Cerebral White and Gray Matter Injury in Newborns

New Insights into Pathophysiology and Management

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KEYWORDS

• White matter • Gray matter • Cerebral • Newborns • Pathophysiology
• Management

KEY POINTS

- Contemporary cohorts of preterm infants commonly show less severe injury, which does not seem to involve pronounced neuronal or glial loss. These milder forms of injury are still associated with reduced cerebral growth.
- Myelination disturbances are one of the hallmarks of chronic white matter injury arising from hypoxia-ischemia.
- Although immature neurons seem to be more resistant to cell death from hypoxia-ischemia than glia, they show widespread disturbances in maturation of their dendritic arbors, which provides an explanation for impaired cerebral growth.
- Numerous immature neurons and preOLs fail to fully mature during a critical window in development of neural circuitry.

PRETERM SURVIVORS SHOW AN EVOLVING SPECTRUM OF BRAIN INJURY

Although major advances in the care of premature infants have resulted in striking improvements in the survival of very low birth weight (VLBW) infants (<1.5 kg), enhanced survival has been accompanied by a significant increase in the number of preterm survivors with long-term neurodevelopmental morbidity.[1,2] In the United States, the rate

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of preterm birth continues to increase, with prematurity complicating 1 in 8 deliveries, and VLBW infants comprise about 1.5% of the 4 million live births in the United States each year.[3]

Despite improved outcomes of children born preterm, there continues to be wide variation in functional disabilities, even among those born at the same gestational age.[4] Premature birth alone is associated with a greater risk for reduction in both cerebral white and gray matter volume, which is associated with poorer cognitive development.[5–12] In the setting of cerebral injury, 5% to 10% of preterm survivors sustain permanent major motor impairment, including cerebral palsy (CP), which ranges from mild motor dyspraxia to severe spastic motor deficits.[13–17] By school age, approximately half show a broad spectrum of cognitive dysfunction, which involves various aspects of learning, memory, language, vision, hearing, attention, and socialization.[14,18–32] Disabilities in multiple neurodevelopmental domains often co-occur[33] and persist to young adulthood.[24–26,34–37]

The diverse spectrum of cognitive and motor outcomes in preterm survivors has led to increasing recognition that widely distributed abnormalities in brain maturation occur. Until recently, preterm infants were at high risk for destructive brain lesions that resulted in cystic white matter injury (WMI) and secondary cortical and subcortical gray matter degeneration. These brain abnormalities lead to substantial deletion of axons and glia from necrotic white matter lesions and secondary loss of neurons in developing gray matter. However, the last decade has been accompanied by an increasing number of studies that support a shift to milder forms of chronic injury, in which tissue destruction is the minor component. Nevertheless, these milder forms of injury are also associated with reduced cerebral growth and adverse outcomes. As discussed later, recent human and experimental studies support that this impaired growth is related to distinctly different forms of disease, which involve aberrant responses to injury that disrupt the maturation of neurons and glial progenitors. These emerging findings suggest that brain injury in most preterm survivors involves a primary cerebral dysmaturation disorder, which may be amenable to a variety of rehabilitative strategies directed at promoting brain maturation and improved neurodevelopmental outcome.

WHAT DEFINES AN INSULT TO THE DEVELOPING BRAIN AND WHY DOES THIS MATTER?

Although the full impact of preterm cerebral insults is often not fully defined until a childhood neurodevelopmental assessment occurs, there is a critical need for improved means to identify insults closer to the time of occurrence in order to implement potential therapies to prevent early injury[38] or promote regeneration and repair of chronic lesions.[39] However, the critical windows for interventions remain poorly defined, because of our limited tools to define primary or secondary insults in terms of their timing/recurrence, severity, and progression. Identification of the timing of the early phase of insults remains challenging, because the approaches are limited for real-time monitoring of cerebral blood flow (CBF), central nervous system (CNS) tissue oxygenation, levels of CNS metabolites, and biomarkers of CNS injury. Such tools are vitally important to develop, because therapies are likely to have variable impact, depending on the timing of their implementation during the course of neonatal brain development. Human brain development is a moving target, which involves cellular activity-dependent events that coincide with multiple waves of neurogenesis, gliogenesis, glial and neuronal maturation, synaptogenesis, myelination, and the establishment of neural networks and connectivity. Hence, the timing of an insult to the developing brain, in a large measure, defines its potential impact on multiple