Routine Neuroimaging of the Preterm Brain

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Neuroimaging of the preterm infant is a common assessment performed in the NICU. Timely and focused studies can be used for diagnostic, therapeutic, and prognostic information. However, significant variability exists among neonatal units as to which modalities are used and when imaging studies are obtained. Appropriate timing and selection of neuroimaging studies can help identify neonates with brain injury who may require therapeutic intervention or who may be at risk for neurodevelopmental impairment. This clinical report reviews the different modalities of imaging broadly available to the clinician. Evidence-based indications for each modality, optimal timing of examinations, and prognostic value are discussed.

INTRODUCTION

Central to the assessment of the preterm infant is identifying the presence and extent of brain injury. Preterm infants are at significant risk of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), posthemorrhagic ventricular dilatation, and other neurologic injuries that may or may not have imaging corollaries. Through neuroimaging, the neonatologist may initiate interventions and plan for supportive care and assess the risk of future neurologic impairment.

In 1968, Abraham Towbin described the frequent finding of IVH at necropsy in preterm infants, with abnormalities almost universally present in those born at less than 28 weeks’ gestation. Not until 10 years later did Papile et al describe the computed tomography (CT) findings of 46 consecutive very low birth weight (VLBW) infants and demonstrate a much higher incidence of IVH than was clinically suspected. That report described 4 separate grades of hemorrhage: "Grade I—subependymal hemorrhage, Grade II—intraventricular hemorrhage without ventricular dilatation, Grade III—intraventricular hemorrhage with ventricular dilatation, and Grade IV—intraventricular hemorrhage with parenchymal hemorrhage." Since the initial report, the Papile classification has been modified to grade I, indicating minimal IVH; grade II, with IVH occupying...
10% to 50% of the ventricular area; grade III, representing IVH with >50% of ventricular area; and last, parenchymal hemorrhage, most likely attributable to hemorrhagic venous infarction.3

These findings led to one of the earliest outcomes studies,4 in which authors described the association of major developmental and neuromotor handicaps with the findings of more severe (grade III and IV) IVH on CT scan performed between 3 and 10 days of age. On the basis of these and other studies, the American Academy of Neurology (AAN) released practice parameters in 2002 suggesting universal cranial ultrasonographic screening for all infants born at less than 30 weeks’ gestation.5 The AAN also recommended that initial screening ultrasonography be performed at 7 to 14 days after birth and repeated at near term corrected age. In 2001, the Canadian Pediatric Society recommended screening all infants born at less than 32 weeks’ gestation at 2 weeks after birth, with a repeat screening 6 weeks after birth.6 Since the publication of those guidelines, cranial ultrasonography capabilities have evolved, and modern ultrasonography technology, along with the use of supplementary acoustic windows, can now provide good structural imaging of the preterm infant brain.7

Imaging the entire brain was once performed by using CT scanning. Use of head CT has given way to improved cranial ultrasonography as well as MRI, which yields better detail and avoids the use of ionizing radiation.8 However, routine use of MRI for screening the preterm infant has been identified as being of questionable value in the Choosing Wisely campaign of the American Academy of Pediatrics.9 The aim of this clinical report is to provide guidance to clinicians for an evidence-based approach to neuroimaging for the preterm infant.

**INITIAL SCREENING EXAMINATIONS**

The VLBW (ie, birth weight <1500 g) infant is at high risk for germinal matrix and IVH as well as ischemic white matter injury as identified by cranial ultrasonography. Risk of severe IVH is inversely related to gestational age, with infants born at less than 24 weeks’ gestation at highest risk.10 In 2017, the Vermont Oxford Network database demonstrated an overall 24.6% incidence of IVH and an 8.1% rate of severe IVH, defined as grade III or IV among more than 50,000 VLBW infants.11 In a recently published survey of the California Perinatal Quality Care Collaborative, 63% of infants born at 22 to 23 6/7 weeks’ gestation had IVH, with 36% demonstrating severe IVH.12 This incidence decreased to 14% of infants whose gestational age at birth was 30 to 31 6/7 weeks having any IVH and 1.4% having a severe grade. Less severe grades of IVH (grades I and II) may have less prognostic influence on clinical outcomes. In a National Institute of Child Health and Development study of 1472 infants born at less than 27 weeks’ gestational age,13 there was no significant difference in neurodevelopmental outcomes at 18 to 22 months of those infants with and without these low-grade hemorrhages.

PVL is a disorder of the periventricular cerebral white matter that may be cystic or diffuse in nature. Most cystic PVL occurs in infants born between 26 and 30 weeks’ gestation, initially appearing as periventricular increased echogenicity (eg, a blush or flare) with cystic evolution over the course of a few weeks. Periventricular hemorrhagic infarcts (PVHs) (ie, formerly grade IV) IH occur mainly in infants born at <26 weeks’ gestation14 and occur infrequently in infants born beyond 30 weeks’ gestation.15 A PVHI is a parenchymal lesion usually associated with a large IVH and, on the basis of current understanding, believed to be caused by venous infarction. A PVHI is not, as once believed, an extension of the IVH into the parenchyma.

Severity of IVH in the most immature infants is consistent with the developmental changes of the subependymal germinal matrix as it decreases in size from 2.5 mm in the 24-week preterm infant to involution at about 36 weeks’ gestational age.3 For these and other reasons affecting vascular integrity, the more moderate and late preterm infants (those born between 32 and 36 6/7 weeks’ gestation) are at less risk for significant intracranial injury. In a retrospective study of moderately preterm infants born between 29 and 33 weeks’ gestation, 60% of a cohort of 7021 infants underwent cranial imaging, and 15% of these 1184 infants had ultrasonographic abnormalities.16 The rates of severe IVH and cystic PVL were 1.7% and 2.6%, respectively, in this population.15 The authors noted that low Apgar scores, maternal risk factors, lack of antenatal steroids, and vaginal delivery were associated with ultrasonographic abnormalities, including intracranial hemorrhage, PVL, and ventriculomegaly. The presence of risk factors such as abnormal neurologic examination, intrauterine growth restriction, abnormal head circumference, low Apgar scores, and need for ventilation or surfactant increased the chance of detecting an abnormality by fourfold in a group of more mature preterm infants born at 33 to 36 weeks’ gestational age.17 In a similar study, infants born at >30 weeks’ gestation who were found to have significant ultrasonographic abnormalities typically had clinically significant events, such as placental abruption, seizures, hypotension, and hydrocephalus, which warranted the cranial ultrasonographic investigations.18 Risk factors also play a role in the more immature preterm
infants as well. In a study of 303 infants born at <30 weeks' gestation, no asymptomatic infants required clinical intervention solely on the basis of screening ultrasonography performed at 7 to 14 days. All infants who required clinical interventions had factors precipitating an ultrasonographic study, including anemia, metabolic acidosis, pulmonary hemorrhage, and hypotension. Similar results have been reported for infants born at <32 weeks' gestation with risk factors for severe IVH including lack of antenatal steroids, outborn status, asphyxia, significant acidosis, and/or hypotension. Thus, the risk for severe IVH is associated with gestational age ≤30 weeks' gestation, with the highest risk in infants born at <24 weeks' gestation. Infants born at >30 weeks' gestation have a low risk of severe IVH unless they have additional clinical risk factors.

TIME OF IVH OCCURRENCE
The overwhelming majority of IVH in the preterm infant occurs within the first 3 days of life. Of those, approximately 50% of hemorrhages occur within the first 5 hours, and approximately 70% occur within the first 24 hours of life. By 7 days, 95% of IVH will have occurred, with a small percentage appearing at 7 to 10 days. In an analysis of infants requiring neurosurgical intervention for posthemorrhagic hydrocephalus, the average age of IVH development was 2 days, with ventriculomegaly apparent by 3 days of age. In this study, temporizing neurosurgical procedures were performed 3 weeks after IVH development. Thus, frequent follow-up of significant IVH until resolution or stabilization will likely allow for early determination of ventricular dilation and the potential need for therapy.

REPEAT BRAIN IMAGING
PVL may initially be observed during the first week of life in the VLBW infant as increased echogenicity of the periventricular white matter, sometimes described as an echogenic “blush” or “flare.” Because the periventricular white matter may normally have slight increased echogenicity, the echogenic choroid plexus can be used as an internal comparison for increased echogenicity. Normal periventricular white matter should be less echogenic than the choroid plexus. These areas of white matter abnormality may become cystic on ultrasonography within 2 to 5 weeks and/or lead to ventriculomegaly from white matter volume loss, which can be visible on repeat ultrasonography at term equivalent age (TEA). In light of these findings, the Canadian Pediatric Society recommended screening at 6 weeks of age, whereas the AAN suggested a near term study. These varying suggested time frames can lead to different timing of studies in the extremely preterm infant. Because 4- to 6-week screening is sensitive for identifying PVL and term equivalent cranial ultrasound findings are associated with adverse neurodevelopmental outcomes, we recommend screening during both time periods.

Sequential ultrasonography appears to have the best yield for identifying lesions associated with cerebral palsy. In infants with cerebral palsy, almost one third were found to have PVL on ultrasonography performed after 4 weeks of age. Among 12,739 preterm infants who were screened at 4 weeks of age and again at near TEA, notably, 14% had cystic PVL that was only visible on the early imaging and had resolved by the time of the later study. Subgroup analysis revealed that in infants born at <26 weeks' gestation, 18.5% of PVL cases were missed by a single ultrasonographic examination performed at TEA. However, a follow-up study demonstrated that infants who had cystic PVL at any time on ultrasonographic imaging had a significantly higher primary outcome of late death or neurodevelopmental impairment than those who never had such findings. Thus, even if the findings were transient, infants with cystic PVL warrant close follow-up observation for neurodevelopmental impairment. Communication regarding neuroimaging results and follow-up plans are recommended between inpatient and outpatient providers.

STANDARD CRANIAL ULTRASOUND IMAGING TECHNIQUE
Cranial ultrasound imaging has traditionally made use of the anterior fontanelle as an acoustic window and should be performed by an American Registry for Diagnostic Medical Sonography board-certified sonographer. Images of the brain are taken in the coronal plane with anterior to posterior views and in the sagittal plane with appropriate angulation on the left and right. Use of the posterior fontanelle may allow more detailed assessment of the periventricular white matter and occipital lobes. These views allow excellent visualization of supratentorial structures but limited views of the posterior fossa and cerebellum. The cerebellum has been shown to be a frequent site of injury, with significant hemorrhage occurring in as many as 9% of preterm infants with a diagnosis made by appropriately performed ultrasonography. For this reason, additional imaging through the mastoid fontanelle is recommended. In cases of limited cerebellar hemorrhage, there was much better imaging sensitivity when mastoid views were obtained (86%) than when only the anterior fontanelle was assessed (16%). However, mastoid views are unable to detect cerebellar microhemorrhages, which can only be visualized with MRI. Apart from hemorrhage, cerebellar hypoplasia is also associated with motor and...
cognitive deficits.\textsuperscript{31} Although most cases of cerebellar hypoplasia have been associated with cerebral white matter injury, other factors, including genetic and neurodegenerative syndromes, medications, infarction, and nutrition, play a role in cerebellar growth and affect neurologic outcomes. Thus, cerebellar imaging may have important diagnostic and prognostic value as part of the screening ultrasonographic examination. The addition of high-resolution linear color Doppler images obtained through the anterior fontanelle can be used to evaluate for patency of the superior sagittal sinus. If there is concern for venous sinus thrombosis, the posterior and mastoid windows can additionally help to evaluate the sagittal and transverse sinuses. Many centers are also measuring the resistive index of the anterior cerebral artery as a marker for vascular compliance and to document normal waveforms and diastolic flow.

\textbf{MRI}

MRI has become increasingly popular as a means of identifying brain injury in the preterm infant. MRI provides the most detailed imaging of the brain and avoids the radiation risks associated with CT.\textsuperscript{34} Specific absorption rates (a measure of power of radiofrequency fields) in patients undergoing magnetic resonance procedures appear to be much lower in neonates than adults and within a safe and acceptable range.\textsuperscript{34} MRI studies may be successfully performed in the preterm population at TEA without the use of any sedating medications.\textsuperscript{35,36} Protocols that rely on feeding the infant 20 to 30 minutes before the scan and swaddling to limit movement have generally been successful in avoiding significant sedation in the majority of cases. With the use of nonsedated MRIs and the increasing availability of MRI-compatible equipment, this imaging has become more readily obtainable. Yet, controversy persists regarding which infants should receive MRI studies at TEA. Abnormal findings on MRIs performed at TEA in a group of infants born at \textless30 weeks' gestation have been shown to be predictive of psychomotor delay and cerebral palsy at 2 years of age.\textsuperscript{37} The predictive value of MRI at TEA for school-aged neurocognitive outcomes is less clear. One study reported that abnormal brain MRI at TEA was predictive of adverse neurodevelopmental outcomes at 7 years of age.\textsuperscript{38} This association with adverse neurodevelopmental outcome at 7 years of age was particularly striking for abnormalities in the white matter, deep gray matter, and cerebellum. However, other studies have reported\textsuperscript{39,40} that adding MRI to early and late cranial ultrasonography did not improve prediction of severe intellectual disability or neurodevelopmental impairment at 6 to 7 years of age. Obtaining routine MRI has also not been shown to have a clinically significant effect on maternal anxiety or improve quality of life, although it may increase the cost of care.\textsuperscript{41} As the Choosing Wisely\textsuperscript{9} campaign identified, there is insufficient evidence that routine brain MRI at TEA improves long-term outcomes, and the effects the results may have on an individual family may not be predictable.\textsuperscript{42,43}

\textbf{RECOMMENDATIONS (TABLE 1)}

- Infants born at a gestational age of \textless30 weeks and selected infants with a gestational age of \textgreater30 weeks who are believed to be at increased risk for brain injury on the basis of identified risk factors are recommended to be screened for IVH with appropriately performed cranial ultrasonography. These risk factors may include, but are not limited to, placental abruption, need for vigorous resuscitation, hypotension requiring pressor support, severe acidosis, prolonged mechanical ventilation, confirmed sepsis, or pneumothorax.

- Routine cranial ultrasonographic screening is recommended by 7 to 10 days of age for infants born at \textless30 weeks' gestational age. Screening before 7 days of age may be indicated for infants with clinical signs and symptoms suggestive of significant brain injury. Repeat cranial ultrasonographic screening is recommended to be performed at 4 to 6 weeks of age and at TEA or before hospital discharge.

- Infants with abnormal cranial ultrasonography findings are recommended to have repeat serial cranial ultrasonography as clinically indicated on the basis of chronological as well as gestational age.
Standard cranial ultrasonographic screening includes views from the anterior and mastoid fontanelles. Additional posterior fontanelle and vascular imaging can be performed for additional information.

CT is no longer considered a part of routine imaging techniques of the preterm brain.

On the basis of available evidence, MRI for infants born at <30 weeks’ gestational age is not indicated as a routine procedure. MRI may be offered at TEA to the high-risk infant after a conversation with the family regarding the limitations of this test for estimation of long-term prognosis. When possible, it is recommended that the brain MRI be performed without contrast in the nonsedated state by using a “feed and wrap” technique.

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ABBREVIATIONS
AAN: American Academy of Neurology
CT: computerized tomography
IVH: intraventricular hemorrhage
PVHI: periventricular hemorrhagic infarct
PVL: periventricular leukomalacia
TEA: term equivalent age
VLBW: very low birth weight

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