Neuroimaging of Extremely Preterm Infants: Perils of Prediction

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Neuroimaging, primarily using cranial ultrasound (CUS), is routinely recommended in premature infants who are born at <30 weeks' gestational age.[1] Most premature infants will be imaged with an early CUS examination (generally by 7–10 days of age) to assess for intraventricular or intraparenchymal hemorrhage and for evidence of early white matter injury. The role, timing, and prognostic value of later neuroimaging studies remain unclear. Recent data suggest that white matter and cerebellar injury, which may be more easily detected on MRI scans, is an important link to later neurodevelopmental impairment (NDI).[2–4] This observation has led to recommendations that a routine brain MRI examination at term postmenstrual age be performed for all extremely low gestational age newborns (ELGAN) as a way to better predict the risk for NDI.[5]

In this issue of *Pediatrics*, Hintz et al[6] describe the first large prospective evaluation of early (4–14 days) and near-term (35–42 weeks postmenstrual age) CUS and near-term brain MRI scans in the prediction of NDI at 18 to 22 months. In a prospective cohort of 480 infants born at <28 weeks' gestation who underwent all 3 scans, the primary outcome of NDI or death was assessed by certified examiners. All brain imaging studies were read centrally for evidence of intraventricular or cerebellar hemorrhage, white matter injury, and moderate to severe ventricular enlargement or the presence of a ventricular shunt. Multivariate models were constructed to include each type of scan individually and in combination, and they were assessed as predictors of NDI or death. Although the rates of abnormal scans and NDI and significant motor impairment were low, the authors found that both late CUS and MRI findings reflective of white matter injury or significant cerebellar injury were independently associated with adverse outcomes. Importantly, early CUS findings were not associated with adverse outcomes when any later neuroimaging was assessed in the model. A second important observation was that the predictive value of a combination of early and late CUS was only marginally improved with addition of late MRI examination both in the determination of NDI or death (receiver operating characteristic area under the curve .809 vs .826) and significant gross motor impairment or death (.885 vs .908).

This study adds important new information about the prognostic value of neuroimaging in ELGANs, and the authors appropriately suggest that current guidelines for neuroimaging in these infants be revisited. From these data, a few specific conclusions appear to be justified. First, CUS examinations in ELGANs should routinely include a mastoid view for visualization of the cerebellum; this view was included in less than half of the CUS scans performed in the current study. In Hintz et al[6] and other studies,[4] cerebellar injury is an important contributor to NDI in these infants, although the sensitivity of CUS in detecting these lesions, and their relationship to outcome, compared with MRI detected lesions is unclear.[7]

In addition, given the poor predictive value of early CUS, all ELGANs should be routinely screened with ≥1 modality of late neuroimaging at or around term gestation. Although MRI is more sensitive in detecting white matter injury than CUS, it is important to note that in this study the predictive value for NDI was only marginally improved with the addition of a near term gestation MRI compared with that of an early and late CUS examination combined. This observation calls into question whether the potential increase in costs and personnel time associated with routine use of late MRI scans in ELGANs is justified by the small additional predictive value. Research using more sophisticated volumetric and tractographic MRI techniques[8] may eventually help guide therapies to prevent brain injury and improve neurologic recovery after extreme preterm birth, but the limitations of current clinical scans should be acknowledged.

Lastly, in the current study a substantial proportion of surviving infants with severe abnormalities on either late CUS or MRI scans were only mildly impaired or unimpaired at 18 to 22 months (26.9% and 16.7%, respectively). These findings point out the perils of prediction for individual infants and our poor understanding of the impact of social or other factors on brain development. They also reinforce the importance of long-term follow-up of at-risk infants at school age and beyond. Perhaps more importantly, we need to understand the potential impact of our predictive uncertainty on the parents of these vulnerable infants. Despite incremental improvements in our ability to assess composite risk of poor neurodevelopmental outcome in ELGANs afforded by better neuroimaging techniques, they cannot yet be used to determine follow-up strategies or target interventions after discharge and thus may be of little or no benefit to many parents.[9]

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