Chapter 1

Definition, Epidemiology, and Etiological Factors of Cerebral Palsy

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Additional information is available at the end of the chapter

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Abstract

CP is not a diagnosis but an "umbrella term for many clinical descriptions. It refers to a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorerders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition. First description was made in 19th century by William Little. CP prevalence is generally reported around 2-3 per 1000 live births in both developed and developing countries (even if for very different reasons). Additionally for term children CP prevalence is 1 per 1000 live births. This rates are 6-10 times higher in preterm birth. The etiology of CP has been reported very diverse and multifactorial as prenatal, perinatal and postnatal. The causes and risk factors are congenital, genetic, inflammatory, infectious, anoxic, traumatic and metabolic. Knowledge of the epidemiology and etiology of cerebral palsy is important. Thus, at least in some cases, early diagnosis and prevention can be achieved.

Keywords: Cerebral Palsy, Definition, Epidemiology, Etiology, Risk factors

1. Definition

Cerebral palsy (CP) is a well-recognized neurodevelopmental condition beginning in early childhood and persisting throughout the lifetime. It was first reported by William little, who was an orthopedic surgeon, in 1843 as cerebral paresis [1, 2]. Little focused on joint contractures and deformities resulting from long-standing spasticity and paralysis. Additionally, he indicated that the cause of the spasticity and paralysis was often due to damage to the brain during infancy and, specifically, preterm birth and perinatal asphyxia [3].

The most comprehensive study until then was published in 1862 by William Little. The association between a large number of patients' clinical presentation and their birth history as recalled by the family was described in this study. Little differentiated between the congenital deformities observed at the time of birth, such as talipes equinovarus, and the limb deformities that developed subsequently to preterm, difficult, or traumatic births, which he termed as spastic rigidity. It was described as a disorder that appeared to strike children in the first year of life, affected developmental skill progression, and did not improve over time [4].

Then, Sarah McNutt described that it continued to raise the profile of the risks of long-term disability arising from birth trauma [5]. At the end of the nineteenth century, Sigmund Freud suggested that CP might be rooted in the brain's development in the womb and related aberrant development to factors influencing the developing fetus [2, 6, 7]. In addition, in the early 1920s, some 30 years after Freud's comments, an American orthopedic surgeon made the next major contribution for understanding of CP [8].

In the twentieth century, newer documented concepts of cerebral palsy have been defined. Mac Keith and Polani [1, 8] described CP as "a persisting but not unchanging disorder of movement and posture, occurring in the early years of life due to a nonprogressive disorder of the brain, the result of interference during its development." In 1964, Bax [9] reported a description of CP suggested by an international working group that has become a classic and is still used. It was expressed that CP is a disorder of movement and posture due to a defect or lesion of the immature brain. Although this definition is usually all that is cited by authors, some additional comments were added by Bax: "For practical purposes it is usual to exclude from cerebral palsy those disorders of posture and movement which are of short duration, due to progressive disease or due solely to mental deficiency." Bax and his group felt that this simple sentence can be readily translated into other languages and hoped that it may be used universally. At that time, it was felt wiser not to define completely what they meant by immature brain, as any such description may be restricted services to those in need. Like its predecessors, this formulation of the CP concept placed an exclusive focus on motor aspects and also stressed the specific consequences of early as opposed to late-acquired brain damage. It was not formally included in the concept that cognitive, sensory, behavioral, and other associated impairments were very prevalent in people with disordered movement and posture due to a defect or lesion of the immature brain, a frequent significant disability. This definition continued to emphasize the motor impairment and acknowledged its variability, previously underscored in the MacKeith and Polani definition; it also excluded progressive disease, a point introduced in Bax's annotation [8]. The heterogeneity of disorders covered by the term of CP, as well as advances in understanding of development in infants with early brain damage, led Mutch et al. [10] to modify the definition of CP in 1992 as follows: an umbrella term covering a group of nonprogressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development.

To underline the idea that a comprehensive approach to CP needs to be multidimensional and that management of patients with CP almost always requires a multidisciplinary setting, classes of disorders commonly accompanying CP have been identified and included in the revised definition [1]. And last definition of CP, which is comprised to prior assessments and

identifications, was made in April 2006. CP describes a group of persistent disorders of the development of movement and posture causing activity limitations that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior by epilepsy and secondary musculoskeletal problems. This description was authored by the members of the executive committee functioning in panels enriched with expertise from consultants and by comments and suggestions from many reviewers responding to drafts provided to the international community. It is offered for international consensus and adoption, with the intent of providing a broad spectrum of audiences with a common conceptualization about cerebral palsy [1]. CP is defined as a group of nonprogressive, but often changing, motor impairment syndromes secondary to lesions or abnormalities of the brain and emerging in the early stages of development [10]. CP is a symptom complex rather than a disease. It is a concept derived from an insult to a growing, developing brain and therefore it is a dynamic changing clinical picture emanating from static pathology [11]. CP may be diagnosed during the first two years of life, especially when functional impairment is mild [12, 13].

This specification contains the concept that CP is a group of neurodevelopmental disorders that involve numerous developing functions. As in other neurodevelopmental disorders, various manifestations of the disordered brain may appear more significantly in different persons or at different life periods, e.g., some aspects of the motor impairment, sensory loss, attentional difficulty, epilepsy, musculoskeletal dysfunction, intellectual disability, and many others maybe more prominent or more problematic at different periods of the life of a person with CP [1].

In 2010, Blair again emphasized that CP is not a diagnosis but an "umbrella term for many clinical descriptions." It has covered a wide variety of clinical conditions that meet the following four criteria:

- The presence of a disorder of movement or posture.

- Secondary to a cerebral abnormality.

- Arising early in development.

- By the time movement impairment exists, the cerebral abnormality is static.

There is no test, genetic, metabolic, immunologic, or otherwise, that demonstrates the existence or absence of CP because there is no specified cause, cerebral pathology, or even type of motor impairment resulting from nonprogressive cerebral pathology acquired early in life. Even as a clinical description, these criteria fail in several aspects to achieve the precision required of a definition [14, 15]. For example, specifying the age at which development is no longer considered "early." There is no agreement on this age [16].

Because it is difficult to definitively differentiate between pre- and neonatally acquired brain damage, all those not postneonatally acquired are usually considered together. The four criteria cannot be addressed until (a) motor development can be clearly recognized as being normal or disordered and (b) the possibility of progressive cerebral disease can be excluded.

Signs suggesting disordered motor control may be recognized very early in life, but accurate prediction has only been confirmed by trained observers in the small proportion of persons with CP born very preterm [17]. Acquisition of the cerebral abnormality may precede recognition of the motor disorder by many months or even years. However, brain-impaired infants, particularly the most severely impaired, are at increased risk of dying before reaching an age at which the criteria for CP can be confirmed. Early death is a competing outcome. On the other hand, it is difficult to definitively exclude the possibility of progression or resolution at any age. Even if cerebral pathology is static, motor abilities change in all children over time, even if that development is grossly abnormal, making functional change an unreliable marker for progressive cerebral pathology. Conversely, a proportion of children described as CP at an early age catch up with their normally developing peers at a later age [18]. Therefore, the choice of an age that must be attained before being counted as CP, as well as the age beyond which development is no longer early, is arbitrary and depends on the interest in using the CP label. Treating clinicians are more flexible in applying the CP label because their primary concern is to balance the psychological effects of labeling a child having CP with the therapeutic opportunities that the label can afford. This balance can change with time. Registers with a long lifespan require primarily a constant definition over time, and this was the guiding principle of the recommendation by Badawi et al. [19] that conditions historically excluded from CP (not "diagnosed" as CP on account of having another diagnosis) continue to be excluded, even if meeting the criteria for CP. By contrast, reliability between current observers is the guiding principle of the more recent multicenter surveillance system in Europe, which adopted a flowchart to decision inclusion or exclusion of cases of cerebral palsy on registration [20]. However, the reality of barriers to achieving interobserver agreement of classification is demonstrated by the relatively poor agreement achieved with this flowchart [21]. Diagnosis of CP is not easy. It needs time to be confirmed. Premature diagnosis leading to over-ascertainment (because of transient anomalies in preterm babies) or under-ascertainment, as stated above, is not an unchanging condition with the clinical aspect in some cases altering as a child develops. There is consensus that 5 years of age was the optimal age for confirmation of diagnosis [22].

2. Epidemiology

CP prevalence is usually reported around 2–3 per 1000 live births in both developed and developing countries for very different reasons [23, 24]. For term children, CP prevalence is 1 per 1000 live births. Additionally, for moderately preterm children (32–36 weeks' gestation), forecasts are 6–10 times higher and for very preterm children (less than 32 weeks' gestation), prevalence is 10 times higher than the moderately preterm children. CP rates for live births show a lower prevalence for babies of birthweight less than 1000 g than for those with a birthweight of 1000–1499 g. This paradoxical effect is caused from the high number of babies who do not live long enough to develop CP and it disappears when forecasting prevalence for neonatal survivors. Changes in perinatal and neonatal mortality accelerated in most countries from the 1960s, with a huge decrease up until the late 1980s, when there was an increase in the

absolute number of children with CP. From 1990s, there has been a plateauing of mortality rates but a downward trend in CP rates, mainly in moderate and very low birthweight (VLBW) children. In most studies, the CP rates in children born at term or with normal birthweight seem rather stable over time. This finding is especially relevant since normal birthweight and term children represent at least one-half of children with CP and, thus, it may be connected to the persisting stagnation of CP prevalence, despite continuous improvement in perinatal care and in mortality rates [25–27].

There were different rates of CP reported in recent five decades from different population. Published rates from geographically defined populations show significant differences, primarily due to variations in methods (**Table 1**). Variations within a reporting system over time tend to be smaller [28].

The proportion of children described as CP increases with decreasing gestational age at birth. The advent of mechanical ventilation to neonatal intensive care has allowed survival of increasingly preterm births, creating a new source of high-risk neonates and perhaps a new cause of brain damage [27].

Area	Year range	Number of cases	Rate of per 1000
Turkey [29–31]	1990–2006	186	4.4
	1988–2003	102	1.1
	1990–1995		5.5
Sweden [32]	1995–1998	170	1.9
Canada [33]	1991–1995		2.7
U.S.A. [34]	2002	416	3.6
Australia [35]	1970–1998	2950	1.61
	1970–1972		1.4
	1996–1998		1.4
United Kingdom [36]	1984–2002	1301	2.0
	1984–1988		2.5
	1999–2001		1.2
Norway [37]	1996–1998	374	2.1
Danimark [38]	1971–1974		1.7
	1975–1978		1.6
	1979–1982		2.6
	1983–1986		3.0
	1987–1990		2.4
France [39]	1980–1989	261	1.78

Table 1. Published rates of CP from population-based samples.

3. Etiological factors

The etiology of CP is very diverse and multifactorial. The causes are congenital, genetic, inflammatory, infectious, anoxic, traumatic, and metabolic. The injury to the developing brain may be prenatal, natal, or postnatal [40]. Due to the lack of a definitive test for CP, multiple and different possible causes also constitute a challenge in this context. For more than 30% of children, there are no risk factors or known etiology [41, 42] but some risk factors have repeatedly been observed to be related to CP [43]. CP may result from one or more etiologies and can occur at any stage from before conception to infancy, with the actual cause difficult to determine in all cases [41, 42, 44]. Known causes according to the timing of the brain insult can be classified, respectively, as prenatal, perinatal, and postnatal.

3.1. Prenatal causes of cerebral palsy

Among the important known causes of cerebral palsy are congenital brain malformations including malformations of cortical development. Modern imaging techniques enable more children with these conditions to be identified [45, 46]. Currently, problems occurring during intrauterine development, congenital disorders, asphyxia occurring in any gestational age, and preterm birth are thought to account for the majority of cases [47]. Neuroimaging studies support the current thought that prenatal causes of CP, such as brain malformations, intrauterine vascular malformations, and infection, are more common than birth asphyxia [48]. Although intrapartum asphyxia was originally thought to be a major reason for CP, it accounts for only 10–20% of cases. The most frequent perinatal or neonatal etiologies in low birthweight infants are periventricular leukomalacia (PVL), periventricular hemorrhage, and cerebral infarction, but in infants of normal birthweight, the most common reason is hypoxicischemic encephalopathy. Knowledge about the cortical dysplasias, of which some have a genetic basis, is increasing rapidly [49]. Periventricular leukomalacia is a risk factor with 60–100% of patients with PVL developing CP. In general, congenital malformations are strongly associated with cerebral palsy [50–54]. Other known antenatal causes of cerebral palsy are vascular events demonstrated by brain imaging (for example, middle cerebral artery occlusion), and maternal TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex) infections during the first and second trimesters of pregnancy are the known causes of long-term neurodevelopmental disabilities. In industrialized countries, the proportion of CP attributable to TORCH infections is estimated to be almost 5% [13]. The less common causes of cerebral palsy include metabolic disorders, maternal ingestion of toxins, and rare genetic syndromes [55].

3.2. Perinatal causes

Antepartum hemorrhage, obstructed labor, or cord prolapse can jeopardize the fetus causing hypoxia, but essential criteria must be fulfilled before cerebral palsy can be attributed to the acute intrapartum period [56, 57]. These criteria are metabolic acidosis in umbilical arterial cord, fetal scalp or very early neonatal blood samples, and early onset of severe or moderate neonatal encephalopathy in infants of >34 weeks gestation [57].

Children with cerebral palsy, who have a history of neonatal encephalopathy, are more likely to have had signs of intrapartum hypoxia such as meconium staining of the amniotic fluid [58]. However, there may be no evidence of perinatal asphyxia in a significant percentage of children with neonatal encephalopathy [19]. In a systematic study, cerebral palsy was more strongly associated with encephalopathy [59]. Severe hypoglycaemia, untreated jaundice, and severe neonatal infection in neonatal period may be responsible for cerebral palsy [55].

3.3. Postnatal causes

Infection and injuries are responsible for most cases of postneonatally acquired cerebral palsy in developed countries. Thanks to introduction of new vaccines, meningitis and subsequent neurological sequelae were decreased in a large number of children. Accidental (motor vehicle accidents and near-drowning episodes) and nonaccidental injuries may responsible for cerebral palsy. Other reasons of postneonatally acquired cerebral palsy contain apparent life-threatening events, cerebrovascular accidents, and following surgery for congenital malformations. Meningitis, septicemia, malaria, and other conditions are the important causes of cerebral palsy in developing countries [55].

The risk factors associated with CP may also be presented as maternal, paternal and sibling factors, prenatal factors, perinatal factors, and postnatal factors.

3.4. Maternal, paternal, and sibling factors

Maternal medical conditions are associated with cerebral palsy. These include intellectual disability, seizures [60], maternal thrombophilia [33], and thyroid disease [50, 60]; prior reproductive loss [61] and CP in a sibling have been reported as an association with CP in the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke [60]. Adolescent pregnants are likely to have low gestational weeks, low birthweight, and birth traumas. Maternal age > 35 years was reported among risk factors of CP [13]. Öztürk et al. [30] also reported that mothers of children with CP were significantly younger, with an increase in adolescent pregnancies. Mothers of children with CP had low gestational weeks, low birthweight, and prolonged labor.

Parental consanguinity [62, 63] and low economic status were found related to CP in two studies [64, 65].

3.5. Prenatal risk factors

Preeclampsia is associated with an increased risk of cerebral palsy in term infants [66] but this association does not seem to exist in preterm infants [67, 68]. It has been suggested that preeclampsia may lead to a release of catecholamines in preterm infants, which accelerates fetal maturation [69], but care is needed in comparing rates in infants of the same gestation, given that preeclampsia itself can be directly responsible for preterm births. Alternatively, the presence of preeclampsia may result in elective preterm delivery, avoiding the inflammatory responses of spontaneous preterm labors with all their associated problems.

Chorioamnionitis and intrauterine infection and/or inflammation are well-known risk factors for CP. Prenatal maternal chorioamnionitis is accounting for as much as 12% of cerebral palsy in term infants and 28% in premature infants [13, 70, 71]. According to the inflammatory hypothesis, maternal infection can lead to elevated fetal blood and brain cytokine levels, which might result in central nervous damage and subsequent CP [13]. Nelson et al. reported that blood inflammatory cytokine levels in term infants that developed CP were significantly higher than control groups [72]. A number of studies have shown that even fever itself might be harmful. There may be toxic products of the infecting organisms or toxic effects of inflammatory mediators produced by the mother, infant, or placenta. It is tempting to consider that cytokines or other inflammatory mediators induced brain damage directly or indirectly [73, 74]. Gilles et al. [75] demonstrated that maternal trauma in pregnancy may be implicated as a possible cause of cerebral palsy. Antepartum hemorrhage is also associated with mortality, CP, and white matter damage in preterm infants [76].

Multiple pregnancies, also reported as a risk factor of CP, increase fourfold in twins and 18-fold in triplets [77]. These are associated with preterm delivery, poor intrauterine growth, birth defects, and intrapartum complications [78, 79].

Intrauterine growth restriction (IUGR) can be responsible to increase risk of neonatal morbidity and mortality, and also seems to affect brain development [80]. In some specific variance in the brain of IUGR infants, as restriction of the volume of gray matter, a reduced amount of the total DNA in glia cells and neurons, and changes in cerebral hemodynamic have been reported. This hypothesis supported by animal studies showed reduced oxygen delivery to the brain and retarded growth of the forebrain and cerebellum [81, 82]. Several mechanisms have been suggested for the relation between IUGR in term babies and CP. The abnormal growth may play a direct role in causing CP or utero brain injury. Alternatively, a separate process, such as placental insufficiency, could cause both the growth retardation and brain injury [83, 84].

Two mutations have been detected, which predispose heterozygous carriers to venous thrombosis. One is a mutation localized to the factor V gene (factor V Leiden mutation, VL) and second is the gene for prothrombin [85, 86]. Nelson et al. reported that placental thrombosis, or neonatal stroke, may have occurred and resulted in CP [72].

Males are at higher risk of CP, perhaps because of the recently identified gender-specific neuronal vulnerabilities [15, 87]. In the fetus, CP has been associated with intrauterine growth restriction [88, 89] maternal factors [90, 91], other risk factors [92], and congenital anomalies not only of the brain, head, eyes, and face, but also with noncerebral anomalies (in the apparent absence of cerebral anomalies), particularly of the heart, limbs, and skeleton [93, 94]. The risk of CP also increases with the number of suboptimal factors affecting a pregnancy [50, 95].

3.6. Perinatal risk factors

According to the results of World Health Report, perinatal asphyxia and high-risk pregnancy were independent factors that correlated with CP in term and near-term newborns. In developing countries, 4–9 million infants experience birth asphyxia annually [96]. Major events likely to cause perinatal asphyxia include prolonged delivery, breech delivery, and emergency

cesarean births [54, 97]. Though intrapartum factors producing asphyxia were traditionally accepted to be the principal cause of CP, this assumption was reconsidered during the 1980s and 1990s, and today it is suggested that 70–80% of cases of CP are due to prenatal factors and that birth asphyxia plays a relatively minor role. Although intrapartum asphyxia is believed to account for around 10% of CP in term and near-term infants, Swedish population-based CP report by the Hagberg group detected birth asphyxia to be the likely cause of CP in 28% of term children with CP [98]. However, "birth asphyxia" is a poorly defined term related to a sequence initiated by hypoxia and its clinical signs are nonspecific [43]. Using indirect signs of birth asphyxia, recent studies suggest that birth asphyxia might not be such an important cause of CP as was previously assumed, but that it might sometimes constitute one element of a multifactorial cause; neonatal signs associated with birth asphyxia might be early manifestations of CP from a variety of causes, of which birth asphyxia is only one; and the majority of pathways to CP commence antenatally [13, 43, 99]. Any factor causing a very preterm birth that lies on a potential causal path to CP must be remembered. Many etiologic studies control or stratify the risk of CP that also increases with the number of suboptimal factors affecting a pregnancy [100].

The lower birthweights and shorter gestations associated with multiple birth contribute significantly to their higher risk of CP, but cannot be the only relevant factors because gestation-specific rates are higher for multiples than for singletons born at term or extremely preterm [101, 102]. The most important risk factor seems to be prematurity, and low birthweight with risk of CP increasing with decreasing gestational age and birthweight. About 28% of CP cases are born very preterm, compared to 1% of all births. As an effect of the success of neonatal intensive care during the last three decades, ensuring an increasing survival of children born extremely preterm, the prevalence of CP among preterm children has risen [103]. These groups of children may contribute significantly to the overall number of children with CP since they are at greater risk of developing CP. Although it can be expected that where mortality rates are high and CP rates are low, It may be that thanks to good clinical practice and developing technology mortality and CP prevalence rate will be reduced. Neonatal intensive care practices, including withdrawal of life support, may have an impact on local CP rates over time; this influence is difficult to assess [13, 104].

Abruptio placentae have also been suggested to be associated with a higher risk of CP, especially moderately preterm (32–36 weeks) groups [105]. Perinatal infections (bacterial, viral, and protozoal) may also cause the development of CP [106].

Other relations with cerebral palsy include prolonged rupture of the membranes in infants of all gestations [52] and in preterm babies [67]; the presence of meconium-stained fluid [107] and tight nuchal cord was also reported as associated with CP [108].

3.7. Postnatal risk factors of CP

Postneonatally acquired CP is said to result from a recognized brain damaging event that is unrelated to factors in the antenatal or perinatal period, but there is a growing realization that the pathway to postneonatally acquired CP often begins before the postneonatal period [19]. The inclusion criteria for a postneonatal time range of the insult vary between reports. Some

researchers have included cases acquired from neonatal causes that might have had their origin during pregnancy, labor, or delivery [109]. Although a strict definition of beyond 28 days is used by others [16], the upper age limit also varied from 2 to 10 years between researchers [110]. Population-based estimates of the frequency of postneonatally acquired CP, as a proportion of all CP, are reported in the literature to change between 1.4 and 24%, with higher rates in undeveloped and developing countries, and lower socio-economic groups [16]. The Surveillance of Cerebral Palsy in Europe, in a cohort of children from eight countries born between 1976 and 1990, reported that the rate of children whose CP was of postneonatal origin was 7.8% [39]. Pharoah et al. suggested that postnatal causes are generally resulted in spastic CP [111]. Most surveillance systems distinguish cases in which motor impairment is obviously acquired postneonatally, usually following cerebral infection or head trauma [16]. Other infection complications, cerebrovascular accidents, trauma, hypoxia, gastroenteritis, and other causes of acute encephalopathy, neoplasmas, and exposure toxins were other reasons that are reported [112]. Infection, however, remains an important cause of acquired CP despite a fall in the overall numbers more than 30 years of the study. With the introduction of new vaccines, the proportion of cases due to infection will be further decrease, providing there is adequate education and regular control [16].

CP is a nonprogressive but permanent disorder. The disease has been better understood by the researchers in due course of time, and then described as "CP is not a diagnosis but an umbrella term." Though there are different rates according to the region, percentage of CP is not low in especially developing and undeveloped countries. Etiological factors of CP are very diverse and may be classified according to time period (prenatal, perinatal, postneonatal) and parenteral factors. It may be that, thanks to good clinical practice and developing technology, the prevalence of CP rate will be reduced and additionally most known risk factors will be avoided.

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