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REVIEW ARTICLE

The Value of Magnetic Resonance Imaging for the Newborn Brain.

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Abstract

Magnetic resonance (MR) imaging (MRI) of the newborn brain has provided vast insight into the normal developing brain. MRI has also yielded important insights into neonatal brain injury timing, mechanisms, and prognostic significance. However, several practical limitations remain while preparing and managing the critically ill infant to complete optimal MR imaging safely. Furthermore, the interpretation of the study requires a multidisciplinary team of experienced clinicians with thorough knowledge of the unique aspects of the newborn brain. In this review, we examine the application and utility of brain MRI for preterm and term infants and those diagnosed with perinatal stroke and congenital heart disease (CHD). Regrettably, the scope of this article is limited to topics covered during the 2020 International Child Neurology Congress (ICNC) neonatal neurology seminar and will not include other indications for MRI in neonates such as metabolic disorders, infections, and brain malformations.

Keywords: Hypoxic-ischemic encephalopathy, brain development, preterm, term.

MRI After Therapeutic Hypothermia

Neonatal encephalopathy (NE) due to a hypoxic-ischemic (HI) insult affects 1-2/1000 live births and can result in death and lifelong neurodevelopmental disability [1, 2, 3, 4]. Therapeutic hypothermia (TH) has now become the standard of care in term infants affected by hypoxic-ischemic encephalopathy (HIE), improving survival and outcome at 18-24 months with trends for a sustained benefit at school age [1, 2, 3, 4, 5, 6, 7]. Brain imaging with MRI has played a central role in clinical trials and is highly predictive of neurodevelopmental outcomes after therapeutic hypothermia in clinical practice [8]. Since its widespread implementation, research has been focused on using modern MRI tools for early prognostication and assessing the efficacy of our neuroprotective strategies. When available, MR spectroscopy (MRS) is utilized for added value, and thalamic N-acetyl aspartate (NAA) concentration, in particular, has been shown to have high accuracy in predicting neurodevelopmental outcomes at two years of age [9]. In addition to the brain areas typically vulnerable to HI injury, there is emerging evidence that the medial diencephalon, specifically the mamillary bodies, can be affected and likely plays a role in subsequent memory impairment [10]. The timing of MRI in HIE is also imperative as TH can slow the evolution of diffusion abnormalities, and repeat imaging may be needed if the exam and the original MRI are not concordant [11, 12]. For infants with milder NE, determining the need for TH can be challenging as significant benefit or harm cannot be excluded [13]. Mild NE seems to be commonly associated with MR abnormalities after TH, and the grade of NE during the first hours of life may not discriminate adequately between infants with and without cerebral injury [13]. Future clinical trials are needed to determine if TH should be the standard of care for term infants with mild HIE. Advanced imaging tools, such as hyperpolarized 13C spectroscopic MRS, are being studied and may prove an excellent biomarker with real-time information about brain metabolism [14].

Preterm MRI

Preterm brain injury is common, and MRI can assist with the identification of injury and prognostication [15, 16, 17]. In addition, MR imaging can assist in delineating alterations in brain growth and development in the preterm infant. MRI is superior to cranial ultrasound, which has the advantage of being a bedside technique due to its better recognition of cerebellar injury and white matter injury (WMI) [16, 17]. These forms of brain injury are common in the very preterm infant < 30 weeks' gestation at birth and unable to be visualized well on cranial ultrasound [17]. Importantly, they both carry prognostic significance.

Finally, the extent and impact of high-grade intraventricular hemorrhage, which remains static in its high incidence over the last two decades, can also be well defined with MR imaging [24]. Despite this improved recognition of brain injury in the preterm infant, there has been a hesitancy for obtaining the term equivalent brain MRI for preterm infants in clinical practice with

Table 1. MRI Findings with Prognostic Implications in Term and Preterm Infants.

MRI in neonates	Neurodevelopmental Outcome
Hypoxic Ischemic Encephalopathy (MRI typically done around 4-6 days of life)	MRI had 95% sensitivity, 94% specificity, 91% PPV and 98% NPV in predicting neurodevelopment [8]. On multiple regression there was a significant relationship between basal ganglia and thalami abnormality and motor (p = 0.002), cognition (p = 0.011) and language (p = 0.013) outcomes [8]. MRS had an additional value, with thalamic NAA concentration being highly predictive of neurodevelopment at two years of age [9]. Emerging evidence indicates that the medial diencephalon, specifically mamillary bodies, can be affected and likely play a role in later memory impairment [10].
Preterm brain injury (MRI typically done at term equivalent age)	No focal lesion was 45% sensitive and 61% specific for normal neurodevelopment at 20 months and 17% sensitive and 94% specific for a normal motor outcome [16]. The presence of periventricular leukomalacia was highly specific for abnormal motor and cognitive outcomes, and most had accompanying asymmetry or abnormal signal within the PLIC [16]. Associated with delayed mental (OR 2.95, 95% CI 1.21 to 7.20) and psychomotor development (OR 3.62, 95% CI 1.34 to 9.76), and higher rates of cerebral palsy (OR 3.09, 95% CI 1.55 to 6.19) [18].
Cerebellar hemorrhage	Larger hemorrhage associated with microcephaly, high risk (>50%) of severe developmental delay, especially if the vermis is involved [19, 20]. Larger hemorrhages have also been shown to have high rates of abnormality of autism screening and demonstrated internalizing behavioral difficulties [21]. With mild hemorrhage (<4mm), no association with cognition or behavior but have a mild increase in mild motor impairments [22, 23].

technical challenges (e.g., transporting a critically ill infant away from the intensive care unit, having the appropriate equipment, e.g., size of the coil) and also because it may increase parental anxiety. Recent evidence has shown reduced anxiety levels in mothers of preterm infants completing the term-equivalent MRI studies compared to having an ultrasound scan [25]. A practical algorithm was proposed in 2018 to use term MRI in the preterm population and is available to assist the provider with decision making [26]. To summarize, brain MRI is valuable in defining brain injury and growth in preterm infants and should be used to guide the need for further rehabilitative strategies.

The Value of MRI in Neonatal Stroke

Perinatal arterial ischemic stroke (PAIS) has been increasingly recognized, affecting 1/4000 to 1/2300 infants [27]. The affected patients often present with focal motor seizures with onset after 12 hours of life. The middle cerebral artery (MCA) territory is more commonly involved, and though cranial ultrasounds have shown improved sensitivity, MRI remains the modality of choice for more accurate diagnosis, prognosis, and selection for neuroprotective studies [28, 29]. Several papers have shown the diffusion abnormalities in the middle part of the posterior limb of the internal capsule (PLIC) and the middle part of the cerebral peduncle to be predictive of subsequent motor deficits [30, 31, 32].

Stroke territory subtypes are equally important, and all children with the main MCA branch affected will have adverse outcomes [32].

Along with motor deficits, cognitive/behavioral problems, impaired language development, post-neonatal epilepsy, and visual field defects are seen in up to half of the children [32, 33]. Early prediction of hemiplegia in PAIS allows better selection of infants for neuroprotective interventions, especially considering the promising results of delayed erythropoietin therapy in animal models with neonatal stroke [34]. Therefore, brain MRI will continue to have an important role as a diagnostic and prognostic tool in infants with PAIS and be crucial to studying neuroprotective interventions.

Congenital Heart Disease and Brain MRI

Survival of neonates with severe congenital heart disease (CHD) has improved dramatically over the last few decades following advances in cardiac medical care, cardiopulmonary bypass, and surgical strategies. At the same time, the rates of neurodevelopmental impairments have remained stagnant. As neonates with CHD are followed through early childhood, there is a well-recognized neurodevelopmental phenotype: earlier motor difficulties tend to improve with cognitive issues prevalent in later life [35, 36, 37]. Approximately 2/3 of babies with CHD will have an acquired brain injury on either pre-or postoperative MRI. These lesions present a spectrum of injury that includes hypoxic-ischemic watershed injury, white matter injury (WMI), and stroke [32]. At least 25% of these injuries are evident prior to cardiac surgery. The type of brain injury varies by CHD subtype and is most familiar with single ventricle physiology or aortic arch obstruction [38]. Clinical risk factors differ by lesion type. Multifocal injuries (WMI, watershed injury) are more common following low cardiac output states, while focal injury (stroke) more often follows balloon septostomy and selective cerebral perfusion [38].

In addition to acquired brain lesions, term neonates with CHD have evidence of brain dysmaturity and delayed network development even prior to corrective surgery and dating back to the fetal period [39, 40]. This vulnerability of the immature brain likely serves as a substrate for WMI, the pattern of brain injury typically seen in preterm neonates (see above) [41]. Lastly, the timing of cardiac repair appears to be an important predictor of brain health with older age at surgery linked to impaired brain growth and more adverse neurodevelopmental outcomes [42, 43]. Future efforts should focus on both pre-and postnatal periods of brain development to identify new opportunities for brain protection in neonates with CHD. Specific emphasis should be placed on using advanced MRI techniques to guide brain-focused care and identify new opportunities to prevent brain injury and promote brain maturation.

In conclusion, brain MRI is an indispensable modality for imaging at-risk newborns and, when possible, should be completed prior to discharge from the hospital. Recent practices have shown that it can be safely and routinely performed at any institution, and the knowledge gained will allow for rational and accurate application in the future [44]. In this review, we again emphasize the superior ability of brain MRI to diagnose and predict the neurodevelopmental outcome in neonates compared to other imaging studies. In clinical practice, it should be used to complement the neurological exam and other diagnostic tests, such as electroencephalogram (EEG), to provide the most comprehensive neurological care. Future research efforts should use advanced imaging tools to develop novel neuroprotective therapies and deliver individualized care.

Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors have made a substantial contribution to conception and design, have drafted the manuscript and revised it critically for important intellectual content, and have given final approval for the version to be published.

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