Can We Define the Pathogenesis of Human Periventricular White-Matter Injury Using Animal Models?

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In this issue, Dr Back et al present an elegant model of periventricular white-matter injury using fetal sheep between 90 and 120 days of gestation. This gestational epoch corresponds especially nicely to the neurodevelopment of oligodendrocytes, seen in the preterm human infant between 24 and 28 weeks of age. Although a number of fetal sheep models have been described and used to mimic hypoxic-ischemic or inflammatory insults to the developing brain (reviewed in Hagberg et al), the model described in this article has the added benefit of correlating the molecular and cell fate commitment of oligodendrocytes with changes in cerebral blood flow as measured by high-resolution spatially defined techniques performed in utero. A careful analysis of oligodendroglial lineage progression has been done and compared with that reported previously by the authors for humans, showing a tight correlation. Given that impaired cerebrovascular autoregulation in the setting of blood pressure instability has been implicated in the pathogenesis of periventricular white-matter injury, the authors used fluorescently labeled microspheres to determine spatial blood flow of the ovine fetus. They found that even basal blood flow was markedly lower in parietal and frontal periventricular white matter than in many thalamic nuclei and the cortex. They are now poised to study the effects of regional and global ischemia and infection on flow to vulnerable regions and subsequent development of white matter as it relates to oligodendrocyte maturation. In fact, in a recent publication, Riddle et al showed that spatial heterogeneity in oligodendrocyte lineage is actually linked to stage at maturation when the insult occurs rather than to cerebral blood flow.

In human preterm newborns, a wide range of abnormalities have been described using magnetic resonance imaging (MRI) that supersede our previous thinking that the disease is restricted to periventricular leukomalacia. In fact, it appears that the periventricular leukomalacia described by Banker and Larroche is now decreasing, but periventricular white-matter injury is not. For example, white-matter injury can be patchy or diffuse, accompanied by ventriculomegaly, or the latter seen in isolation. Hemorrhage can also be seen in these fragile newborns in both the cerebrum and the cerebellum.

Do the animal models reflect these variations? The recently described baboon model sustains a spectrum of neuropathologies, including those described above for humans. The value of the baboon model is that no insult is being created or inflicted on the animals; rather, they are just being born prematurely and being subjected to that which would be experienced by the human preterm newborn. The white-matter injury seen in the baboons ranges from small patches of reactive astrocytosis to cystic lesions. Hemorrhages seen in the baboons ranged from ventricular, white matter, germinal matrix, subarachnoid, to cerebellar in location. Importantly, gray-matter injury is also seen in this model, as well as in the fetal sheep model described by Back et al. Hippocampal damage, as well as cortical and deep gray-matter injury, is documented. Although the degree of ischemia certainly predicts gray-matter damage in the fetal sheep model, it appears that the heterogeneity seen in the periventricular white matter is more closely associated with oligodendrocyte lineage susceptibility.

Therefore, it is important to get the modeling precise because the degree of injury and the age at which the insult is experienced will dictate the outcome. In a few recent studies, the degree of white-matter injury seen on early MRI in newborn humans can predict neurodevelopmental outcome in the first few years of life. A study by Shah et al showed that cerebellar volumes are smaller in preterm infants at term equivalent compared with term controls. The reduction in volume was associated with the degree of white-matter injury. Cognitive and motor developmental outcomes were principally mediated by the white-matter injury. A study by Miller et al also showed that an abnormal outcome was associated with increasing severity of white-matter injury, as well as ventriculomegaly and intraventricular hemorrhage.

In the chronically instrumented fetal sheep, a number of insults can be created, such as intermittent ischemia or hypoxia, systemic hypotension, raised intracranial pressure, and even the administration of infectious agents or drugs that can disturb brain development. This capability allows for the creation of a variety of lesions that can be studied pathogenetically in greater detail.

Like other models before it, this model attempts to address the complexities of the pathophysiology of white-matter injury in...
the premature brain. The information gained from this model and future studies that might manipulate the inflammatory response in these animals might shed light on the genesis of periventricular white-matter injury in the human.

References

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