Early Human Development xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

MRI as a biomarker for mild neonatal encephalopathy

Brian H. Walsh[a,b,*], Terrie E. Inder[a]

[a] Department of Pediatric Newborn Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, USA
[b] Department of Neonatology, Cork University Maternity Hospital, Cork, Ireland

ARTICLE INFO

Keywords:
Magnetic resonance imaging
Perinatal asphyxia
Mild neonatal encephalopathy
Hypoxic ischemic encephalopathy
Biomarker

ABSTRACT

Historically, there has been limited neuro-imaging data acquired on infants with mild neonatal encephalopathy (NE). This likely reflects the traditional assumption that these infants had a universally good prognosis. As new evidence has emerged challenging this assumption, there has been a renewed interest in the neuro-imaging findings of these infants. To date, magnetic resonance imaging (MRI) studies in infants with mild NE have demonstrated abnormalities in 20–40% of cases suggestive that the injury occurs during the peripartum period with a predominant watershed pattern of injury. The severity of the injury on MRI in infants with mild NE varies, but includes patterns of injury that have been associated with long-term neuro-developmental impairment.

1. Introduction

Perinatal asphyxia, around the time of delivery, can result in a hypoxic-ischemic (HI) insult to the brain. If severe enough, this HI insult causes neural injury and the clinical syndrome termed neonatal encephalopathy (NE). NE remains a major cause of mortality and morbidity among newborns, occurring in approximately two to five infants per 1000 live births [1]. The potential long-term morbidities following NE include cerebral palsy, cognitive impairments, epilepsy, blindness and hearing impairments [2]. While long-term neurodevelopmental follow up remains the gold-standard to identify these outcomes, magnetic resonance imaging (MRI) has been proven to be a robust surrogate predictor. It has the advantage of being able to delineate the initial brain injury sustained, and highly correlates with long-term outcome even when performed in the first days of life [3,4].

The frequency of morbidities among infants with NE is associated with the severity of the initial encephalopathy [5]. Infants with moderate to severe NE are reported to have at least a 50% to 80% incidence of significant neuro-developmental disability, respectively [6], while those with mild NE were classically considered to have a good prognosis [2]. For this reason there has been very limited published MRI data on those mild NE. However, there is increasing evidence demonstrating that neuro-developmental impairments occur in a significant number of those with mild NE [7–10]. Given the lack of published neuro-imaging data on these infants, and the emerging evidence for long-term impairment occurring, several research groups have now begun to study the imaging findings in these infants in detail.

This paper will review the use of MRI in infants with NE, and the evidence for brain injury occurring in those with mild NE. Specifically, the data will be presented from recent cohorts detailing the frequency, severity and pattern of brain injury that occurs among those infants with mild NE.

2. MRI in neonatal encephalopathy

MRI studies have documented the distribution and frequency of brain injury associated with NE. The commonest injury patterns involve either injury to the watershed (WS) region, or to the deep grey nuclei consisting of the Basal Ganglia and Thalamus (BGT). The WS region refers to the intravascular border zone. Injury in this region involves the periventricular white mater, and may extend out to involve the cortex with increasing severity [3]. WS injury is classically associated with sub-acute asphyxia, hypotension and impaired autoregulation, [3,11] and occurs in 40–60% of HI cases [1]. Contrary to this, injury to the BGT is associated with acute severe asphyxia, and occurs in 40–80% of cases [1,3,11]. A less common, but potentially catastrophic pattern of injury following severe asphyxia, is that associated with both BGT and brainstem injury, occurring in 15 to 20% of cases [1]. Other specific structures that have been repeatedly demonstrated to be associated with HI injury and outcome include the hypothalamus, and internal capsule [12,13]. Several MRI grading system of brain injury following perinatal asphyxia have been developed from this data [3,14,15]. Although the grading systems differ, they each have been extensively validated, and demonstrated to be highly predictive of long-term outcome among both normothermic and hypothermic infants with NE [14–16].

* Corresponding author at: Department of Neonatology, Cork University Maternity Hospital, Wilton, Cork, Ireland.
E-mail addresses: Bhwalsh@bwh.harvard.edu (B.H. Walsh), tinder@bwh.harvard.edu (T.E. Inder).

https://doi.org/10.1016/j.earlhumdev.2018.02.006

0378-3782/ © 2018 Elsevier B.V. All rights reserved.

2.1. Timing of MRI in neonatal encephalopathy

Cerebral injury following a hypoxic-ischemic insult in a term born infants is most evident on conventional T1 and T2 echo sequences between the first and second weeks of life [17]. Limitations on the acquisition of MRI during the first few days after delivery often relates to the fact that infants with NE may be typically unstable from a cardiorespiratory point of view making transport out of the NICU challenging. For these and other reasons of optimal visibility of the full extent of the cerebral injury, standard clinical practice evolved to perform MRI scans between days 10 to 14 on these infants. The introduction of diffusion weighted Imaging (DWI) in the 2000s altered practice as MRI abnormalities became visible earlier.

DWI can demonstrate injury from the first day of life. The diffusion restriction is maximal in normothermic infants on days two to three and will then slowly normalize, often before the injury is evident on conventional sequences. This 'pseudo-normalization' occurs at about days 6 to 8 of life in normothermic infants, but is delayed until days 11 to 12 in infants that receive TH [18,19]. With the ability to detect injury early, many clinicians have now chosen to perform both an early scan, after the completion of TH, and a later scan in the second week of life. The advantages of performing two scans includes; being able to provide families and clinicians information on the presence of brain injury sooner; ensuring that the true extent of the injury is documented on the later conventional sequences; and assistance in timing of the injury given the known evolution of the injury patterns from DWI to conventional sequences.

Recent publications have demonstrated that DWI imaging is highly correlated with outcome. However, there have been limited serial MRI scans in infants with NE to ensure that the injury does not evolve further between the early and late scans. Therefore, as most of the published outcome data has relied on the later conventional T1 and T2 sequences [3,4,13], the later scan continues to be performed to confirm the extent of the injury. This has significant implications in particular for infants with mild NE who are typically discharged earlier than those with more severe encephalopathy. Within our own cohort, while the median duration of admission for infants with both moderate and severe NE was 11 days, for infants with mild NE it was only 8 days (IQR 6 to 12). Therefore most infants with mild NE were being discharged prior to a late MRI being performed. The need to return following discharge to ensure accuracy of extent of injury has obvious concerns.

Fortunately several recent studies have now demonstrated the validity of the earlier scan to determine the ultimate extent of the injury [20,21]. Chakkarapani et al. compared early (days 3 to 6) and late (days 10 to 14) MRI scans performed on 43 cooled infants. They reported excellent agreement for both the predominant pattern of injury ($\kappa = 0.89$), and injury severity (BGT predominant severity $\kappa = 0.67$, WS predominant severity $\kappa = 0.87$), between the early and late scans. Similarly the study of Skranes et al. compared the imaging findings between MRI scans performed early (days 3 to 7) and late (days 9 to 27) in a cohort of 41 cooled infants. Again the authors found excellent agreement for the severity of brain injury present ($\kappa = 0.85$), between the early and late scans. Therefore, while not dismissing the additional benefits of a second scan, these studies can reassure the clinician that the prognosis and severity of injury is more likely than not to remain the same. In our experience, consistent with that reported above, around 15% of MRs will demonstrate a change in characteristic from the early (2–5 days) to later (7–21 days).

3. MRI in mild neonatal encephalopathy

As stated above, infants with mild HIE were previously considered to have a favourable outcome, and were not included in the therapeutic hypothermia trials. For these reasons, since the introduction of cooling there has been limited research focusing on the MRI injury that occurs with mild encephalopathy. Despite this, there has been published data demonstrating MRI injury among infants with mild NE for several decades [4].

Mercuri et al. recruited a cohort of 52 infants with HIE between 1991 and '98. All infants underwent an MRI consisting of conventional T1, T2 and inversion sequences within the first month of life. Within their cohort, 37 infants had moderate and 15 had mild encephalopathy [22]. While the frequency of an abnormal MRI was greater among those with moderate NE, occurring among 94% [35], there remained a significant minority of infants with mild NE, 34% [5], that demonstrated MRI injury. The MRI abnormalities among those with mild NE consisted of both white matter injury (WMI), and basal ganglia injury. Similarly the early work on MR spectroscopy (MRS) demonstrated lactate peaks occurring frequently among those with mild NE (84%) when imaged in the first day of life, and that the lactate to creatinine ratios were frequently higher in those with mild compared to moderate NE [23].

A further study was that of van Kooij et al. which performed serial MRI scans during both the neonatal period and late childhood on a cohort of infants with NE. In their study, van Kooij et al. found that half of those with mild NE had significant MR injury during the neonatal period. Perhaps more importantly they found that approximately half continued to have an abnormal MRI (18/33) in late childhood [24]. Thus proving that the MR abnormalities among those with mild NE are not transient, but represent true injury.

While many studies now define the grade of encephalopathy based on the early assessment when determining the need to provide TH, one of the true strengths of these older cohort studies is that they defined the grade of encephalopathy as the most severe grade demonstrated during the first week of life, in keeping with the work of Robertson and Finer [2,22,24]. We can therefore be confident in the grading provided, and can disregard the argument that those with mild NE and MRI injury represent infants whose encephalopathy evolved and worsened over time. Rather we can state that MRI injury truly does occur among those with mild encephalopathy.

3.1. Frequency of abnormal MRI in mild neonatal encephalopathy

Given the limited published data that has focused on mild NE, it has been difficult to detail the true incidence of both any MRI abnormality, and more specifically MR injury consistent with hypoxia-ischemia (HI), among this population. The Children's Hospital Neonatal Database have recently reported on one of the largest datasets of infants with mild NE [25]. In their network they found that of 132 infants with mild NE, 59% (79/132) had an abnormal MRI. However, the exact nature of the injury is not well defined in the dataset, and therefore difficult to determine if the injuries were consistent with hypoxia-ischemia or represented a range of pathologies. Data published by our own group further illustrates this point [26]. Of 48 infants with mild NE, we found that 54% (26/48) of infants had an abnormal MRI. HI injury represented the majority of MRI abnormalities detected, being present in 38% of the entire population, and 70% of those with an abnormal MRI. Other abnormalities detected on MRI included interventricular haemorrhage, isolated cerebellar lesions and areas of gliosis. While these are important findings, and further support the need to image these infants, they are important to differentiate from typical HI injury, especially as we consider potential neuroprotective strategies in this population.

3.2. Hypoxic-ischemic brain injury in mild neonatal encephalopathy

There is some variation in the reported incidence of MRI defined hypoxic-ischemic cerebral injury in infants with mild NE. As noted above, our cohort reported that hypoxic-ischemic cerebral injury occurred in 38% of those with mild NE. Two alternate cohort studies have recently reported significantly higher rates of 60–100% hypoxic-ischemic cerebral injury on MRI among infants with mild NE. However the sample sizes were small [27], and one was conducted in a low resource setting with potential confounding variables [9]. One of the few

Download English Version:

https://daneshyari.com/en/article/8777662

Download Persian Version:

https://daneshyari.com/article/8777662

Daneshyari.com