Value of sequential MRI in preterm infants

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Neurology® 2013;81:2062–2063

Since the introduction of neonatal intensive care in the 1970s, there has been a pronounced decrease in overall mortality of premature infants as well as a decrease in the incidence of severe white matter injury, best known as cystic periventricular leukomalacia (c-PVL).[1] While cranial ultrasonography readily visualizes large lesions in the white matter (periventricular hemorrhagic infarction and c-PVL), this technique is not sufficiently sensitive to recognize the much more common and less severe noncystic white matter lesions.[2] The absolute number of extremely preterm infants is increasing because of improved survival rates.[e1]

Because these vulnerable infants are at particular risk of developing less severe white matter injury, techniques other than cranial ultrasonography are required to assess such injury and its subsequent effects on brain development. Over the last 2 decades, MRI has evolved and can identify at least a portion of these less severe white matter lesions, which are less likely to be associated with cerebral palsy but more likely to underlie the especially prominent cognitive and behavioral problems in very preterm infants.[3–5] More advanced magnetic resonance techniques, such as diffusion tensor imaging (DTI) and magnetic resonance spectroscopic imaging (MRSI), provide more detailed information about white matter microstructure (DTI) and metabolism (MRSI). Indeed, an initial report published 15 years ago[6] showed DTI evidence for immature white matter microstructure in premature infants at term-equivalent age. The important addition of the work of Chau et al.[7] published in this issue of *Neurology*® is the *sequential* study of very preterm infants. Chau et al.[7] have studied large numbers of extremely preterm infants sequentially with advanced magnetic resonance techniques. Another well-established group reported serial MRI data in this journal in 2011 and demonstrated that the rate of cerebral cortical growth predicted cognitive, but not motor, skills in childhood.[e2]

Chau et al.[7] report a prospective study of 157 preterm infants, born between 24 and 32 weeks' gestation, with MRI shortly after birth and again at term-equivalent age. In 140 of the 157 infants, they were able to perform MRI twice. An additional strength of their study is the combined use of DTI and MRSI. Thus, they assessed both white matter microstructure with fractional anisotropy (FA) (and radial and axial diffusion) and brain metabolism with the ratio of *N*-acetylaspartate (NAA)/choline. FA is known to increase in parallel with the maturation of the oligodendrocyte lineage and early myelination, while the NAA/choline ratio, which largely reflects neuronal integrity and metabolism, also increases with brain maturation.[6] Ninety-one percent of their survivors were assessed at 18 months' corrected age with the Bayley Scales of Infant and Toddler Development III for their motor, cognitive, and language composite scores. In this large group of preterm infants, brain MRI scans were normal in only 56 infants (34%), but severe white matter injury was observed in only 10 infants (6%), and only 3 of these had c-PVL, in agreement with other studies.[e3] Overall, white matter injury was seen in 48 infants (30%). Isolated basal ganglia injury was uncommon and seen in only 4 infants. Using FA measurements in white matter tracts and MRSI in the basal nuclei, they concluded that impaired maturation of brain microstructure and metabolism from within a few weeks after birth was associated more strongly with early cognitive and language outcomes than with motor outcome.

The findings of Chau et al.[7] are consistent with the concept of the "encephalopathy of prematurity," i.e., the ultimate brain abnormality in premature infants 1) involves both gray and white matter, and 2) includes primary injury, especially to cerebral white matter, and secondary disturbances of maturation.[3] These subsequent maturational defects involve premyelinating oligodendrocytes (pre-OLs) in cerebral white matter,[8,9,e4] and neuronal-axonal structures in cerebral cortex, white matter, and thalamus/basal ganglia.[3]

The conclusion of Chau et al.[7] that the maturational defects detected by their MRI and MRSI measurements were independent of white matter injury requires qualification. In the neuropathologic studies establishing a relation between cerebral white matter injury, i.e., periventricular leukomalacia and neuronal-axonal disturbances,[3,10,e5,e6] the majority of

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

white matter lesions were highly likely to be below the resolution of conventional clinical MRI scans. Thus, in the largest such study of the encephalopathy of prematurity, 82% of the cases had necrotic foci in white matter of <1 mm in diameter.[10] Perhaps more importantly, in all cases, as is characteristic of periventricular leukomalacia, more diffuse white matter abnormality consisting particularly of marked astrocytosis and microgliosis was present. It is quite possible, but not yet proven, that this diffuse lesion is critical in the genesis of the maturational disturbances of pre-OLs and of neuronal-axonal structures. The potential mechanisms and temporal characteristics involved have been reviewed elsewhere.[3,11] The importance of the disturbance in pre-OL maturation, shown in the human lesion postmortem[e7,9] and in experimental models,[e7] is supported by the demonstration of radial rather than axial diffusivity abnormalities in the infants studied by Chau et al.[7] This finding is consistent with a failure of pre-OL ensheathment of axons. An especially notable feature of the present work is the delineation of a means to identify the *evolution* of these maturational deficits in vivo by sequential scans. This accomplishment could greatly facilitate both definition of mechanisms and means of intervention.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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