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Prenatal and perinatal causes, risk factors, diagnosis and prevention of neonatal cerebral palsy

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SUMMARY: Cerebral Palsy (CP) is a major cause of neonatal and childhood disability and is closely linked to pregnancy and perinatal period. CP is a group of developmental movement or posture disorders, which are due to non-progressive damage to the developing brain and lead to reduced activity and other nervous system functions such as learning, hearing, seeing, and thinking. This article deals with the epidemiology, etiology, risk factors, diagnosis and prevention of CP.

INTRODUCTION

A group of conditions involving permanent, non-progressive motor dysfunction that affects muscle tone, posture, and/or movement is described with the definition "Cerebral Palsy (CP)" and is due to non-progressive damage to the developing brain (1). Motor disorders are often accompanied by sensory, learning, communication disorders, perception or behavior problems and convulsions.

CP is a major cause of neonatal and childhood disability and is closely linked to pregnancy and perinatal period. It is thought that its frequency may reflect perinatal care. It was first described by William Little in 1843 (1), who identified a number of perinatal causes, in order to have a representative and complete definition of CP (2).

CP is a clinical diagnosis, as there is no accurate compatible laboratory or histological test. On the contrary the usefulness of Imagery with computed tomography and especially Magnetic Resonance Imaging (MRI) is recognized. Despite the high value of these tools, some children with proven CP have normal neuroimaging which underlines the difficulty of this pathology.

EPIDEMIOLOGY

Despite the difficulties in recording CP, it seems that the frequency is remarkably similar in developed countries and corresponds to approximately 1.4-2/1000 births (1, 3). Its trend has remained stable for the past 40 years, despite the important advances in perinatal care. A modest increase of the incidence appears in the last decades of the 20th century (1980-2000), which may be related to the increase in the survival of very low birth weight premature infants. Recent data show that this increase has been stabilized and more is falling (4). The prevalence of CP is higher in preterm neonates in comparison to term neonates. Moreover, the prevalence of CP decreases with both birth weight (BW) and decreases dramatically with gestational age (GA) (1). More specifically the percentages are as following:

Regarding the birth weight:

- <1500 g – 59.2 per 1000 live births
- 1500 g-2499 g – 10.2 per 1000 live births
- >2500 g – 1.33 per 1000 live births

Regarding the gestational age:

- GA <28 weeks – 82 per 1000 live births
- GA 28-31 weeks – 43 per 1000 live births
- GA 32-36 weeks – 6.8 per 1000 live births
- GA >36 weeks – 1.4 per 1000 live births

ETIOLOGY

The etiology of CP is multifactorial, including anything with a negative impact in the development of fetal or neonatal brain (5). Brain damage leading to CP can be found in the prenatal and in the perinatal period. About 10% of CP concerns the distant postpartum period (concomitant or late CP), with the main causes being craniocerebral injury, brain infections, hypoxia and severe dehydration. Events in childbirth along with distant postpartum causes

make up about 20% of all CP cases. On the contrary 80% of CP is due to an endometrial problem or is the result of an hypoxic ischemic injury. This cerebral hypoxia is the consequence of the difficulty to maintain the normal blood pressure and the oxygenation, in very premature infants (6-7).

RISK FACTORS

At all gestational ages, neonates who are younger or older than expected have a progressively increased risk of CP. This applies to all types of CP, the severity of which is related to the degree of weight deviation. The risk is higher in boys who are Small for the Gestational Age (SGA), but disappears or reverses for the neonates who are Large for the Gestational Age (LGA) (8-9).

Except for *prematurity* and *birth weight* which are the most common risk factors for CP, there are also several prenatal and perinatal risk factors, such as: intrauterine growth restriction, multiple pregnancy, perinatal asphyxia, perinatal trauma, perinatal ischemic brain episode (Stroke), congenital abnormalities-genetic syndromes, placental pathology, maternal heavy alcohol consumption or smoking, maternal obesity, preeclampsia, low Apgar score (<7 at the first 5 minutes of birth), respiratory distress syndrome and infections (1). The aforementioned prenatal and perinatal risk factors are analyzed below.

Intrauterine growth restriction

Intrauterine growth restriction may be the first sign that endometrial pathology is developing. This is an indication of close monitoring, investigation of the cause, possible treatment or induction of labor with favorable conditions before brain damage occurs. The concern is greater for boys, twins or multiples, large weight deviation, or the coexistence of other risk factors (e.g. maternal infection, thrombophilia, etc.) (8-9).

Multiple pregnancy

The increased risk of CP in multiple pregnancies is now confirmed by the literature. It is recorded 5-10 times higher and the main reason is the higher ratio of premature births to multiple births. Twins are responsible for 5-10% of CP and have twice the risk of CP, while triplets have 13 times the risk (10). Prematurity, low birth weight, congenital anomalies and abnormal vascular connections are all causes related to multiple pregnancy that may contribute to CP (1, 11).

Perinatal asphyxia

An issue with much debate remains the perinatal asphyxia in CP. It is known that brain damage occurs prenatally in 70-80% of CP. The ratio of CP related to perinatal events is <1/1000 in full-term births. But this is the most important group of children with CP (usually spastic quadriplegia), because strategies to prevent brain damage are possible and are being investigated. The primary mechanism that leads to the cessation of placental blood flow seems to play a critical role in the neurological outcome. Thus, the systemic and cerebral impact of an acute event (e.g. placental abruption) differs from the effects of events with a longer course, such as recurrent bradycardia). Additional lesions of the placenta or cord increase the chance of brain damage (12-13). Various clinical indicators indicating stress or predicting asphyxia have been used during or after childbirth to detect the newborn at high risk for brain damage (e.g. pulse lesion, meconium, Apgar score, resuscitation). Probably the combination of these indicators has a greater value (13-14).

Perinatal trauma

Traumatic damage to the Central Nervous System can also occur in "normal" childbirth, but the frequency increases significantly in cases of interventional childbirth or abnormal fetal projection (15). Traumatic damage to the perinatal brain (subdural, epidural, subarachnoid, intraparenchymal bleeding), can lead to hypoxemic or ischemic brain tissue damage. Intracranial hemorrhages occurred intrauterine due to fetal injury, coagulation disorders or vitamin K deficiency. The outcome of perinatal trauma is generally good. Death is rare, usually due to cataclysmic bleeding in the posterior cranial fossa or coagulation disorder. Most neonates develop normally and only 10-15% develop neurological problems, including spastic and hypotonic CP (16).

Perinatal ischemic brain episode (Stroke)

It is due to occlusion of a cerebral artery or vein, or thrombosis of the venous atrium leading to local/ischemia/infarction and focal damage, usually isolated, well separated, preserving the rest of the parenchyma. It is an important factor of CP, since congenital hemiplegia in the full-term is the most common form and stroke is the number one cause (1). Stroke mimics and may coexist with other patterns of neonatal ischemic brain injury (17). Risk factors for perinatal stroke,

detected in 2/3 of cases, may coexist and interact or sometimes overlap with risk factors for CP. The diagnosis confirming with MRI.

Generally, pregnancy and especially the perinatal period is a pre-thrombotic condition. The fetus may have prothrombotic disorder or antiphospholipid antibodies, coagulation disorders, sepsis, hyperrrhythmia. A complete blood and thrombosis test is required, although many times it is not initially diagnostic and must be repeated. Parental screening is indicated, especially in a positive family history of thrombosis (17-18).

Congenital abnormalities-Genetic syndromes

They are responsible for 10% of the CP. The use of new techniques has enriched diagnostic cytogenetic analysis and now deficiencies, duplications, permutations, dichotomies are detected and chromosomal from molecular disorders can be distinguished. The most common symptom of these diseases is impaired brain function. The incidence of chromosomal abnormalities in an unselected population of apparently healthy neonates is estimated at 0.32%. These conditions should be looked for when there are suspicious clinical signs in the newborn, such as muscular hypotension or microcephaly (19).

Placental pathology

It remains unclear whether combinations of placental lesions act synergistically or sequentially and trigger brain damage. Chronic placental abruption that reduces placental abruption when combined with subacute thrombocytopenic processes that began > 1 day before delivery is dramatically more likely to have a poor neurological outcome than a combination of abnormalities that begin at the same time (20).

Maternal heavy alcohol consumption or smoking

Prenatal maternal heavy alcohol consumption produces a spectrum of clinical conditions that include an increased risk for brain deficits in neonates (21). Moreover, smoking before, during and after pregnancy is not an uncommon behavior among the general population and related with adverse effects on the health of both mother and child. Pregnant women may not realize that smoking during pregnancy expose fetuses to the dangers of smoking. As a result, the fetus suffers from all the harmful effects of

smoking, which in the most extreme cases can lead to CP or death, as there is no level of fetal exposure to second-hand smoke that can be considered safe (1).

Maternal obesity

It is well known that maternal obesity may be associated with adverse obstetric complications (22-23). Specifically, maternal obesity is associated with low Apgar scores at the first 5 minutes of birth (22, 24), preterm birth (25), and with neurodevelopmental outcomes (26). Furthermore, maternal obesity is associated with an increased risk of gestational diabetes, hypertension, and preeclampsia, which may be associated with adverse neurodevelopmental outcomes (27-28).

Preeclampsia

Preterm and small for gestational age neonates born to mothers with preeclampsia during pregnancy are at increased risk of CP. Preeclampsia is marked by hypertension during pregnancy and proteinuria and affects about 3% to 5% of pregnant women. Some studies showed that in comparison with normal pregnant women, the rate of CP is double among patients with preeclampsia (29). For these reasons, these neonates should be closely monitored for early diagnosis of CP.

Low Apgar score (<7 at the first 5 minutes of birth)

Apgar score is a measure of vitality shortly after birth. The causes of CP are closely linked to factors that reduce infant vitality. Low Apgar score (<7 at the first 5 minutes of birth) was strongly associated with CP (1, 30).

Respiratory distress syndrome (RDS)

According to most studies, the risk of CP is twice as high in moderately late and late preterm infants with RDS compared with infants without RDS born during the same gestational weeks (31).

Infections

Infections are prominent since 2/3 of newborns in Neonatal Intensive Care Unit (NICU) show infection mainly early. It is found that 1 in 5 newborns with sepsis, meningitis, necrotic enterocolitis develops CP. The relationship between infection and neurodevelopmental disability is particularly clear when associated

with bronchopulmonary dysplasia (BPD), steroid administration in NICU, and parenchymal brain damage on ultrasound. These three major factors predict poor outcome in newborns. It is also found that when severe cerebral hemorrhages are reduced, the rates of CP do not improve. This indicates that cerebral hemorrhage is not the main route for CP and that other pathogenetic mechanisms are involved (32-33).

The term neonate which born after an infection of the mother, has 2-4 times increased risk for CP. The neonate may be born with sepsis and may present shock, meningitis or pneumonia with pulmonary hypertension. Moreover, the neonate may be born with a suffocation due to placental dysfunction (inflammatory lesions in the placenta), and this is the most likely mechanism. Theoretically, proinflammatory cytokines can cause direct brain damage as in premature (34-35).

Cytokines also affect the function of the myometrium and placenta and cause complications in childbirth (placental abruption, bleeding, uterine atony, etc.). Maternal fever increases oxygen demand, while subsequent hyperventilation and respiratory alkalosis lead to a 50% reduction in uterine blood flow, a 30% reduction in fetal blood flow, and fetal metabolic acidosis. The combined exposure to infection and suffocation in childbirth has a synergistic effect on the brain and dramatically increases the risk of CP (34-36). Finally, various neonatal viral, bacterial, protozoan or fungal infections are known that cause CP. The damage may be due to a direct effect of the infection or to a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS) (37).

It is estimated that maternal infection is responsible for 12% of the spastic form of CP, 19% of unexplained CP and 35% of unexplained spastic quadriplegia. Most of these children had a picture compatible with asphyxia and a diagnosis of Hypoxic Ischaemic Encephalopathy (HSE).

DIAGNOSIS

The diagnosis of CP is traditionally made around the age of 12 to 24 months. Early diagnosis at the age of 12 weeks is now possible for about half of the population, through diagnostic tests in NICU and the identification of risk factors (38). The diagnosis of CP is based on the medical history, in the assessment of psychomotor development, in the neurological examination and in the

laboratory tests, such as MRI. The main feature of CP is motor disability, however, it can also accompany by mental retardation, sensory disorders, learning difficulties, epilepsy, speech and emotional disorders (1).

Motor paralysis disorders related to CP are usually accompanied by problems in: vision, hearing, knowledge/perception, communication/speech, behavior, sleep, urinary incontinence, salivation and swallowing/feeding.

Neuroimaging methods detect more than 95% of CP and are very helpful for the physician to assess the degree of complication (39). Moreover, during the first year of life, many changes occur: the "correction" of the age, the variability of position, the tone and the voluntary mobility (7).

PREVENTION

There are prenatal, intrapartum and postnatal measures available in order to reduce the likelihood of neonatal CP (1).

Specifically, prenatal care is generally provided by midwives, obstetrician-gynecologists and maternal-fetal medicine subspecialists and should be initiated in the first trimester of pregnancy, ideally by the first 10 weeks. Appropriate medical history in combination with physical examination, and laboratory tests can help identify pregnant women at increased risk of pregnancy complications, or fetal abnormalities such as CP (40). Early identification of these women gives the provider an opportunity to discuss these issues and their management with the pregnant woman and, in some cases, offer interventions to prevent or minimize the risk of an adverse outcome.

Additionally, prenatal administration of magnesium sulfate has been recommended in order to decrease the incidence and severity of neonatal CP, in case of pregnant women with risk for preterm delivery (1, 3, 41). Furthermore, 17alpha-progesterone is indicated in order to prolong pregnancy (42).

The administration of corticosteroids may protect against CP (43), but it may associate with hyperactivity later in children's life (44). Moreover, it is not clear whether a repeat dose in contrast to a single dose has impact in the risk of CP in women who are at risk of preterm delivery (45).

The delaying of the umbilical cord clamping for approximately 30-60 seconds after the delivery in

vigorous neonates has been recommended as an intrapartum measure. This is due to the belief that a reduce in intraventricular hemorrhage in preterm neonates may be related with an improvement in neurodevelopmental outcomes (1).

Furthermore, maintaining sufficient cerebral perfusion, adequate ventilation maintaining and normal metabolic status and additionally, controlling neonatal seizures and threatening any causes of encephalopathy are all postnatal measures for the prevention of neonatal CP (1). Moreover, caffeine is indicated in case of extremely low birth weight neonates, and also induced hypothermia for a subgroup of neonates which diagnosed with hypoxic-ischemic encephalopathy (42).

CONCLUSION

The etiology of CP is heterogeneous and multifactorial, with infections of the pregnant woman or newborn, as well as neonatal injuries and poor cerebral oxygenation (hypoxia / suffocation) or hematoma (ischemia) before, during and/or after birth, to be, based on research evidence, the main causes of its occurrence. Moreover, multiple risk factors are involved in the development of the leading causes to brain damage, such as pre-eclampsia, placental abruption, maternal infection-bleeding, multiple pregnancy, prematurity and neonates with low birth weight. The dynamic nature of the CP, the risk factors, the type of damage and the type of CP should be clearly identified early, in order to ensure a better life for the affected neonate.

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