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MRI of the Neonatal Brain: How, Why, Who, and When?

In this Issue...

Magnetic resonance imaging (MRI) is an invaluable technique for assessing the immature brain, providing complementary information to cranial ultrasound. However, the quality of MRI scans may be hampered by patient motion, which can result in poor-quality data sets unsuitable for interpretation. Care must be taken to ensure that the neonate remains still throughout the examination. This usually requires sedation but not general anesthesia. Additional approaches include the use of fast imaging sequences or motion correction techniques. Sequences should be obtained in 3 planes and must be optimized for the neonatal brain. In acquired lesions, the MRI appearances change rapidly as the brain continues to develop, and the timing of the scan is of utmost importance. Images should be reviewed by an expert knowledgeable about the appearance of the immature brain across gestation and about the various pathologies that may occur, in order to avoid reporting false-positive results and overlooking true lesions. The pattern of acquired lesions can be used to assess the etiology and the timing of an injury, to predict neurodevelopmental outcome, and to understand the immature brain's response to injury.

In this issue, we will review recent publications on the role of MRI in assessing the neonatal brain, with a view toward enhanced understanding of congenital and acquired brain lesions, and the improved ability to predict outcome.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Identify those neonates who require a referral for a brain MRI
- Restate the rationale for and the optimal timing of neonatal brain imaging
- Summarize the patterns of lesions that predict an increased risk for future abnormal motor and/or cognitive and behavioral outcomes

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THIS ISSUE

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COMMENTARY

Cranial ultrasound is an excellent tool for screening high-risk neonates, particularly when performed serially. Scanning through the posterior or mastoid windows also improves the ability of cranial ultrasound to assess less readily visualized brain structures (eg, the cerebellum). Although MRI complements ultrasound, it has the additional benefit of being able to capture the appearance of the immature brain in all planes with superb resolution. The application of advanced MRI techniques, such as diffusion-tensor sequences, allows us to identify early ischemia and to map developing white matter tracts.

How? The majority of commercial scanners operate at 1.5 Tesla, but imaging at 3 Tesla has advantages for the neonatal brain.[1] (Note: Tesla is the unit used to measure the strength of a magnetic field.) In order to avoid patient injury, attention must be paid to ensuring that any internal or attached devices, such as reservoirs or ventriculoperitoneal shunts, are compatible with the field strength being used. A coil that fits closely to the neonatal head and an imaging protocol optimized for the neonatal brain are both required. The latter should include diffusion-weighted or tensor imaging.[2] Motion artifact is the main reason for an unsuccessful examination, and sedation is usually required. It may be necessary to resort to fast sequences or motion correction techniques in order to obtain clinically relevant data.[3] Neonates require cardiovascular monitoring throughout an MRI examination. In sick neonates who die without antemortem imaging, a postmortem examination may be useful.[4]

Why? Neonatal imaging can provide information about the pattern of acquired brain lesions in high-risk neonates[5-10] that will vary with the clinical history.[11-16] This, in turn, is closely associated with specific patterns of later impairment. Neonates who develop signs of hypoxic-ischemic encephalopathy (HIE) following an acute sentinel event (eg, placental abruption) sustain bilateral and usually symmetrical lesions within the basal ganglia and thalami (BGT), and exhibit an abnormal appearance in the posterior limb of the internal capsule (PLIC). The appearance of the PLIC is a powerful predictor of later cerebral palsy.[5] The severity of lesions within the BGT determines the severity and nature of this motor impairment, and the likelihood of associated difficulties with cognition, feeding, and, later, seizures. The appearance of the PLIC facilitates the prediction of outcome in term-born neonates with perinatal stroke[6] and in preterm infants imaged at term-equivalent age with focal lesions or periventricular leukomalacia (PVL).[17-19]

Who? Neonates who should be imaged include all those with such neurologic signs as poor feeding, abnormal tone, seizures, and abnormal head circumference. Neonates may have had a brain abnormality diagnosed antenatally on ultrasound or MRI (eg, ventricular dilation, a small cerebellum, or absent corpus callosum). Although the quality of fetal MRI scanning is improving, a neonatal MRI will still provide superior-quality images and should be performed. To date, no evidence suggests that MRI should replace ultrasound as a screening tool for the preterm infant at discharge or at term-equivalent age. The majority of preterm infants will have evidence of mild ventricular dilation, slightly reduced cortical folding, and areas of long T1 and long T2 — so-called diffuse excessive high-signal intensity — in the white matter. The more obvious these changes, the more likely it is that there will be future developmental problems.[20] MRI in preterm infants should be reserved for those in whom the ultrasound is abnormal or there are unexplained neurologic signs. In the case of an abnormal ultrasound, MRI should provide additional, complementary information for predicting motor impairment.[21] Neonates with evidence of central nervous system infection, whether preterm or term, warrant the use of MRI as well.

When? The optimum timing for the use of MRI in the term infant with suspected perinatal injury is within 1 to 3 weeks postdelivery, when the lesions are the most obvious on conventional sequences. In the severely ill neonate, information may be required earlier, in order to make informed decisions about the withdrawal of intensive care. In such situations, diffusion-weighted imaging should always be used, as recently acquired lesions may not be obvious on conventional sequences. In the preterm infant, the best prognostic information may be obtained at term-equivalent age, although with severe lesions, an earlier image may have the ability to predict a poor outcome.

In summary, MRI is a valuable adjunct to ultrasound in preterm and term infants. Correct timing and appropriate imaging techniques are critical in obtaining relevant information.

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MRI PATTERNS OF PERINATAL BRAIN INJURY AT TERM AND NEURODEVELOPMENTAL OUTCOMES

Okereafor A, Allsop J, Counsell SJ, Fitzpatrick J, Azzopardi D, Rutherford MA, et al.
Patterns of brain injury in neonates exposed to perinatal sentinel events.
Pediatrics. 2008;121(5):906-914.

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NEWSLETTER ARCHIVE

Ricci D, Mercuri E, Barnett A, Rathbone R, Cota F, Haataja L, et al. **Cognitive outcome at early school age in term-born children with perinatally acquired middle cerebral artery territory infarction.** *Stroke.* 2008;39(2):403-410.

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Burns CM, Rutherford MA, Boardman JP, Cowan FM. **Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia.** *Pediatrics.* 2008;122(1):65-74.

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Steinman KJ, Gorno-Tempini ML, Glidden DV, Kramer JH, Miller SP, Barkovich AJ, et al. **Neonatal watershed brain injury on magnetic resonance imaging correlates with verbal IQ at 4 years.** *Pediatrics.* 2009;123(3):1025-1030.

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There have been little new data available in the literature since the studies by Myers[1] in 1975 and Barkovich[2] in 1992 addressed the relationship between the duration and severity of a hypoxic-ischemic insult and the pattern of brain injury sustained. Their results provided an important basis for the more current studies on therapeutic intervention discussed below.

Okereafor and colleagues used MRI to document the pattern of brain injury in a cohort of neonates who developed HIE following a documented sentinel event (including uterine rupture, cord prolapse, placental abruption, and antepartum hemorrhage). In many neonates with HIE, no overt asphyxial event is evident; by excluding these infants from the cohort, the authors hypothesized that the MRI imaging correlate for an isolated acute hypoxic-ischemic event could be identified. Imaging was performed at a median of 10 days of age. The dominant pattern of injury was within the BGT, which was observed in 32 of 43 infants (74%). Of those 32 infants with BGT lesions, 28 (88%) had an abnormal appearance of the PLIC. Although BGT lesions were associated with abnormal findings in the cortex and brainstem, only 6 of the 32 infants (19%) had additional severe white matter injury (only 1 infant in the entire cohort, a twin born at 37 weeks, sustained significant isolated white matter injury). Normal imaging was associated with a normal outcome in all but 1 neonate, who was later diagnosed with Rubinstein-Taybi syndrome. A total of 8 infants with BGT lesions died, and all but 3 of the survivors developed cerebral palsy. Of the 3 infants without cerebral palsy, 2 exhibited some evidence of motor impairment and 1 was normal.

The study confirms the findings of earlier animal experiments that reported the BGT to be most susceptible to injury in acute hypoxic-ischemic insults. This vulnerability has been attributed to the relatively high metabolic rate of these tissues, as demonstrated in Chugani's early positron emission tomography studies,[3] and also to the high density of glutamate receptors.[4] It also confirms the findings of many previous MRI studies in neonatal HIE that BGT injury is associated with the development of cerebral palsy.

Whereas term-born neonates with perinatally acquired focal lesions may present with seizures, full encephalopathy is unusual and Apgar scores may be normal in these infants. Ricci and associates found abnormal development in a cohort of children who sustained a perinatal cerebral infarct. The relationship between the distribution of the infarct and cognitive outcome has been recognized, with involvement of 3 specific sites on a neonatal scan known to be highly predictive of a later hemiplegia: (1) the hemispheric white matter (WM) with or without cortex; (2) the BGT; and (3) the PLIC.[5]

The authors extended their neurodevelopmental follow-up by examining later cognitive outcomes, assessing cognitive function in a group of 28 term-born children with focal perinatally-acquired infarction. Subjects were between 5 and 10 years of age, with cognitive development assessed using either the Wechsler Preschool and Primary Scale of Intelligence (in 20 children) or the Wechsler Intelligence Scale for Children (in 8 children), depending on the age of the child. The investigators found no significant association between the side or extent of the lesion and cognitive outcome. The majority (21 of 27; 78%) of these children had intelligence quotient (IQ) scores within the normal range (mean, 104; range, 82 to 144). Low scores were associated with the presence of a hemiplegia and/or ongoing seizures. Only 6 children had low IQ scores, and 3 had evidence, either clinically or on imaging, that was suggestive of an additional or underlying neurologic diagnosis.

Neonates who sustain bilateral WM infarction (so-called watershed or parasagittal lesions) do not develop significant motor impairment unless the lesions are extensive. Two recent studies have evaluated WM injury in term neonates and related the imaging findings to outcome. Burns and coworkers examined the pattern of injury sustained in neonates with symptomatic hypoglycemia (previous studies[6,7] had documented the association of hypoglycemia with parasagittal or watershed infarction in the posterior WM). The authors reviewed the neonatal imaging findings in 35 term-born neonates with symptomatic hypoglycemia and extended the imaging phenotype. They found WM abnormalities occurring in 94% of the infants, which were severe in 43%, with only 29% of the infants exhibiting a predominantly posterior pattern. Cortical abnormalities were reported in 51% of the infants: 30% had WM hemorrhage, 40% had BGT lesions, and 11% had an abnormal PLIC. Of the 35 infants studied, 3 had middle cerebral artery territory infarctions. A total of 23 infants (65%) demonstrated impairments at 18 months, which were related to the severity of WM injury and involvement of the PLIC. *(Please note that the actual percentage of infants totals 65.7% (66%); the article, however, documents the percentage as 65%).*

Steinman and colleagues also reviewed neonates with a history of neonatal encephalopathy, studying children who showed no motor impairment at 4 years of age. WM and BGT were scored on a scale of 1 to 5 and 1 to 4, respectively. Of particular interest is the authors' finding that none of the infants exhibited WM grade 5 or BGT grade 4, confirming the association of these patterns with the development of motor impairment. The authors also demonstrated an association between lower verbal and performance IQs, and an increasing degree of both watershed and basal ganglia injury on univariate analysis. Once the confounding effects of these 2 variables were addressed using multiple linear regression, only the association between the severity of watershed injury and verbal IQ remained significant (P=.01).

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FETAL AND NEONATAL IMAGING OF CEREBELLAR ABNORMALITIES: RELATIONSHIP TO OUTCOME

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NEWSLETTER ARCHIVE

Bolduc ME, Limperopoulos C. **Neurodevelopmental outcomes in children with cerebellar malformations: a systematic review.** Association of Women's Health, Obstetric and Neonatal Nurses and the National Association of Neonatal Nurses. *Dev Med Child Neurol.* 2009;51(4):256-267.

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MRI of the fetal brain is being increasingly used when there is a suspected abnormality on antenatal ultrasound. The most common reasons for referral include ventricular dilation, and an abnormal appearance of the posterior fossa and cerebellum. MRI provides detail that is superior to that with ultrasound and may detect additional abnormalities that influence prognosis. This information is used to counsel parents prenatally, many of whom may opt for termination of the pregnancy. As with all newly introduced techniques, the clinical significance of some findings is unclear and can only be assessed by longitudinal studies. The long-term follow-up should ideally include a repeat MRI examination postnatally, in addition to regular clinical assessments until school age.

A recent article by Bolduc and Limperopoulos reviewed all the publications addressing the issue of neurodevelopmental outcomes in children with cerebellar malformations. The studies reviewed had imaged the infants at different ages, which could potentially render comparisons more difficult. Unlike acquired lesions in the immature brain, however, malformations may remain relatively static in their appearance with increasing age. This review, which included details from 46 published studies over the 10-year period from 1997 to 2007, highlights the extensive problems associated with classification changes, case identification, data recording, and variations in outcome measures between studies. The authors concluded that, on the whole, children with inferior vermis hypoplasia and mega cisterna magna achieve favorable outcomes, whereas those with such disorders as molar tooth sign/Joubert syndrome, total vermis hypoplasia, pontocerebellar hypoplasia type II, and cerebellar agenesis experience moderate or severe delays in development. Reports on Dandy Walker malformations are conflicting. However, those infants with a normal lobulation of the vermis and no other brain abnormalities exhibit outcomes that are more favorable. This review emphasizes the difficulties involved in accurate detection and classification of abnormalities in the posterior fossa, where fetal imaging is at the forefront, yet may not be able to provide the detail within the vermis that can be obtained later in development. It is possible that prediction of neurodevelopmental outcome might improve further with the ability to more accurately define the phenotype.

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MRI OF THE NEONATAL BRAIN IN CONGENITAL HEART DISEASE

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NEWSLETTER ARCHIVE

Petit CJ, Rome JJ, Wernovsky G, Mason SE, Shera DM, Nicolson SC, et al. **Preoperative brain injury in transposition of the great arteries is associated with oxygenation and time to surgery, not balloon atrial septostomy.** *Circulation.* 2009;119(5): 709–716.

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Better attention has been paid of late to the increased incidence of neurologic impairments in neonates with congenital heart disease (CHD). This paper reports the findings of preoperative MRI in neonates with complex congenital heart defects. Several studies over the last few years have identified acquired brain lesions in infants with CHD.[1-3] In addition, alterations in cerebral perfusion, antenatally, may potentially disturb brain development without causing overt lesions. Petit and coworkers have reported the findings of preoperative MRI in a cohort of neonates with transposition of the great arteries (TGA). Previous studies had shown an association between acquired focal brain infarction and balloon atrial septostomy (BAS).[2]

A high incidence of smaller focal WM lesions, referred to as mild or moderate PVL, has also been described in neonates with serious CHD.[3] The timing of these lesions is difficult to ascertain, but with the advent of MRI facilities suitable for examining sick neonates, it is clear that these lesions may be present prior to definitive surgery and may be acquired perinatally or even antenatally. Fetuses with CHD have been shown to have alteration in cerebral perfusion; those with hypoplastic left heart syndrome may exhibit a "brain sparing" effect.[4]

The authors also reported the preoperative imaging findings in 26 term neonates with TGA, 14 of whom had undergone BAS. The mean age at BAS was 17.1 ± 19.1 hours. Mean gestational age was 39.0 ± 1.2 weeks and mean birthweight of the group was 3.46 ± 0.61 kg. Of the 26 neonates, 6 had an additional ventricular septal defect (VSD) and 20 had an intact septum. Patients were imaged with conventional and diffusion-weighted sequences at 1.5 Tesla immediately prior to their definitive surgery (post-BAS), while under anesthesia. The authors did not detect any cases of stroke, as revealed in an earlier study[2] but PVL lesions were reported in 10 of the 26 neonates (38%). PVL was observed in 6 (43%) of the neonates who underwent BAS and in 4 (33%) of those who did not. This was not found to be significant, although the numbers are small and larger studies might yield different results. However, mean daily partial pressure of oxygen (PO_2) preoperatively was significantly lower in the PVL group compared with the non-PVL group (*P*=.02). A multivariate analysis showed that lower mean preoperative PO_2 and longer time to surgery were associated with PVL and were additive risk factors. The PVL group had a mean preoperative PO_2 of 36.9 ± 1.5 mm Hg, compared with 41.9 ± 5.0 mm Hg in the non-PVL group. In addition, the PVL group underwent surgery at a mean age of 5.6 ± 2.9 days, compared with 3.9 ± 2.2 days in the non-PVL neonates. Patients in whom BAS was performed underwent an arterial switch procedure at a mean of 4.1 days postdelivery, compared with 5.1 days in the non-BAS group.

The clinical significance of the PVL lesions detected has yet to be ascertained. Studies of similar lesions in the preterm population have shown that unless severe, they may not affect short-term development,[5] although they are associated with other markers for delayed or abnormal development on MRI of the brain at term-equivalent age.[6] Whereas the results of previous studies have proposed that neonates may be placed at increased risk for brain injury by undergoing BAS, the current study suggests that the practice of BAS to improve systemic and arterial mixing, and to maximize systemic oxygen delivery, when successful, decreased the risk for preoperative WM injury. The authors discussed potential etiologies for the PVL lesions detected but could not establish a causal relationship. An MRI study to assess the brain in the near-term fetus with CHD may help establish timing of WM injury.

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An Additional Resource

McQuillen PS. Magnetic resonance imaging in congenital heart disease: what to do with what we see and don't see? *Circulation.* 2009;119(5):660-662.

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