

BRAIN INJURY IN PRETERM INFANTS

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Perinatal care advances over the past twenty years have helped to diminish the mortality and severe neurological morbidity of extremely and very preterm infants. However, motor and/or cognitive disabilities associated with mild-to-moderate white and grey matter injury are frequently present in this population. The major neuropathological substrate of preterm brain injury is encephalopathy of prematurity which characterizes the multifaceted white and grey matter lesions, and reflects a combination of destructive and dysmaturational effects. It can be associated with haemorrhages, notably in germinal matrix and cerebellum and with focal micro-or macroinfarcts. Clinical signs of brain injury are often subtle or even absent, therefore several new non-invasive methods are used to identify and estimate central nervous system dysfunction. They provide insight into hemodynamics, electrical activity and brain structure. Knowing and understanding the causes and the mechanisms of brain injury yield to a number of more or less successful neuroprotective approaches that reduce the negative influences on the developing brain. Since brain injury and consequently its long term neurodevelopmental outcome remains the most important complication of the premature birth, a regular and comprehensive follow-up of motor, cognitive and behavioral development of these children is essential, as it provides early detection of potential delays and intervention.

Descriptors: PRETERM INFANT, BRAIN INJURY, ENCEPHALOPATHY OF PREMATURITY, NEURODEVELOPMENTAL OUTCOME

Introduction

Preterm birth is a leading cause of long-term neurological disabilities in children. The rate of preterm birth remains around 10% worldwide; with rates, varying from 5-18% across 184 countries studied, and it has not changed over the last two decades (1). Perinatal care advances over the past twenty years have helped to diminish the mortality and severe neurological morbidity of extremely and very preterm neonates. However, motor and/or cognitive disabilities associated with mild-to-moderate white and grey matter injury are frequently present in this population (2).

The major neuropathological substrate of preterm brain injury is encephalopathy of prematurity (EP). This term was introduced by Joseph Volpe and coined to characterize the multifaceted white and grey matter lesions in the preterm brain, which reflect a combination of destructive and dysmaturational effects (3, 4). EP is also associated with haemorrhages, notably in germinal matrix and cerebellum and with focal micro-or macroinfarcts. Due to responsible insults occurring at the time of rapid brain growth, a host of developmental programs may be affected, resulting in maturational defects that compound the acquired lesions. The course of EP is multifactorial and includes cerebral hypoxia-ischaemia and systemic infection/inflammation, which results in glutamate, free radical and/or cytokine toxicity to pre-oligodendrocytes (pre-OLs), axons and neurons (3, 4).

Contributory roles of impaired nutrition, pain, stress, drugs and other factors associated with neonatal intensive care also seem possible (4, 5). Due to the heterogeneity of lesions that comprise EP, the spectrum of neurodevelopmental abnormalities in preterm survivors is wide and includes, often in combination, a variety of cognitive, behavioral, socialization, attention and motor deficits (6).

The purpose of this review is to explain the concept of brain injury in preterm infants, which comprises destructive and developmental disturbances, diagnostics and its subsequent neurodevelopmental consequences.

Neuropathology of brain injury in preterm infants and pathophysiologic mechanism

The neuropathology of brain injury in premature infants termed EP consists of multiple lesions: periventricular leukomalacia (PVL) and accompanying neuronal/axonal abnormalities; severe germinal matrix-intraventricular haemorrhage (GMH-IVH), especially with periventricular hemorrhagic infarction; and posthemorrhagic hydrocephalus (5).

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GMH-IVH is the most common variety of haemorrhage in newborns. Although the gradual decrease in the incidence of GMH-IVH has been noted, it has remained unchanged in last two decades, with overall incidence of 25% (5, 7). The vasculature in the germinal matrix is very fragile and in combination with the lack of cerebral autoregulation and fluctuations in cerebral blood flow (CBF) it causes a rupture of vessels, which results in haemorrhage either restricted to the germinal matrix but more often also extends to the lateral ventricle. Papile classification is commonly used to grade the severity of GMH-IVH: grade I represents haemorrhage confined to subependymal germinal matrix, grade II is haemorrhage in lateral ventricles without dilatation, grade III haemorrhage occupies more than 50% of ventricle with distention resulting in ventricular dilatation (8). The associated parenchymal involvement known as a periventricular hemorrhagic infarction (PVHI) is due to the impaired venous drainage of the medullary veins in the periventricular white matter. The incidence of the lesions increases with decreasing gestational age, and 10-15% of very low birth weight (VLBW) infants with GMH-IVH exhibit PVHI (9).

Posthemorrhagic ventricular dilatation (PHVD) develops in approximately 25 to 50% of preterm infants within 7 to 14 days after the onset of a severe GMH-IVH. Adverse effects of intraventricular blood and progressive ventricular dilatation on the adjacent vulnerable periventricular white matter (WM) of the preterm infant have been reported as unfavourable outcome in group of infants with PHVD (10). Cerebellar haemorrhages (CBH) are recognized as a common problem in very immature infants with reported incidence 15 to 20% depending on the gestational age (GA); they tend to be associated with supratentorial lesions, most often severe GMH-IVH (11, 12).

The preterm WM is susceptible to a broad spectrum of injury severity that ranges from diffuse non-destructive lesions to the severe necrotic lesions of periventricular leukomalacia (PVL). PVL consists of localized necrosis deep in periventricular WM, with loss of all cellu-

lar elements. These necroses can be macroscopic in size and evolve over several weeks to multiple cystic lesions - "cystic PVL" (3, 4, 13). Nowadays, this severe lesion is observed in less than 5% of infants with VLBW, and therefore accounts for a small minority of PVL. Much more commonly focal necroses are microscopic in size and evolve over several weeks to glial scars that are not readily seen by neuroimaging. This form of PVL, which accounts for the vast majority of cases, is termed "non-cystic PVL" (3, 4, 13). Research studies using magnetic resonance imaging (MRI) report that 50% to 80% of extremely and very preterm neonates have diffuse white matter injuries (WMI) which correspond to only the minimum grade of severity. Furthermore, data from recent studies have shown that PVL is frequently accompanied by neuronal/axonal disease affecting the cerebral WM, thalamus, basal ganglia, cerebral cortex, brain stem, and cerebellum (3, 4, 13).

EP, both PVL and the associated neuronal/axonal disease, occurs during a period of rapid and complex events in brain development (3, 4, 13). The developmental events between 24-40 weeks involve in particular the following: cerebral WM (pre-OLs, axons, microglia), and neurons (subplate and late migrating GABA-ergic neurons); two proliferative zones; and key neuronal structures - thalamus, cerebral cortex and basal ganglia (14-16). Because of the rapidity and complexity of these developmental events, they are postulated to be vulnerable to exogenous and endogenous insults which produce the developmental disturbances, including impaired cell-cell interactions, involving intercellular trophic support, retrograde effects ("dying back"), and anterograde effects (e.g., Wallerian degeneration, transsynaptic degeneration). At the end stage, WMI results in cell death or process loss, or both. Thus, diffusely apparent WMI is characterized by marked astrogliosis and microgliosis, and initially by a decrease in premyelinating pre-OLs. Subsequently, the decrease in cells of the oligodendroglial lineage is counteracted by an increase in oligodendroglial progenitors. However, in PVL, these cells which of-

ten lack processes seem not to have the capacity for full differentiation to mature myelin-producing cells, and hypomyelination. Impairment of myelination and of cortical and thalamic development by neuronal/axonal disease are hallmark of WMI (14-16).

Clinical risk factors for WMI relate to hypoxia-ischemia and/or inflammation. Premature newborns are predisposed to cerebral hypoxia-ischemia because of a combination of the vascular anatomy consisting of arterial border zones within the WM, as well as an impaired ability to autoregulate CBF; the consequences pressure-passive hypotension and decrease in systemic blood pressure that can result in ischemia to the arterial border zones. Multiple studies have confirmed that both hypocarbia and hypercarbia can also significantly perturb CBF. Thus, hypocarbia may promote hypotension and increased risk for IVH and WMI (17). Additionally, insignificant series of clinical and experimental studies suggests that maternal intrauterine infection, foetal systemic inflammation as well as postnatal infections are also involved in the pathogenesis of WMI. Bacterial endotoxin can cause WMI via vasoactive mechanism that can result in cerebral ischemia or via stimulation of systemic cytokines and activation of microglia. Microglia derived TNF- α and INF- γ interact synergistically to cause early pre-OL death. Endogenous exposure to IL-1 β disrupts oligodendrocyte maturation and myelination (17).

Diagnosis of preterm brain injury

Neuroimaging is of the major diagnostic importance of brain injury in preterm infants; cranial ultrasonography (cUS) and MRI are the main imaging methodologies. Additionally, diagnostic and prognostic value of electroencephalography (EEG) and amplitude integrated EEG have also been established.

Electroencephalography

Serial EEG studies have been shown of value in identifying preterm infants with PVL and presumed neuronal disease. Thus, decreased continuity, lower

background activity or both were observed mainly at day 1 to 4 of life with subsequent identified PVL with cUS; these findings referred to acute-stage abnormalities. Deformed slow activity and subnormal sharp waves were observed mainly at day 5 to 14 and resolving within 1-2 months; these findings referred to chronic-stage abnormalities, which were more severe and persisted longer in patients with extensive c-PVL compared with milder PVL, suggesting that EEG findings correlate with PVL severity. Positive rolandic sharp waves were present in 65-90% of cases with severe PLV and 25% of cases with mild or moderate PVL. Frontal positive or occipital negative sharp waves or both were present in 100% cases of severe PVL and 60-90% of mild or moderate PVL. Abnormal sharp waves accompany echodense lesions on cUS and precede the development of echolucent-cystic lesions. In addition to abnormalities of EEG background activity, 30% of infants with PVL were presented with seizures, and 65% with episodes of apnea (4).

Neuroimaging

Cranial ultrasonography remains the preferred neuroimaging technique for routine screening of intracranial pathology in preterm infants. Early cUS examination mostly detects hemorrhagic lesions, whereas a subsequent cUS usually allows diagnosis of WM abnormalities (2, 4, 12). It is effective in identification of all degrees of severity of GMH-IVH. The major elemental lesion is haemorrhage in germinal matrix, which is usually seen as dense echogenicity that correlates with haemorrhage. Intraventricular bleeding results in echogenic material that fills a portion of lateral ventricular system. The PVHI lesions are triangular, usually unilateral and located on the side of larger GMH-IVH and commonly in frontal or parietal regions. They evolve into one larger or several smaller periventricular cysts adjacent to the ventricle, and their size and site is predictive of outcome. PHVD that develops as complication after GMH-IVH is demonstrated very well with cUS. Measurements can be taken of the ventricular index (VI), anterior horn width and occipital

horn width, and these measurements can be used to optimize timing of intervention (2, 4, 12).

Cerebellar haemorrhages more than 4 to 5 mm in size can also be detected by cUS. Smaller (punctate) haemorrhages in the cerebellum are far more common but can only be diagnosed with MRI especially with susceptibility-weighted imaging (SWI). MRI repeated at term equivalent age presented atrophy of the affected cerebellar hemisphere following larger CBHs. A unilateral PVHI can also be associated with a marked loss of contralateral cerebellar - crossed cerebellar atrophy (11, 18).

Using higher resolution ultrasound probes and a wider view of insonation, assessment of the WM has improved considerably, although it remains difficult as subtly increased echogenicity is a very subjective finding (18). Some data suggest that white matter echogenicity which is equal to or higher than the echogenicity of the choroid plexus and persist at least 7 days, is significant for white matter injury. The value of cUS comes from sequential imaging, showing the duration of the echogenicity and in some cases the evolution to more echogenic and/or inhomogeneous echogenicity or to cystic lesions. They are visible only for a few weeks and may have fully resolved by term equivalent age (TEA), but their presence is predictive for subsequent cerebral palsy (CP). The fluid in cysts subsequently resorbs with adhesion of the walls over the next weeks. As a result, their manifestation at TEA may be subtle: white matter loss and irregular dilatation of the adjacent ventricle (2, 4, 12).

Several studies performed in the last 10 to 15 years demonstrated that the role of cUS was limited when it comes to recognizing milder WM: MRI is considered to be the "gold standard" (19, 20). Counsell et al coined the term DEHSI (diffuse excessive high signal intensity) and reported that high signal intensity (SI) in the WM was a common finding in very preterm infants. They subsequently reported that these infants with increased SI in the WM at TEA had volume reduction in the periventricular WM, the

corona radiata, and within the central region of the centrum semiovale dorsomedial nucleus as well as the thalamus and the globus pallidus; and these imaging findings were associated with a significantly lower developmental outcome (18, 19, 20).

Protecting the brain of the preterm infant

Over the last decades, advanced neurodiagnostic techniques have brought critical information regarding the risk factors and neuropathological mechanisms responsible for the pathway to disability, and have additionally provided multifaceted neuroprotective efforts to prevent or limit structural and functional cerebral injury. Neuroprotection encompasses all strategies applied pre-, peri- and/or postnatally that promotes normal development and prevents disabilities: organizational, therapeutic, and environment-modifying measures (21).

Therapies that exert neuroprotective effects when delivered antenatally include, corticosteroids and magnesium sulphate among others; both were originally applied for other purposes and were later proved to impact short- and long-term neurodevelopmental outcomes. Prevention of GMH-IVH is among the most investigated aspects of neonatal neurologic care. The most powerful intervention for prevention of GMH-IVH and improvement of outcome has been a routine use of antenatal corticosteroids. They are a mainstay of prophylactic treatment in preterm birth and exert vasoconstrictive effects on the cerebral vasculature, minimizing changes in cerebral blood flow (21). Based upon current evidence, rational prevention of GMH-IVH after delivery consists of appropriate resuscitation, delivery management, proper administration of vitamin K, judicious use of fresh frozen plasma and correction of hemodynamic disturbances (delayed cord clamping, targeted therapy of the PDA and hypotension) (4). The use of indomethacin, a non-specific cyclooxygenase inhibitor that decreases prostaglandin synthesis, on the first day of life also decreases the incidence of IVH, but its use does not

change the rates of neurodevelopmental disabilities (22). Furthermore, delayed clamping of the umbilical cord by 30 to 45 seconds after delivery increases the amount of blood flowing from the placenta to infant, limiting the impact of the consequent circulatory compromise. It improves regulation of CBF, enhancing oxygen delivery and modifying GMH-IVH risk (23).

The nature of the pathway to WMI suggests a combination of strategies applied both preventatively and after injury targeting specific ischaemic and inflammatory factors. Cogent respiratory management and sensible use of common measures including administration of fluids, transfusions and inotropes may prevent large fluctuations in blood pressure thus minimizing the risk for ischemia. Some agents, such as antenatal corticosteroids, afford protection when administered prenatally. On the other hand, several strategies that target specific components of the inflammatory pathway have been explored for postnatal use (prevention of free radical generation, scavenging of free radicals, mediation of excitotoxicity, antiapoptotic agents and melatonin, erythropoietin, caffeine) but appropriate timing and rational application of each approach remain incompletely defined (24, 25).

In the last decades, interventions designed to minimize stress of the environment known as Developmental care, such as positioning, clustering of the nursery care, modification of external stimulation and individually tailored care have also been demonstrated to influence neurodevelopmental outcome (26).

Outcomes after brain injury in the preterm infant

The risk of neurodevelopmental disability increases progressively with decreasing GA, with the highest risk in children born at the lower limit of viability. The most overt signs of brain injury are motor impairments. Early signs of evolving CP are persistent neuromotor abnormalities and a delay in acquisition of motor milestones (27). Two European studies reported the rate of CP from 1% at 34 weeks of gestation to 22% at

26 weeks (28). The most common type of CP associated with preterm birth is spastic diplegia; approximately half of preterm children with CP have a mild to moderate form with spasticity in lower extremities but are functional walkers. Spastic quadriplegia occurs with increasing frequency at lower gestational age while spastic hemiplegia is more common in children born after 32 weeks of gestation and at term. Many preterm children with persisting motor abnormalities after birth do not develop CP, but have minor neuromotor dysfunction (MND) which includes toe walking, postural instability, asymmetric gait, motor planning difficulties, graphomotor impairment, poor visual abilities, problems with sensorimotor integration and fine motor dysfunction. The data pooled from 11 studies that reported the prevalence of mild to moderate motor impairment in preterm children demonstrated the prevalence of mild motor impairments from 22.2% to 72.2% and moderate impairments from 9.5 to 23.8% (28). These estimates suggest that the prevalence of MND is three to four times higher in preterm than in term children. In contrast to major disabilities that can be identified early (e.g. CP, intellectual disability, sensory impairments and epilepsy), cognitive, learning, behavioral, social, and emotional problems may frequently remain hidden until school age or later, and persist into adolescence and adulthood (27, 29).

Preterm outcome studies have generally found that compared with children born at term, preterm children had higher rate of cognitive impairment, especially if born before 26 to 27 weeks of gestation, and had severe brain injury and/or motor impairment (30). Although the risk of intellectual disability is higher and mean intellectual quotient (IQ) is often statistically significantly lower in preterms than IQ for term controls, the majority of children and young adults born preterm have an IQ within normal range (28). Preterm populations also demonstrate a range of cognitive impairments, including language difficulties, visio-perceptual dysfunction, specific learning disabilities, working memory deficits, executive dysfunction, and de-

layed information processing (31). Most studies of young adults born preterm have found that they had lower academic achievement scores and educational levels when compared to participants born at term (32). The range of behavior problems in children born preterm varies from 7% to 20% (28). The most common behavioral problem associated with preterm birth is attention-deficit-hyperactivity disorder (ADHD), which occurs in 9% to 16% of school-aged children born preterm (33). Preterm outcome studies have also reported more internalizing behaviors, lower social competence, and more psychiatric problems in children, adolescents and young adults born preterm. Despite all the difficulties associated with preterm birth, the majority of adults who were born preterm have reported a similar quality of life as individuals born at term. Most graduates from secondary schools have jobs and are contributing members of their communities (34).

Abbreviations:

ADHD - attention-deficit-hyperactivity disorder
 CBF - Cerebral blood flow
 CP - Cerebral palsy
 cUS - Cranial Ultrasound
 DEHSI - diffuse excessive high signal intensity
 EEG - Electroencephalography
 EP - Encephalopathy of prematurity
 GA - Gestational age
 GMH - IVH - germinal matrix-intraventricular haemorrhage
 IQ - intellectual quotient
 MND - minor neuromotor dysfunction
 MRI - Magnetic resonance imaging
 PDA - Persistent ductus arteriosus
 Pre - Ols - pre-oligodendrocytes
 PVHD - Posthemorrhagic ventricular dilatation
 PVHI - periventricular hemorrhagic infarction
 PVL - pre-oligodendrocytes
 SI - Signal intensity
 SWI - Susceptibility-weighted imaging
 TEA - Term equivalent age
 WM - White Matter
 WMI - White matter injury
 VLBW - Very low birth weight

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Sažetak

OŠTEĆENJE MOZGA NEDONOŠČADI

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Zahvaljujući poboljšanju perinatalne skrbi, u posljednja dva desetljeća, smanjen je mortalitet i teška neurološka oštećenja kod nedonoščadi. Unatoč tome motoričke i kognitivne smetnje povezane s oštećenjem mozga, još su uvijek prisutne u toj populaciji djece. Glavni patomorfološki supstrat oštećenja mozga kod nedonoščadi je encefalopatija nedonoščadi, koja predstavlja kombinaciju destruktivnih i dismaturacijskih procesa. Povezana je krvarenjem u germinativnom matriksu i cerebelumu te žarišnim mikro ili makroinfarktima. Klinički znaci ozljede mozga mogu biti suptilni ili čak odsutni pa se stoga veliku važnost daje suvremenim neinvazivnim metodama kojima se može dijagnosticirati ozljeda. One omogućavaju uvid u hemodinamičko stanje, električnu aktivnost i strukturu mozga. Poznavanje razloga i mehanizama ozljede pridonosi i neuroprotektivnim mjerama, kojima se smanjuju negativni utjecaji na mozak u razvoju. Budući da su ozljeda mozga te neurološke i razvojne posljedice najvažnija komplikacija nedonoščadi, redovno praćenje motoričkog te kognitivnog razvoja i ponašanja u toj skupini djece omogućuje rano otkrivanje mogućih poremećaja i pravovremenu intervenciju.

Deskriptori: NEDONOŠČAD, OZLJEDA MOZGA, ENCEFALOPATIJA NEDONOŠČADI, NEURORAZVOJNI ISHOD

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