

Imaging Insights of Alterations and Adaptations in the Preterm and Late Preterm Brain

Preterm birth is associated with increased risk of brain injury and adverse neurodevelopmental outcome.¹ The last 2 decades have brought improvements in the survival of preterm infants, but with controversy over whether the rates of neurodevelopmental impairment have increased, remained static, or decreased.²⁻⁴ In the United States alone, >60 000 infants weighing <1500 g are born annually.⁵ Magnetic resonance imaging (MRI) provides an opportunity to characterize the nature and timing of cerebral injury and alterations in cerebral development in preterm infants both during their intensive care unit stay and throughout childhood.⁶ This issue of *The Journal* presents 3 important articles that further delineate the impact of preterm birth on cerebral development.

Adams et al⁷ use diffusion tensor (DT) MRI to identify alterations in cerebral white matter microstructure within the corticospinal tract in 55 preterm infants from 28 weeks postmenstrual age to term equivalency. They report 4 principal findings: (1) Infants with white matter injury on conventional MRI demonstrated the greatest diffusion abnormalities; (2) the greatest alterations were found in radial diffusivity, consistent with a selective vulnerability of oligodendrocytes; (3) postnatal infection was the strongest perinatal risk factor for altered white matter microstructure; and (4) abnormalities became more prominent as the infants grew toward term equivalency, suggesting an enhanced and lasting developmental impact of early white matter lesions.

White matter injury is the most common neuropathological lesion in preterm infants. It appears to be mediated by the maturational vulnerability of immature oligodendroglia to free radicals and/or excitatory amino acids generated as a result of ischemia and inflammation. The study of Adams et al is consistent with previous work confirming vulnerability in the white matter of the corticospinal tract with greater technical elegance on DT-MRI, and extends our understanding of the impact of early injury by a greater developmental deficit in white matter development by term equivalency. The time course of an increased developmental deficit in white matter microstructure by term equivalency might be consistent with secondary axonal injury accompanying both primary oligodendroglial and neuronal injury. Diffuse axonal degeneration by apoptosis has been found throughout the white matter of preterm infants,⁸ often many weeks after birth. The finding of progressive abnormality also reinforces the concept of a more protracted period of vulnerability to cerebral white matter in-

jury in preterm infants. Recent studies have demonstrated that after an initial insult to the cerebral white matter in the immature brain, there is a compensatory increase in oligodendroglia progenitors,^{9,10} presumably to replace the injured cells. It appears that these progenitors fail to undergo normal maturation, however, remaining trapped at a developmentally vulnerable phase for repeated injury late in the neonatal course.¹¹ Thus, the enhanced vulnerability to insults, such as postnatal infection and ischemia, may extend through to term equivalency for newly generated oligodendroglia.

Adams et al do not provide neurodevelopmental outcome data. They hypothesize, consistent with other studies, that the white matter disturbance will relate most strongly to subsequent motor dysfunction, such as developmental coordination dysfunction, which occurs in close to 50% of preterm infants in early childhood.

In addition to these findings in the cerebral white matter, in this issue of *The Journal* Lawrence et al¹² further extend our understanding of the impact of very preterm birth (<33 weeks) on cerebral development. The authors studied 22 young adults who were born at <33 weeks gestation and had no major injury (eg, cystic periventricular leukomalacia, grade III/IV intraventricular hemorrhage) or cerebral palsy. The performance of these 20-year-olds on a verbal paired associate learning task was equivalent to that of normal term-born controls; however, functional MRI performed during the task showed activation in the left parahippocampal gyrus rather than the hippocampus, as occurs in normal controls. Furthermore, the hippocampal volumes were diminished and the neighboring parahippocampal gyrus was enlarged in the adults born preterm compared with controls. This finding suggests the occurrence of a compensatory cerebral reorganization after neuronal injury to the hippocampus to allow successful task performance in young adulthood. This remarkable finding highlights two important conclusions. The first is the importance of neuronal injury in the preterm infant, including injury to the hippocampus. Other neuropathological and MRI studies in preterm infants have demonstrated that close to one-half of infants display injury and alterations in neuronal regions, including the cerebral cortex, hippocampus, cerebellum, brainstem, thalamus, basal ganglia, and subplate neurons.¹

The second conclusion is the presence of adaptive developmental cerebral mechanisms that allow compensatory cognitive and language function after neuronal injury associated

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DT	Diffusion tensor
MRI	Magnetic resonance imaging

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with preterm birth. The most immature preterm infants displayed the greatest reduction in hippocampal volume and the greatest compensatory increase in parahippocampal volume and functional activation. Although many preterm infants have adverse neurodevelopmental outcomes, perhaps the more remarkable finding is that a substantial fraction have normal neurodevelopmental outcomes. This study suggests that this diversity of outcome might be related not only to the extent of cerebral injury, but also to the degree of adaptive cerebral reorganization. In the future, these MRI techniques may be of great assistance in evaluating the impact of infant and childhood intervention programs on cerebral development. As the preterm infant grows through infancy and childhood, an understanding of the factors that enhance positive compensatory mechanisms in cerebral development and function would be valuable.

Finally, Van Soelen et al¹³ increase our awareness of structural alterations in brain development in late preterm infants born between 32 and 37 weeks gestation. The authors studied 192 late preterm and term-born twins at 9 years of age and found a reduction in cerebellar volumes in relation to earlier gestation, independent of birth weight, sex, and intracranial volume. The cerebellum in the very preterm infant has been increasingly recognized to be vulnerable to injury and altered development, with adverse neurodevelopmental impact on motor, language, and social-behavioral outcomes.¹⁴

What are the implications of these three studies for the clinician? They highlight the power of neuroimaging to reflect the vulnerability of three major cerebral regions in preterm and late preterm infants: the cerebral white matter, cerebellum, and hippocampus. Thus, they ask the neonatal clinician to broaden awareness of the impact of preterm birth on the brain beyond that of intraventricular hemorrhage with vulnerability extending to the late preterm infant. They confirm the perinatal risk factors of immaturity, likely mediated by physiological instability, ischemia, and postnatal infection for cerebral injury and altered development. They demonstrate two ends of the spectrum: ongoing vulnerability of white matter during the period in the neonatal intensive care unit, followed by compensatory neuronal adaptation during childhood. The role of additional factors in the vulnerability of the preterm brain and its capacity for compensatory adaptation, including drug exposures, nutrition, the environment, and parenting, should be highlighted for future research focus. The insights from these studies continue to assist our journey in the understanding of the impact of preterm birth on cerebral development: "Go as far as you can see; when you get there you'll be able to see farther" (Thomas Carlyle). ■

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