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·Review·

Vulnerability of premyelinating oligodendrocytes to white-matter damage in neonatal brain injury

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Premature birth is a significant economic and public health burden, and its incidence is rising. Periventricular leukomalacia (PVL) is the predominant form of brain injury in premature infants and the leading cause of cerebral palsy. PVL is characterized by selective white-matter damage with prominent oligodendroglial injury. The maturation-dependent vulnerability of developing and premyelinating oligodendrocytes to excitotoxic, oxidative, and inflammatory forms of injury is a major factor in the pathogenesis of PVL. Recent studies using mouse models of PVL reveal that synapses between axons and developing oligodendrocytes are quickly and profoundly damaged in immature white matter. Axon-glia synapses are highly vulnerable to white-matter injury in the developing brain, and the loss of synapses between axons and premyelinating oligodendrocytes occurs before any cellular loss in the immature white matter. Microglial activation and astrogliosis play important roles in triggering white-matter injury. Impairment of white-matter development and function in the neonatal period contributes critically to functional and behavioral deficits. Preservation of the integrity of the white matter is likely key in the treatment of PVL and subsequent neurological consequences and disabilities.

Keywords: prematurity; neonatal brain injury; white matter; oligodendrocyte; myelin; periventricular leukomalacia

Types of Neonatal Brain Injury

Brain injury in the newborn leads to devastating neurological consequences and is the leading cause of neurological disabilities, including motor and cognitive deficits. Several forms of neonatal brain injury are associated with the development of cerebral palsy (CP)[1-4]; these include periventricular leukomalacia (PVL), intraventricular hemorrhage, periventricular hemorrhagic infarction, neonatal stroke, hypoxic-ischemic encephalopathy, and combined gray and white matter injury (Table 1).

The leading cause of CP is PVL in premature infants. PVL is traditionally classified as a white-matter disorder, and is the predominant form of brain injury. However, the white-matter damage underlying PVL is now recognized as the major component of a more generalized injury to the cerebrum that includes neuronal and axonal injury, and has been renamed "encephalopathy of prematurity"[5]. The classical lesion of PVL involves macroscopic cystic or non-cystic necrotic lesions with pan-cellular degeneration. Current data indicate that the incidence of cystic PVL is declining, whereas diffuse cerebral white-matter injury is emerging as the predominant lesion. Diffuse non-cystic lesions selectively trigger injury to premyelinating oligodendrocytes (OLs) and subsequent disturbances in myelination. Neuronal loss and axonal damage also occur in patients with PVL.

The occurrence of periventricular hemorrhagic infarction in association with germinal matrix hemorrhage, with or without intraventricular hemorrhage, has significantly declined over the past two decades, due in part to the antenatal administration of corticosteroids[4]. No specific preventive or therapeutic strategies, however, exist for PVL. Thus, PVL has become the major brain injury in premature in-

Table 1. Types of neonatal brain injury

Types	Lesions
Periventricular Leukomalacia	Prominent white-matter lesions
	With focal white-matter necrosis (relatively rare)
	With diffuse white-matter injury (more common)
Intraventricular Hemorrhage	Germinal matrix hemorrhagic lesions
	With ventricular expansion
Periventricular Hemorrhagic Infarction	Associated with high-grade hemorrhagic lesions
Neonatal Stroke	With cortical infarction
Hypoxic-Ischemic Encephalopathy	Cortical neuronal injury
	Thalamic and basal ganglionic injury
	Brainstem neuronal loss and gliosis
	Cerebellar injury
Combined Gray and White-Matter Injury	Single cerebral artery distribution infarcts
	Bilateral large hemispheric infarcts

fants leading to CP and cognitive impairments. In addition, hypoxic-ischemic encephalopathy, asphyxia and neonatal stroke can also cause CP, which is often associated with combined gray and white matter lesions[2,3].

Pathophysiology of Neonatal Brain Injury

Multifactorial Etiology

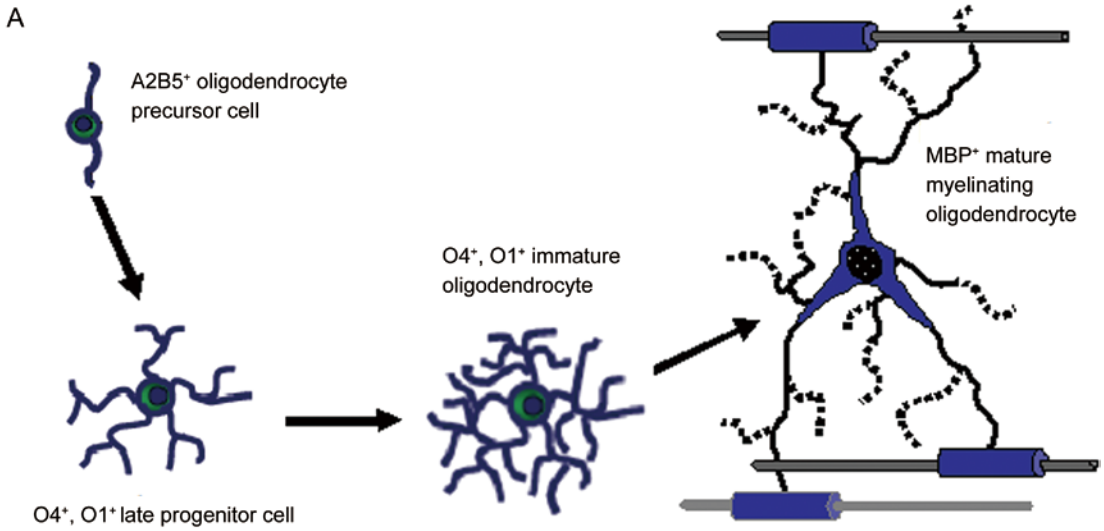
Although the etiology of neonatal brain injury is multifactorial, hypoxia/ischemia and maternal intrauterine infection are thought to be the primary causes of PVL[4]. Banker and Larroche (1962)[6] described the classic neuropathological hallmarks of PVL; they emphasized the focal necrotic lesions deep in the white matter, and proposed that anoxic injury was the most likely etiology, based in part on the stereotypical locations of focal necrosis in the border zones between the anterior, middle and posterior cerebral arteries. Premature infants are especially vulnerable to brain injury due to hypoxia/ischemia because of underdeveloped lungs that often cannot deliver enough oxygen and a heart that is relatively weak in pumping blood to the brain, as well as insufficiencies in processing oxygen and in energy metabolism. Numerous studies using a combination of hypoxia and hypoperfusion of the developing brain have successfully induced selective white-matter injury. Leviton and Gilles[7] (1984) noted the presence of a more diffuse lesion in the surrounding white matter that had been documented by magnetic resonance imaging (MRI) and subsequent pathological studies, and proposed that maternal infection is of critical importance to PVL, based originally on epidemiological studies and on the experimental demonstration of white-matter lesions after injection of the endotoxin lipopolysaccharide[8]. Numerous studies have subsequently demonstrated an increased risk of PVL associated with maternal intrauterine infection. Abundant clinical and epidemiologic studies show that *in utero* exposure to bacterial infection increases the incidence of PVL or peri/intraventricular hemorrhage in immature newborn infants.

Chorioamnionitis gives rise to a fetal inflammatory response that contributes to brain injury and subsequent CP[4,9,10]. Pro-inflammatory cytokines released during intrauterine infection cause injury to the immature brain. Endotoxemia and systemic inflammation induce rapid and profound changes in endothelial function. Intrauterine exposure to infection severely alters fetal pulmonary function and cardiovascular control, contributing to hypoxic-ischemic brain injury, especially in the periventricular white matter. During endotoxemia, enhanced nitric oxide formation contributes to the inappropriate vasodilation and peripheral vascular failure associated with endotoxic shock. Thus, *in utero* ex-

posure to bacterial infection can severely alter fetal cardiovascular function, result in dysregulation of cerebral blood flow, and lead to hypoxic-ischemic brain injury.

The Vulnerability of the Oligodendroglial Lineage

Abundant evidence shows the selective vulnerability of OL lineage cells in newborn neurological injury. The pattern of neonatal brain injury is highly age-dependent[4,10,11]. The age window of highest risk for PVL in the human brain is between 24 and 32 gestational weeks, when the cerebral white matter is predominantly populated by developing OLs (premyelinating OLs, or OL precursors, termed "preOLs")[12,13]. Injury to preOLs with subsequent hypomyelination is the major pathologic lesion in PVL, and preOLs are thus a major cellular substrate for PVL[4]. PreOLs are more vulnerable to excitotoxic, oxidative, and inflammatory forms of injury than mature OLs[4]. The OL developmental lineage is well characterized[14-16]. During OL development, cells pass through a series of distinct phenotypic stages that are characterized by dramatic changes in morphology, along with the sequential expression of unique developmental stage-specific markers: A2B5 (early precursors), O4 (preOLs, or later-stage progenitors), O1 (immature OLs), and myelin basic protein (MBP) (mature OLs) (Fig. 1A). The well-defined characteristics of the lineage provide a powerful system to study OL biology and injury in a developmental context[11,14-17].



B

Maturation-Dependent Factors of Importance in the Vulnerability of the Oligodendroglial Lineage to Excitotoxic, Oxidative or Inflammatory Injury:

- Enhanced expression of glutamate receptors in premyelinating oligodendrocytes (preOLs)
- Enhanced expression of glutamate transporters in preOLs
- Enhanced calcium permeability in preOLs
- Increased sensitivity of preOLs to oxidative stress
- Increased sensitivity of preOLs to nitrosative stress
- Impaired antioxidant defenses in preOLs
- Greater toxicity of proinflammatory cytokines to preOLs than to mature oligodendrocytes

Fig. 1. The oligodendroglial developmental lineage and maturation-dependent factors of importance in its vulnerability to excitotoxic, oxidative or inflammatory injury. A: During oligodendroglial (OL) lineage progression, cells undergo dramatic morphological changes and express sequentially stage-specific markers: A2B5 (early precursors), O4 (premyelinating OLs and later-stage progenitors), O1 (immature OLs), and myelin basic protein (MBP) (mature OLs). B: The premyelinating OLs are more vulnerable than mature OLs to multiple forms of injury.

Several maturation-dependent factors are responsible for the intrinsic vulnerability of preOLs in immature white matter to excitotoxicity, oxidative stress and inflammation (Fig. 1B), and these major events work together in a synergistic manner to cause white-matter injury. Glutamate can cause the maturation-dependent death of preOLs by non-receptor- and receptor-mediated mechanisms. The non-receptor-mediated mechanism involves glutamate competition for the cystine transporter and promotion of cystine efflux under conditions of high extracellular levels of glutamate, leading to the depletion of intracellular glutathione, which requires cysteine for biosynthesis, and cell death by oxidative stress[18]. The receptor-mediated mechanism is more likely to occur *in vivo*, as lower levels of glutamate are required to cause excitotoxicity mediated by glutamate receptors (GluRs). The sources of glutamate in cerebral white matter after hypoxia-ischemia appear to be mainly glutamate transporters[19]. Glutamate levels in white matter are regulated by high-affinity, sodium-dependent glutamate transporters on OLs, astrocytes, axons, and microglial cells. When ATP levels fall and the energy-dependent Na^+-K^+ cellular gradient is lost, the glutamate transporters fail and operate in reverse. OLs appear to be quantitatively the most important cells for glutamate transport in white matter, and the major source for extracellular glutamate in hypoxia-ischemia or inflammation[20]. Microglial cells, activated by inflammatory stimuli, also release glutamate by various mechanisms including reversal of a Na^+-dependent transporter, operation of the cystine-glutamate antiporter, and vesicular release. Inflammation, pro-inflammatory cytokines, and oxidative stress can disrupt glutamate homeostasis and inhibit glutamate transport in OLs and astrocytes[19,21]. Because excitoxicity in preOLs is mediated in considerable part by the generation of oxidative species, amplification of excitoxicity and oxidative stress *via* effects on glutamate transport is entirely plausible. The expression of glutamate transporters is transiently, developmentally enhanced in cerebral white matter in human infants during the time of peak vulnerability to PVL, suggesting that glutamate transport is involved in the maturation-dependence of preOL toxicity and in the genesis of human PVL[19,21].

Recent studies[22,23] have shown prominent white-mat-

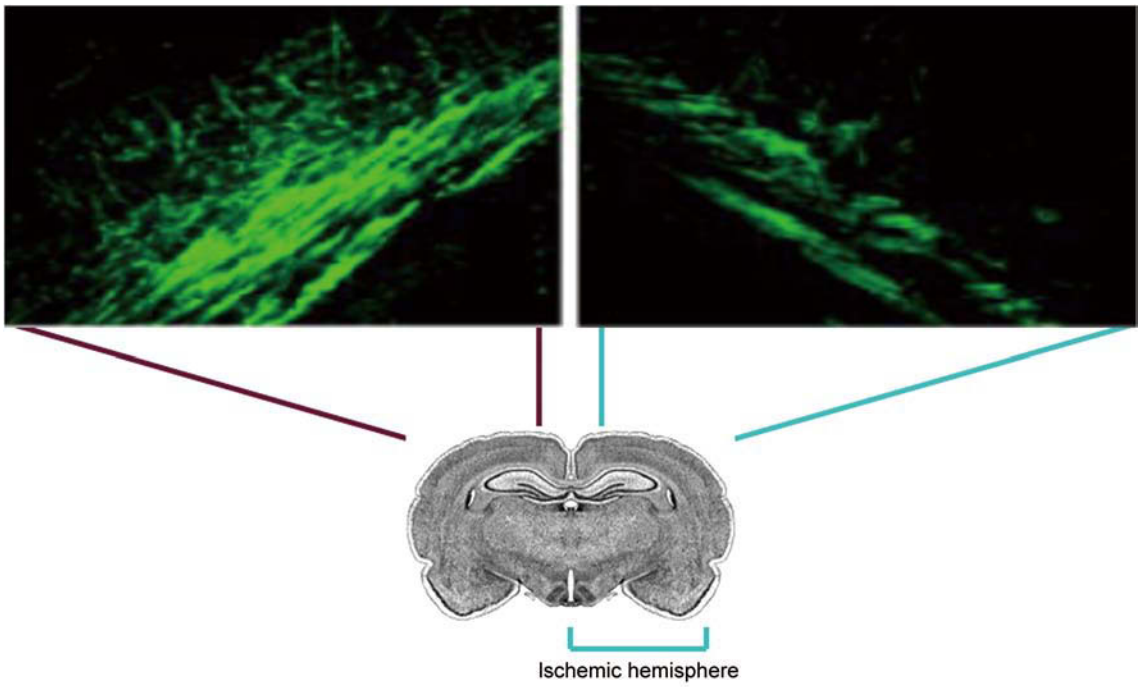


Fig. 2. A mouse model of periventricular leukomalacia (adapted from Shen *et al.*, J Vis Exp, 2010[23]). Mice at postnatal day 6 were subjected to unilateral carotid ligation plus hypoxia (6.5% O_2 for 35 min). Brain sections were analyzed by immunostaining with myelin basic protein (MBP) 96 h after hypoxia-ischemia. Prominent MBP loss is shown in the ipsilateral white matter as compared to the contralateral side.

ter damage in animal models of PVL (Fig. 2). Characterization and analysis of the animal models have shown that synapses between axons and preOLs are quickly eliminated or profoundly damaged in immature white matter[22]. Axon-glia synapses thus are highly vulnerable to white-matter injury in the developing brain, and importantly, the loss of synapses between axons and preOLs occurs before any cellular loss[22]. Hypoxia-ischemia causes a drastic decrease in the number of postsynaptic densities associated with glutamatergic axon-glia synapses defined by the expression of vesicular glutamate transporters (vGluTs), vGluT1 and vGluT2, on axon terminals that form contacts with preOLs in periventricular white matter[22].

Microglial Activation and Astrogliosis as Key Triggers for Neonatal White-Matter Injury

The selective damage of OL lineage cells in PVL is unlikely to be due solely to autonomous cell-intrinsic vulnerability. Numerous studies have demonstrated that microglial activation and astrogliosis play important roles in triggering white-matter injury in PVL.

Microglial cells are found throughout the CNS and participate in the onset and progression of inflammatory responses. Microglia, when activated, are highly damaging to CNS tissue and function through the production of neurotoxins, glutamate, nitric oxide, and inflammatory cytokines[24,25]. Microglia have indeed emerged as a potential convergence point in the potentiation of CNS white-matter injury by the deleterious effects of inflammation and neurotoxicity as seen in PVL[26]. PVL lesions may be the consequence of disruption of the interactions among microglia and OLs and axons. At the time of injury, resident microglia may promote endogenous regenerative capacity and may have the capacity to promote repair in the white matter, but persistent microgliosis can cause an extension of that injury by inappropriate or pathological activation of cytotoxic pathways. The toxic interactions of microglia with neurons and OLs have been previously described[24,25]. Despite the critical role of microglial activation in PVL and many other CNS diseases, its molecular mechanisms remain poorly defined. Pro-inflammatory cytokines are elevated in the injured CNS, and have also been implicated in cell death. Recently, many studies have examined the effects of cytokines on neuronal and glial excitotoxicity. In particular, emerging data indicate that the dynamic susceptibility of both neurons and OLs to excitotoxicity is acutely potentiated by the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α)[27].

Astrocytes are more resistant to various forms of injury or cell death than are neurons and OLs. However, astrogliosis is a common event in CNS injury and disease. Primary and secondary glial cell death can cause and aggravate CNS diseases. Like neurons, glial cells are vulnerable to glutamate insult. In particular, astrocytes, microglia, and OLs are all equipped with glutamate receptors and transporters that mediate the deleterious effects of the excitatory amino-acid. Astrocytes are responsible for most glutamate uptake in synaptic and non-synaptic areas and are consequently the major regulators of glutamate homeostasis. In addition, astrocytes but not OLs contain glycogen. In the absence of glucose, astrocyte glycogen is converted to lactate and transferred *via* the extracellular space to neighboring axons. Within axons, lactate is converted back to pyruvate and fuels oxidative energy production to sustain axonal function and stave off injury[28]. Microglial cells produce cytokines, which can impair glutamate uptake and reduce the expression of glutamate transporters. OLs are highly vulnerable to excessive glutamate signaling, which can lead to injury or killing of these cells. A thorough understanding of these triggering events will undoubtedly lead to better therapeutic strategies to treat CNS diseases affecting glia and in particular, those that involve damage to immature white matter.

Overlapping Mechanisms of Excitotoxic, Oxidative, and Inflammatory Injury to the Oligodendroglial Lineage and the Immature Brain

The consensus of our current understanding of the pathogenesis of neonatal brain injury is that multiple forms of injury including excitotoxic, oxidative, and inflammatory mechanisms are involved, and interactions among these mechanisms are likely and important for the pathogenesis of injury to the OL lineage and the immature brain[4,9,10].

Excitotoxic Mechanisms

Glutamate excitotoxicity underlies the pathogenesis of many brain disorders. Previous research has focused largely, if not exclusively, on neuronal excitotoxicity[29,30]. However, emerging data indicate that preOLs share with neurons a high vulnerability to excitotoxic injury[31-37]. Although the main function of OLs is the formation and maintenance of the myelin sheath around axons in the brain, much atten-

tion has focused recently on the possibility that these cells are capable of responding to or influencing neuronal activity and that some of these functions may be essential for neuroprotection and brain repair[9]. GluR expression on OLs is developmentally regulated, and GluR-mediated excitotoxicity is the principal mechanism for preOL death with oxygen-glucose deprivation *in vitro*[38-40] and in cerebral white matter injury *in vivo*[36,37]. GluRs have *N*-methyl-*D*-aspartate (NMDA) and non-NMDA subtypes. Although non-NMDA subtype GluRs appear to play a critical role in hypoxic-ischemic injury to preOLs[38,39], recent studies indicate that OLs *in situ* also express NMDA subtype receptors on cellular processes, while non-NMDA receptors are mostly localized on the soma, and that overstimulation of non-NMDA receptors leads to rapid cell death, while overstimulation of NMDA receptors leads to loss of cellular processes[41-43]. Thus, both NMDA and non-NMDA GluRs may play important roles in preOL excitotoxicity and white-matter damage in the developing brain.

Neonatal brain injury is primarily due to hypoxia/ischemia and infection/inflammation. Hypoxia-ischemia causes energy failure and extracellular glutamate accumulation. Thus, glutamate excitotoxicity is often a primary event during hypoxia-ischemia. Although infection/inflammation may not directly cause excitotoxicity to the brain, injured, dying or dead cells due to infection/inflammation can release glutamate into the extracellular milieu, causing secondary excitotoxicity to the cells or neighboring cells. In addition, inflammatory processes may contribute to white-matter injury by inducing a failure of glutamate homeostasis, leading to excitotoxic injury and oxidative stress. Taken together, the two major initiating events in PVL, hypoxia/ischemia and infection/inflammation, lead to glutamate excitotoxicity and oxidative damage.

Oxidative Mechanisms

There is compelling evidence that oxidative and nitrosative insults are intensely involved in the pathogenesis of the human PVL lesion[44,45]. Abundant evidence shows that oxidative damage markedly increases in the brain during reperfusion after hypoxia-ischemia and/or during systemic infection/inflammation. Thus, oxidative stress is a final common mechanism of PVL. PreOLs exhibit maturation-dependent vulnerability to oxidative damage, and, for example, are much more vulnerable than mature MBP-expressing OLs to iron and nitric oxide toxicity. The preOLs are exquisitely vulnerable in part because there is a developmentally-regulated lack of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase and catalase.

Inflammatory Mechanisms

Systemic infection/inflammation, initiated in the maternal intrauterine environment, is involved in the pathogenesis of many cases of PVL. The initiating microorganisms for the fetal inflammatory response syndrome are diverse. Activation of microglia in the context of infection is postulated to occur in considerable part by way of a relatively small number of specific cell-surface receptors, i.e. toll-like receptors (TLRs), which respond to specific molecular motifs, i.e. pathogen-associated molecular patterns (PAMPs), shared by the products of many microorganisms[4,46]. Because similar molecular motifs are shared by many microbial products, the relatively small number of specific TLRs is the basis for an immediate response or innate immunity to many different organisms. This evolutionarily ancient cellular system provides the first line of host defense against a large variety of pathogens. Initial work focused on lipopolysaccharide, a toxic product of Gram-negative organisms like *E. coli*, a major cause of maternal intrauterine infection and early neonatal sepsis. In addition to the white-matter injury, prominent findings are the infiltration of white matter by activated microglia and upregulation of pro-inflammatory cytokines. Studies have shown that the lipopolysaccharide receptor TLR4 is required for OL injury triggered by microglial activation. Recent work has been extended to Gram-positive organisms - a spectrum of microbes also capable of activating microglia and innate immunity to produce cell death in the brain. Group B *Streptococcus* (GBS) is one of the most common organisms involved in maternal-fetal/neonatal infection/inflammation in premature infants. Recent studies have shown that whole GBS and a secreted factor from GBS (GBS-F) induces neuronal death in co-cultures of OLs/neurons and microglia[24,25]. Microglia and OLs express TLR2, the TLR for PAMPs from Gram-positive organisms like GBS. Experiments both with co-cultures of microglia-OLs/neurons and in animal models have shown that microglial activation is necessary for oligodendroglial and neuronal toxicity induced by infection/inflammation[24,25].

Currently, molecular characterization of the toxic products and their generation is lacking, as well as the

identification of activators of the innate immune system in the immature brain. The cellular mechanisms by which systemic infection/inflammation produces these responses in the developing brain remain unclear. Microglial activation contributes significantly to pro-inflammatory cytokine production in the developing brain in hypoxia/ischemia and infection/inflammation[4,5,9,24]. TNF-α and interleukin-1β are well characterized cytokines induced in both hypoxia/ischemia and infection/inflammation[4,5]. TNF-α levels are increased during hypoxia/ischemia. Activation of microglial GluRs stimulates the microglial production of TNF-α in a Ca^{2+}-dependent manner[47]. TNF-α can potentiate the toxicity to preOLs caused by interferon-γ[24,25,47]. Other microglial mediators that may play a significant role in excitotoxicity include interleukin-1β, glutamate, nitric oxide and peroxynitrite, and proteases. Microglial activation is a likely contributor to preOL injury in PVL. Anti-inflammatory compounds or agents that inhibit microglial activation, such as minocycline, have been reported to attenuate brain injury in models of excitotoxicity and hypoxia/ischemia[48,49].

Myelination and Plasticity in Children with Neonatal Brain Injury

Increasing evidence indicates that myelination is regulated by activity or experience, and plasticity in myelination or remyelination processes is implicated in neurodevelopmental disorders[50]. Children with neonatal brain injury and CP are known to show remarkable neural plasticity after early brain injury. Transcranial magnetic stimulation techniques have been used to treat such children, and neurophysiological techniques, such as quantitative electroencephalography, visual-evoked potentials and somatosensory-evoked potentials, are useful tools for the determination of plasticity in these patients. There is also evidence demonstrating anatomical plasticity and brain re-organization in children with neonatal brain injury and CP. Currently, diffusion tensor imaging is widely used for the evaluation of white-matter tract injury in various brain diseases, since this form of imaging is more sensitive than conventional MRI in the detection of micro-structural damage. Previous data demonstrated white-matter injury on diffusion tensor imaging while conventional MRI failed to demonstrate any structural abnormality in preterm infants[51,52]. Nevertheless, until recently there has been no cross-correlation study between motor pathway injury and motor dysfunction. A characteristic feature of PVL is the disruption of corticospinal axons, while the cortical pyramidal projection neurons are relatively intact and subsequently make aberrant intracortical axonal projections. The rapidly expanding understanding of CNS axonal regeneration indicates that with early intervention there are realistic prospects of inducing corticospinal axons to regrow through the cystic areas of PVL and find their appropriate targets. Myelin inhibits axonal growth, but this should not pose an encumbrance to axonal regrowth, since the corticospinal tract is poorly myelinated before term. Corticospinal axons are actively growing, innervating the spinal cord and expressing GAP43 during the preterm period, and are thus likely to have a high degree of plasticity. Interventions providing early regeneration of corticospinal projections and re-innervation of the spinal cord in preterm infants with PVL would be likely to reduce disability, not only by re-establishing the cortical input to spinal motor centers but also by facilitating their subsequent normal development. Diminished motor cortical connectivity within the motor control areas, along with injury to the corticospinal tracts, could be a relevant pathophysiological mechanism producing motor dysfunction, whereas reduced thalamic connectivity to the anterior cingulate cortex might be more related to impaired cognitive function in patients with CP.

It is now recognized that gray-matter injury is commonly associated with PVL and other forms of neurological injury in the newborn[5,53,54]. However, it remains unclear whether gray-matter injury is involved in the pathogenesis of motor deficits in these diseases. Recent data demonstrate that descending motor pathway injury along with overlying cortical volume reduction and decreased functional connectivity could be a leading pathophysiological mechanism for motor dysfunction in patients with PVL. Increased $GABA_A$ receptor-binding potential, especially within the areas of decreased connectivity, could be related to a compensatory plasticity process after brain injury. Axonopathy may contribute importantly to white-matter abnormalities[55]. There is a marked reduction in the density of pyramidal neurons in layer V overlying white-matter injury. Layer V neurons give rise to the corticospinal tract descending through the white matter and may have been lost by retrograde degeneration. No decrease was observed in the density of layer III pyramidal neurons, which, unlike layer V neurons, do not proj-

ect into white matter. Neuronal deficits in PVL also involve the thalamus and basal ganglia. The thalamus is particularly involved and is characterized by neuronal loss, gliosis, and intrathalamic axonal degeneration, and involves the mediodorsal and reticular nuclei. The latter topography is noteworthy because of the relation of these nuclei to working memory and attention, deficits of which are common in survivors of prematurity.

In addition, white-matter neurons are abundant in the premature brain and consist in large part of subplate neurons and late-migrating interneurons. Subplate neurons are critically involved in the development of the cerebral cortex and the thalamus during the third trimester of human gestation[5]. These neurons are selectively vulnerable to hypoxia-ischemia in neonates. The consequences of injury to subplate neurons for the development of cortex and thalamus could be considerable. These abnormalities of neurons/axons in the cerebral cortex, thalamus, basal ganglia, and white matter in PVL are likely the anatomic correlates of the findings from a large number of advanced MRI studies of decreased volumetric development of these neuronal structures and white-matter diffusion changes consistent with axonal abnormalities in the encephalopathy of prematurity. Understanding the compensatory plasticity process after brain injury has tremendous implications for the treatment of children with neonatal brain injury and CP.

Conclusions and Perspectives

The vulnerability of preOLs is a critical factor in neonatal brain injury, and particularly in PVL. The diffuse form of white-matter damage is a leading cause of CP, especially in premature infants with very low birth weight. The underlying pathophysiological mechanisms of diffuse white-matter injury include excitotoxic, oxidative and inflammatory forms of injury to the immature brain. Maternal-fetal infections or chorioamnionitis are key risk factors that exacerbate hypoxic-ischemic brain injury resulting in white-matter injury and the development of CP. Currently, there is no specific treatment for PVL, and no specific agent has been unequivocally established for a clinical trial in premature infants. Hypoxia/ischemia, infection/inflammation, excitotoxicity and oxidative damage are known pathogenic events and mechanisms, which may interact in an amplifying manner, rendering developing white matter highly vulnerable in the pathogenesis of PVL. Further elucidation of age-specific mechanisms is necessary for the development of age-specific therapy for newborn neurological injury and CP. Understanding the compensatory plasticity process after the brain injury provides new insights into the pathogenesis and treatment of newborn neurological injury and CP. As we continue to improve our understanding of the mechanisms of injury to the immature brain, preventive and therapeutic strategies for neonatal brain injury and CP will evolve.

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