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REVIEW ARTICLE

Neuroimaging in Neonatal Hypoxic Ischemic Encephalopathy

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Abstract Magnetic resonance (MR) imaging is emerging as one of the most important tools in identifying the etiology of neonatal encephalopathy as well as in predicting long-term outcomes. This makes it imperative to have a broader understanding of normal myelination of the neonatal brain on MR imaging and to be familiar with the spectrum of imaging features in ischemic and non-ischemic neonatal encephalopathy. Hypoxic ischemic injury (HIE) is one of the most common causes of neonatal encephalopathy and imaging appearances are influenced by factors such as the stage of maturation of the neonatal brain and severity as well as duration of ischemic insult. Other common causes of neonatal encephalopathy include infectious diseases, congenital disorders and inborn errors of metabolism.

Keywords Neonatal encephalopathy · HIE · Hypoxic ischemic insult · MRI brain

Introduction

Magnetic resonance (MR) imaging, with its ability to perform high-resolution imaging in the absence of ionizing radiation forms an attractive diagnostic tool for evaluating the developing neonatal brain. This article reviews the use of MR techniques to evaluate common causes of encephalopathy, describes normal imaging appearances in various stages of maturation and elaborates on pattern recognition of hypoxic-ischemic brain injury.

Encephalopathy in the Newborn - Hypoxic Ischemic Insult

Neonatal encephalopathy may result from a variety of underlying conditions including infectious diseases, metabolic disorders, trauma and congenital disorders, [1–3] but is most commonly caused by hypoxic-ischemic injury. HIE is amongst the leading causes of death and cerebral palsy, occurring in 1–6 of 1000 live births [4]. It accounts for approximately 15 %–20 % of neonatal mortality in full-term neonates [3] and up to 50 % mortality in preterm infants born before 32 wk of gestation. Approximately 50 % of the cases of cerebral palsy are seen in premature infants [3].

The underlying pathophysiological mechanisms in HIE include diminished cerebral blood flow (ischemia) and reduced blood oxygenation (hypoxemia). The resultant brain ischemia leads to an inefficient pathway of cell metabolism using anaerobic oxidation as opposed to the usual process of oxidative phosphorylation. The alternate pathway causes rapid depletion of energy, activating a cascade of inflammatory mediators and excitatory neurotransmitters (particularly glutamate), that results in free radical formation, calcium accumulation, and acidosis and lipid peroxidation [4]. The mechanism for cell death resulting from this severe energy depletion may either be caused by cell necrosis or programmed neuronal cell death (apoptosis). In the premature neonatal brain, hypoperfusion results in a pattern of periventricular border zone white matter injury [5], whereas in the full-term neonate, similar insult leads to subcortical white matter and parasagittal cortical injury. Injury to the developing

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oligodendrocyte precursors or premyelinating oligodendrocytes is presumed to be the underlying cause of periventricular leukomalacia in preterm neonates [2].

The degree of maturation of the neonatal brain influences the state of regional metabolism and the extent of brain's vulnerability to the insult. The pattern of hypoxic-ischemic injury differs in neonates below and above 36 wk of gestational age. In the event of severe hypoperfusion, susceptible regions are those which reflect increased metabolic activity and demonstrate progressive myelination particularly the thalamus and brainstem in premature neonates (born before 36 wk of gestation) and the lateral aspects of the thalamus, globus pallidus, posterior putamen, hippocampus, brainstem and sensorimotor cortex in full-term neonates (born at 36 gestational wk or later) (Fig. 1). In the event of mild to moderate hypoperfusion, the pattern of injury is primarily along the watershed zones [6].

Neonatal encephalopathy due to HIE typically presents in the early hours after birth. Hence in the absence of a clear sentinel event or delayed presentation, other etiologies including metabolic and infectious causes need to be excluded [1]. Perinatal clinical events including poor Apgar scores, history of resuscitation, altered cord arterial pH, systemic organ failure and associated respiratory failure increase specificity in the diagnosis of hypoxic ischemic injury. The interval lag between the event of hypoxic-ischemic insult and the timing of the MR study also tend to influence the pattern of distribution of the injury. Additionally, specific clinical settings like hypoglycemia associated with perinatal events may demonstrate characteristic patterns such as predominant parieto-occipital involvement [7] (Fig. 2), while raised unconjugated bilirubin in cases of kernicterus results in hyperintense T1 signal in the globus pallidus. Note must also be made of the fact that certain medications may modify MR findings. Antiepileptics such as oral phenobarbital and dilantin contain a preservative called propylene glycol that may introduce a peak on magnetic resonance spectroscopy (MRS) that closely mimics a lactate resonance peak [2].

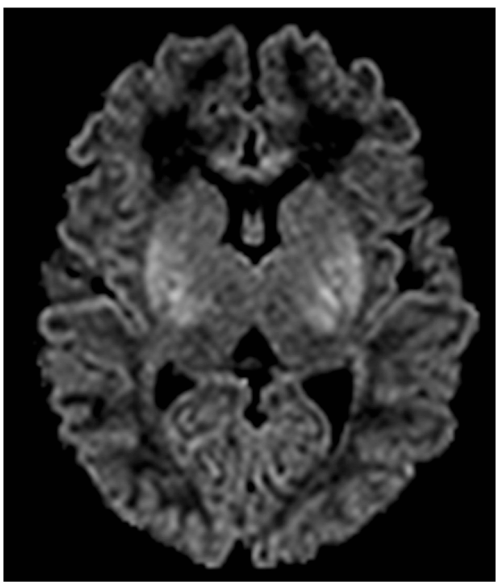

Fig. 1 Axial diffusion weighted image: Profound HIE in a term infant with basal ganglia thalami pattern of injury with diffusion abnormalities in the posterior putamen and ventro-lateral thalami

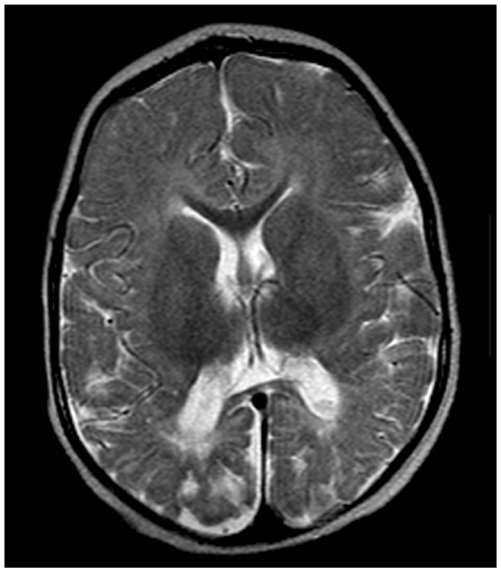

Fig. 2 Axial T2 weighted image: Chronic sequelae of hypoglycemic injury with signal abnormality and volume loss in a parieto-occipital distribution

MR Techniques and Protocols

Standard adult MR sequences require to be tailored for implementation in neonatal brain imaging keeping into consideration that greater water content with lower lipid and protein constituents in the neonatal brain result in longer T1 and T2 relaxation times. It is useful to prioritize sequences while scanning unstable patients and cases of motion artifacts. At authors' institution, sequences are typically applied in the following order:

1. **Diffusion -weighted imaging (DWI) with apparent diffusion coefficient (ADC) maps:** Potentially the most informative sequence in neonatal encephalopathy without a known underlying etiology.
2. **Axial T1-weighted sequences**: Suitable for assessing myelination, detecting ischemia, and subacute hemorrhage and subacute dural venous sinus thrombosis.
3. **Axial T2-weighted sequences**: Useful for delineating the gray and white matter interface in the premature brain and identifying any white matter signal intensity abnormalities.

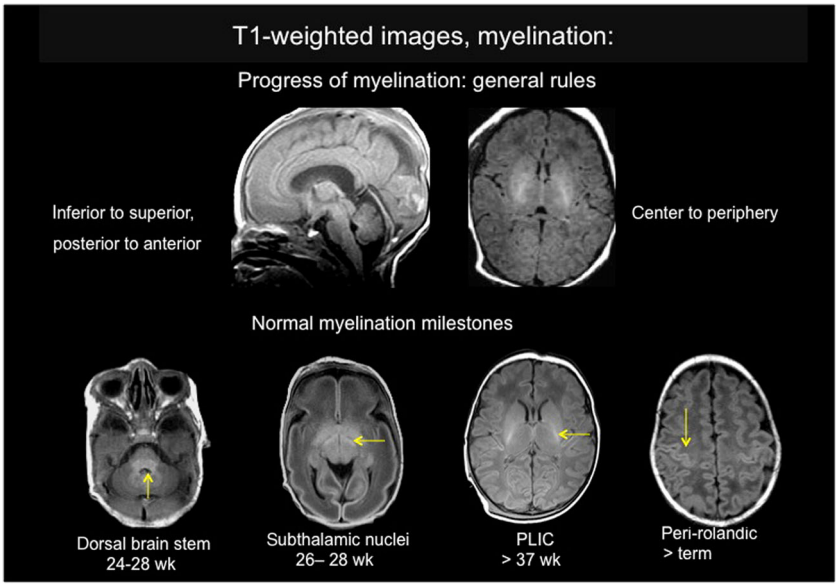

Fig. 3 Normal myelination patterns with posterior to anterior and caudal to cranial progression

4. **Gradient-echo T2*- and susceptibility- weighted sequences**: Valuable in demonstrating hemorrhage and detecting venous thrombosis.
5. **MR spectroscopy**: MRS with (TE) of 135–144 ms is useful for detecting lactate, which is a marker for anaerobic metabolism, which may be seen in cases of acute hypoxic-ischemic insults or in metabolic disorders and is identified as an inverted doublet at 1.3 ppm [8, 9]. In suspected metabolic disorders, an appropriate MR spectroscopic sequence, for example a short TE (30–35 ms) will allow further identification of the specific metabolite peak that is characteristic of that disorder. Example: peak at 0.9 ppm in maple syrup urine disease and glycine peak at 3.56 ppm in nonketotic hyperglycinemia.

Based on initial imaging features, additional sequences may be applied. Thin section 3D gradient-echo images enable multiplanar reformatting; time-of-flight or phase contrast MR venography may be performed when there is a suspicion for venous sinus thrombosis. The radiologist should review neonatal brain MR images immediately after their acquisition so that any further imaging deemed necessary, can be performed during the same evaluation.

Normal MR Findings

Normal myelination patterns in the newborn are better visualized on T1-weighted MR images. Myelination initially occurs in the dorsal brainstem by 24 to 28 wk of gestation, followed

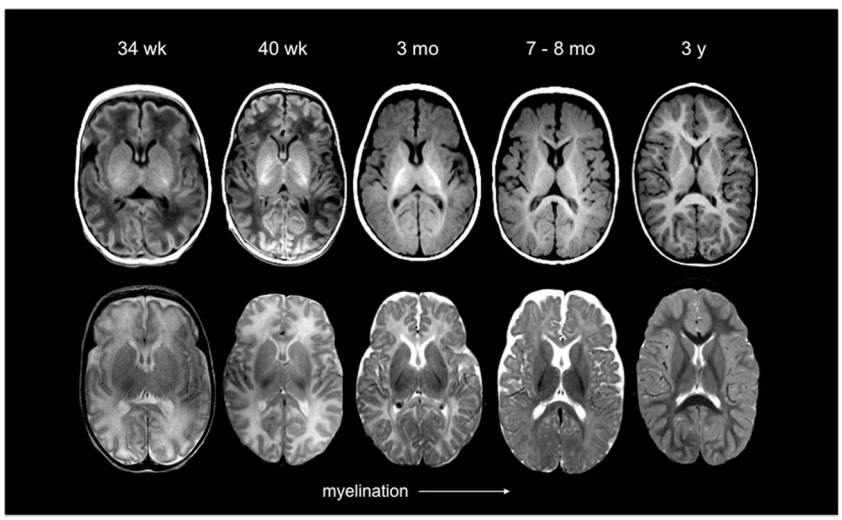

Fig. 4 Normal maturation patterns in neonates and infants

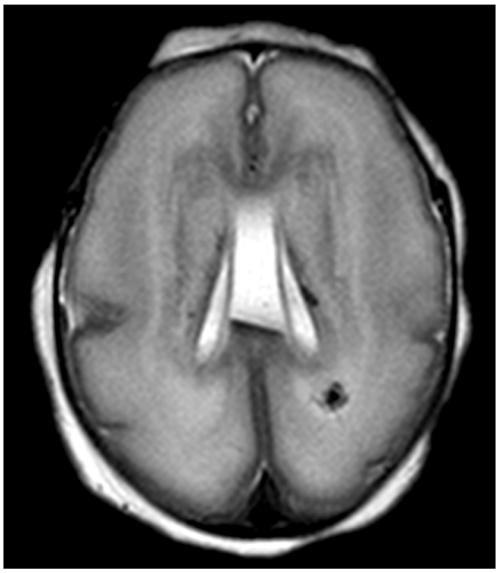

Fig. 5 Axial T2W image: Preterm 28-wk-old neonate with germinal matrix hemorrhage and white matter injury

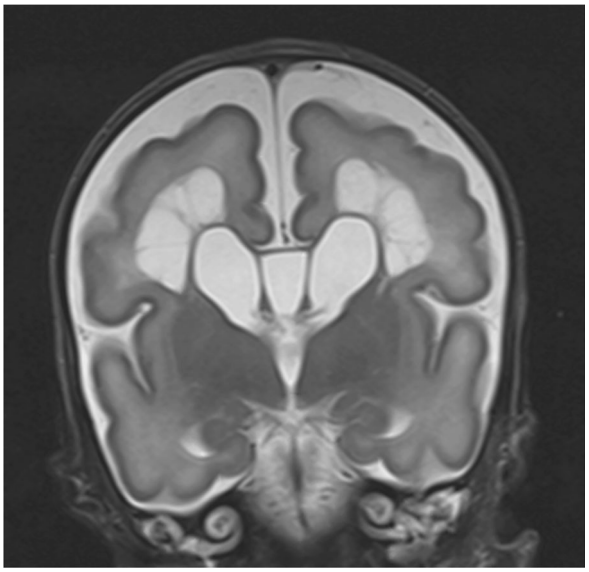

Fig. 7 Coronal T2W image: Cystic periventricular leukomalacia involving the deep white matter

by myelination in the thalamic and sub-thalamic nuclei at around 28 wk. Hyperintense T1 signal is usually seen within the posterior limb of the internal capsule at around 36–37 wk of gestation. Corticospinal tracts demonstrate progressive myelination in a caudo-cranial direction with myelination in the perirolandic white matter and corona radiata visualized at 38–40 wk. In general, myelination occurs progressively with posterior to anterior and caudo-cranial gradients. The deep central structures myelinate earlier than the peripheral parenchyma (Figs. 3 and 4).

There are few studies on the development of sulcal pattern corresponding to approximate gestational age. Gyral and sulcal development is initially appreciated in the perirolandic and medial occipital regions followed by the fronto-basal and fronto-polar areas and the anterior temporal lobe. The sylvian fissure appears initially at the 14th wk of gestation, the calcarine, cingulate and parieto-occipital sulci at around 16–18 wk, and the rolandic sulcus at around 20 wk of gestation. The superior temporal and intra-parietal sulci are visible by around 23–26 wk and the pre- and post-central, superior frontal, and middle temporal sulci at 26–28 wk

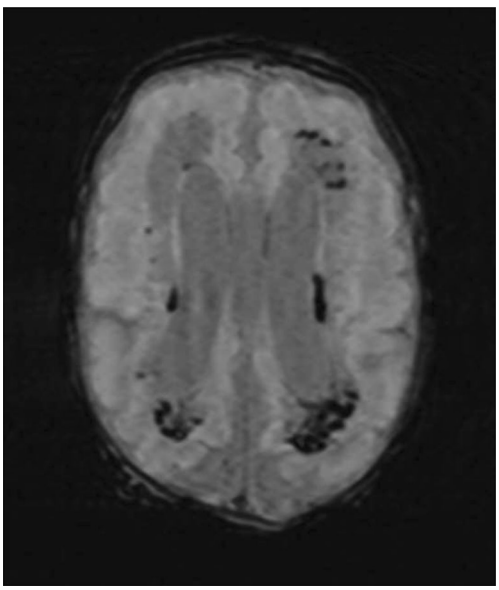

Fig. 6 Susceptibility weighted image: Germinal matrix hemorrhage as low signal intensity foci along the margins of the lateral ventricles with intraventricular extension

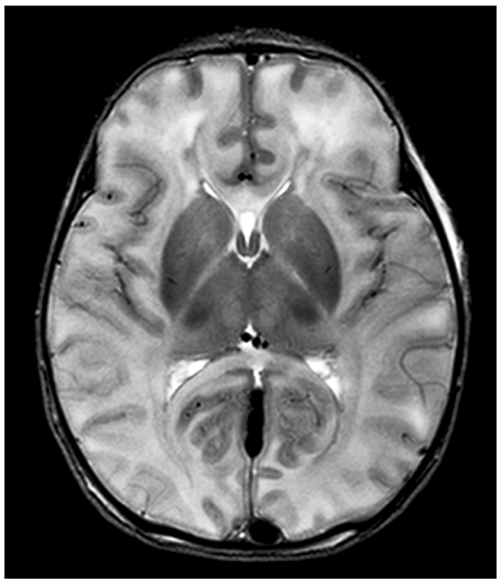

Fig. 8 Axial T2W image: Severe global HIE in a term infant with diffuse swelling and T2 signal abnormalities involving the ventro-lateral thalamus and posterior putamen

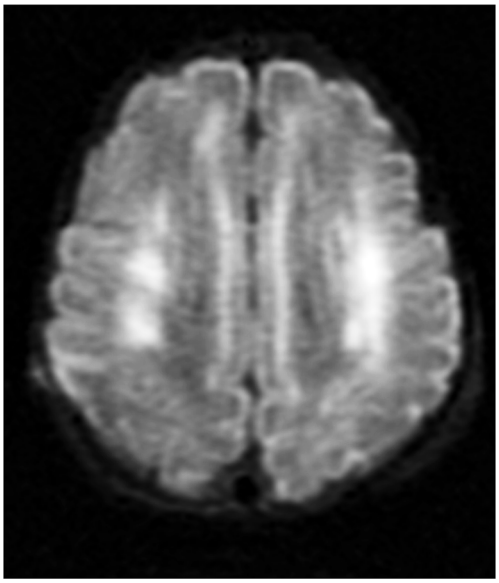

Fig. 9 Axial diffusion weighted image: Subcortical white matter injury in mild-moderate HIE

Nearly all primary and most secondary sulci are present by around 34 wk of gestation [10].

MR Findings in Preterm Neonates

Severe hypoxic-ischemic injury in the premature brain demonstrates a typical pattern with involvement of the basal ganglia, thalami, dorsal brainstem and anterior vermis. Additionally, there may be regional injuries involving the corticospinal tracts, hippocampal formations, and the cerebellum [11]. Germinal matrix hemorrhage (Fig. 5) and periventricular leukomalacia may be associated with mild to moderate hypoxic insult to the preterm brain [12]. Neonatal cranial sonography can be performed as a bedside procedure and is valuable for the detection of germinal matrix hemorrhage. However, MR based susceptibility-weighted imaging and gradient-echo sequences are more sensitive for detecting small hemorrhages within the germinal matrix (Fig. 6). MR also has the additional benefit of being able to identify the extent of associated periventricular venous infarction [13].

Periventricular venous infarcts occur secondary to thrombosis of medullary veins that drain the periventricular brain parenchyma and are usually identified as unilateral triangular lesions with internal hemorrhage on coronal images. Preterm neonates with periventricular venous infarcts involving the peritrigonal region with associated absent myelination in the posterior limbs of the internal capsule are more likely to develop congenital hemiplegia [11]. Preterm neonates with cerebellar hemorrhagic injuries, especially those with vermian involvement are shown to have increased incidence of long-term disabilities [14].

Periventricular leukomalacia may represent as diffuse injury to immature myelinating oligodendrocytes; identified as non-cavitating areas of white matter injury or as focal cystic areas within the deep white matter secondary to necrosis (Fig. 7). The common sites of involvement are the trigones of lateral ventricles, these being the watershed zones. Infection or inflammation are believed to enhance the severity of hypoxic-ischemic injury by inducing inflammatory cytokine release that disturbs cerebral vascular autoregulation [15].

In the initial phase of injury within the first two to five days, multiple discrete foci of T1 and T2 hyperintensity are visualized in the periventricular white matter. Further, after six to seven days, these areas demonstrate relatively low T2 signal due to T2 shortening effect [2]. There is no blooming on susceptibility-weighted images or on T2* imaging. Early restriction of diffusion is seen due to ischemia and coagulative necrosis with subsequent normalization in five to seven days.

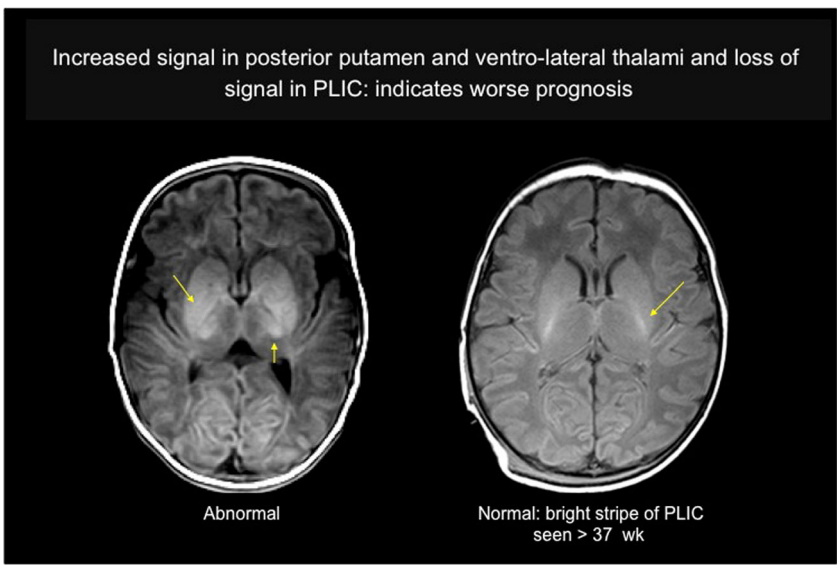

Fig. 10 Axial T1W images: Obscuration of posterior limb of internal capsule (PLIC) in severe HIE compared to bright stripe of PLIC in normal neonates

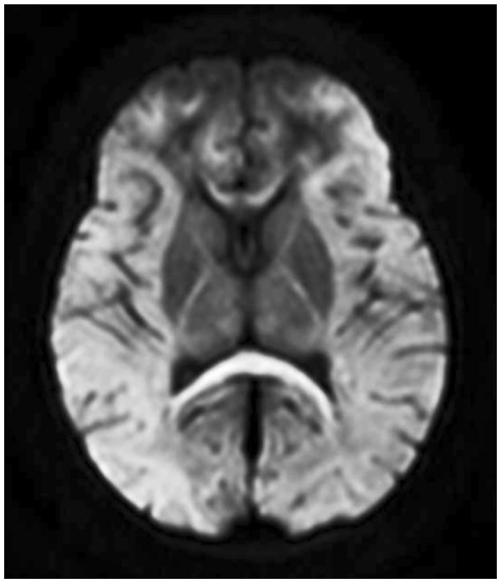

Fig. 11 Axial DWI image: Diffuse cortical and subcortical diffusion abnormalities in a term neonate with severe HIE

In the chronic stage, periventricular leukomalacia demonstrates diffuse reduction in the periventricular white matter volume with passive dilatation and undulation of the ventricular walls. There may be associated atrophy of the posterior body and splenium of the corpus callosum.

The commonly seen scattered punctate white matter foci in the preterm brain do not always correlate with adverse developmental outcome [16]. Whether these white matter changes are within the normal spectrum or represent underlying structural changes is unclear; in authors' experience, diffuse hyperintense T2 signal changes are deemed clinically significant when associated with other features of perinatal insult and supportive clinical history for significant injury.

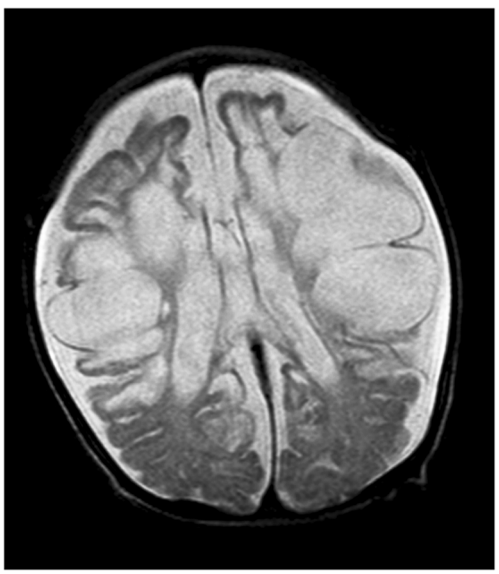

Fig. 12 Axial T2W image: Chronic sequelae of profound HIE with extensive cystic encephalomalacia

MR Findings in Full-Term Neonates

Various maternal and fetal conditions during gestation may cause diminished cerebral blood flow, resulting in hypoxic ischemic injury in the full term neonate. Conditions related to the fetus include fetal bradycardia, thrombosis and feto-maternal hemorrhage. Maternal conditions leading to fetal hypoxic ischemic injury include anemia, hypotension, vascular diseases, eclampsia and preeclampsia, and abruptio placentae. Postnatal conditions such as congenital cardiac anomalies, meconium aspiration, hyaline membrane disease and pneumonia may also lead to asphyxia and thus, encephalopathy. Vulnerable regions for potential injury in cases of severe hypoxic-ischemic insult typically involve the ventro-lateral thalamus, posterior putamen, perirolandic cortex, and corticospinal tracts [6, 17] (Fig. 8). Watershed zones including the parasagittal cortex and subcortical white matter are typically involved in mild-moderate injury (Fig. 9) [18]. There is relative sparing of the deep gray matter, brainstem and cerebellum. The presence of acute injury can be appreciated on routine T1and T2 sequences around day 1–3 after injury. These findings are gradually more apparent; with T1 hyperintense signal changes after injury and T2 prolongation between six and ten days post injury [2]. Obscuration of the normal T1 high signal within the posterior limb of the internal capsule is a useful neuroimaging marker of adverse outcome [19] (Fig. 10).

Diffusion restriction is an extremely useful and sensitive finding that enables early detection of injury and may be present on the first day with evolution over time with

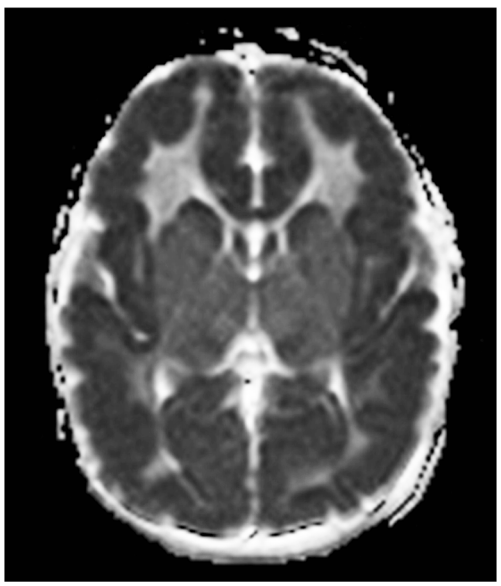

Fig. 13 Axial diffusion weighted image: Inborn error of metabolism; Molybdenum co-factor deficiency with diffusion restriction in the cortex of a term neonate

delayed injury (Fig. 11) [20]. However, when performed during the very early phase within a few hours, this may underestimate the extent of injury [12]. Changes on diffusion weighted imaging are most apparent at three to five days post insult and normalize by seven to ten days [8]. It is noteworthy that normal ADC values may be present in a small group of patients with injuries to the basal ganglia and thalami, presumably secondary to the injury having occurred prior to delivery, or secondary to delayed cell death [21]. Hence, it is worthwhile to repeat scanning with a proton MR Spectroscopy [22] after 24 h or to follow-up with an MRI after two to four days.

Diffuse supra-tentorial injuries on diffusion-weighted images may be challenging to interpret and it may be useful to compare with the normal appearing cerebellum, which is usually spared in hypoxic ischemic injury [23]. In moderate or severe injuries usually involving the central gray matter, white matter may demonstrate a delayed injury, with subsequent atrophy [24]. Apoptotic cell death may account for the raised ADC values. Generalized atrophy and multicystic encephalomalacia ensue in chronic stages (Fig. 12). Focal injuries result in ulegyria (especially in perirolandic cortex) with T2 weighted high-signal-foci within the posterior putamen and thalami.

Impact of Hypothermia on MRI Findings

Therapeutic hypothermia has shown to result in improved neurodevelopmental outcomes and increased rate of survival without residual neurologic abnormalities. The exact mechanism of therapeutic hypothermia is poorly understood although various hypotheses have been postulated, including, decreased brain metabolism, stabilization of the blood brain barrier, reduced inflammatory response and suppression of apoptosis [25]. Multiple studies have demonstrated a decrease in the extent of abnormalities detected within the cerebral cortex, white matter, basal ganglia and thalami in infants undergoing therapeutic hypothermia compared to those not undergoing hypothermia. Additionally, the time course for the evolution of diffusion changes in HIE is delayed in infants treated with therapeutic hypothermia and occurs approximately around the 10th day compared to the 6–8 d interval for normothermic infants. This extended time window of changes seen in cooled infants needs to be considered in the timing and interpretation of the MRI studies for these subset of patients [26–28]. Currently, establishing the optimal time window for imaging neonates after hypothermia is a field of ongoing research and in authors' experience, it is yet to be firmly established, and further studies are needed.

Imaging-Based Differential Diagnosis of Neonatal Encephalopathy

Metabolic encephalopathy resulting from inborn errors of metabolism, congenital malformations, central nervous system infections and severe birth trauma are among the broad groups of differential diagnosis for neonatal encephalopathy [29]. Amongst the common causes of metabolic neonatal encephalopathy are lactic acidosis (pyruvate dehydrogenase deficiency being the commonest), molybdenum cofactor deficiency, urea cycle disorders and aminoacidemias including maple syrup urine disease apart from other inborn errors of metabolism [30] (Fig. 13).

Conclusions

MR imaging has evolved as a cornerstone in the diagnostic evaluation and prognostication of hypoxic ischemic injury. It is important to be aware of various imaging patterns in HIE and that they are influenced by the duration and severity of the insult as well as the degree of maturation of the neonatal brain. Imaging findings should be reviewed in the context of the clinical setting to determine the underlying etiology.

Contributions MS: Concept and design of the study, revision and critical appraisal of the paper; PK: Draft and material, revision of the paper. MS will act as guarantor for the paper.

Compliance with Ethical Standards

Conflict of Interest None.

Source of Funding None.

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