

Periventricular Leukomalacia

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Cerebral white matter damage results in periventricular leukomalacia (PVL), which is a common form of brain injury in preterm infants. PVL is a serious health issue, leading to some form of neurologic and/or cognitive deficit in as many as 90% of surviving preterm infants with a birth weight less than 1500 g (Khwaja et al., 2008). PVL is primarily a white matter disorder, with essentially complete loss of cells in necrotic areas of white matter and loss of premyelinating oligodendrocytes with accompanying astrogliosis and microglial activation in other areas. There is often some neuronal loss, particularly of subplate neurons, which are important for early organization of the developing cortex. PVL primarily results from hypoxia/ischemia in preterm infants, although infection and inflammation also contribute to the damage.

The particular vulnerability of the preterm infant brain to PVL likely results from several developmental features of the fetal brain. The preterm infant brain has significantly lower cerebral blood flow compared to term infants or adults, and this reduced blood flow makes this stage of brain development particularly vulnerable to ischemic damage. Slightly reduced blood flow that might go unnoticed in term infants could have serious consequences for preterm infants. The specific damage induced by cerebral ischemia in the preterm brain likely also results from the presence of two cell types that are abundant in developing white matter at this stage. Microglial cells are found in brain at very early stages of development, but they are particularly abundant in white matter during the last trimester of gestation, the period of greatest risk of PVL. Additionally, in the third trimester of development, human fetuses are beginning to myelinate axons in the forebrain, and during this early stage of myelination, the oligodendrocyte progenitor

cell differentiates into the late oligodendrocyte progenitor/premyelinating cell. The premyelinating cell is most abundant in white matter, and it remains in human parietal white matter for as long as three months at the end of gestation before it starts to myelinate axons (Back et al., 2001).

Within the oligodendrocyte lineage, the premyelinating cell is particularly vulnerable to oxidative damage and other insults. In tissue culture studies of rodent cells, late oligodendrocyte progenitor cells are far more vulnerable to oxidative damage than mature oligodendrocyte, in part because they are more sensitive to loss of glutathione. Increased reactive oxygen species can be produced by the oligodendrocyte progenitor cells themselves, leading to their death (Back et al., 1998). In PVL tissue, the premyelinating cell expresses high levels of protein nitration and lipid peroxidation, hallmarks of oxidative damage (Haynes et al., 2003). Thus, ischemic damage during the last trimester of gestation appears to have its greatest impact on premyelinating cells, leading to their death.

As noted above, the abundance of microglia in white matter during the third trimester also contributes to the damage. Microglia are likely to be the major source of the reactive oxygen species, and proinflammatory cytokines released by activated microglia also contribute to the death of premyelinating oligodendrocytes. Microglia would be particularly activated in tissue that is also exposed to infection or other sources of inflammation, which, as noted above, are contributing factors for PVL.

Other sources of damage result from excitotoxicity during ischemia/reperfusion. Premyelinating oligodendrocytes express Ca^{2+} -permeable glutamate receptors and the major brain glutamate transporter EAAT2. During ischemia, extracellular glutamate accumulation, both from neurons and from reversal of the glutamate transporters upon energy depletion, could

induce Ca²⁺-mediated premyelinating cell death.

Therapeutic approaches to reducing the incidence of PVL are coming from careful monitoring of changes in brain blood flow to reduce the likelihood of ischemia and from reducing potential oxidative damage or excitotoxicity, but PVL remains a serious concern for preterm infants.

References

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