-reported quality-of-life scores were broadly similar to those of typically developing children except for equivocal differences in schooling and physical well-being in children with severe motor impairments [80].

Quality of life is most difficult to assess in severely affected individuals with impaired communication. For these individuals, assessments must rely on information from caregivers. When comparing parent-reported quality of life for children with CP in Europe, poor gross motor function and low intelligence

quotient were associated with low quality of life in most domains. However, parents of less severely impaired children rated the following domains lower than parents of children with very severe impairments: moods and emotions, self-perception, social acceptance, and school environment [81]. Caregiver assessments may be influenced by confounding factors. For example, high levels of parental stress correspond with poor parent-reported quality of life in all domains [81].

Ability to complete activities of daily living and function within society are important domains affecting an individual's quality of life. Although CP is caused by a fixed nonprogressive neurologic injury, an individual's motor performance and daily activity performance often improves over time, although at a slower pace than typically developing individuals. A 2018 study tracked motor performance in 421 individuals aged 1 to 20 years and reported the age at which individuals reached 90% of the average maximal performance level [82]. Individuals with CP who were able to walk (GMFCS levels I to III) continued to improve in motor performance until age 6 to 8 years. For those without intellectual disability who were able to walk, limits of daily activity performance were similar to typically developing peers, but it took longer for individuals with CP to achieve these limits. These individuals continued to improve through age 11 to 14 years (self-care activities), 26 to 32 years (domestic activities), and 22 to 26 years (community activities). In comparison, typically developing individuals reach 90% of the average maximal performance level for self-care, domestic activity, and community activity at about 7, 18, and 15 years of age, respectively. Individuals who are severely affected functionally (GMFCS IV and V) had poorer motor performance and attained significantly lower limits of daily activity performance. Individuals with CP and intellectual disability also reached lower maximal daily activity performance levels and at an earlier age than typically developing peers [82].

SUMMARY

CP is a heterogeneous disorder with many well-recognized risk factors in the prenatal, perinatal, and early postnatal periods. CP is the most common physical disability of childhood, and all pediatricians should be aware of the general strategies for diagnosis and treatment. The diagnosis may be made in infants as early as 6 months of age through a combination of neurologic assessment, neuroimaging findings, and recognition of clinical risk factors. Management of CP and its associated comorbidities is complex and requires a multidisciplinary approach. Further research is needed to identify strategies for prevention of CP and to inform clinicians about which interventions are most effective in improving the functional outcomes of children with CP.

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