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Original Article

Radiology Section

Evaluation of Role of Magnetic Resonance Imaging in Newborns with Suspected Hypoxic Ischaemic Injury and its Association with Clinical Staging: A Cross-sectional Study

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ABSTRACT

Introduction: Hypoxic Ischaemic Injury (HII) also known as Hypoxic Ischaemic Encephalopathy (HIE) is one of the most common causes of neonatal morbidity and mortality in most countries of the world. Perinatal asphyxia being the most frequent cause of HII, some of its long-term sequelae includes impaired neurological development, cerebral palsy, recurrent seizures, etc. Magnetic Resonance Imaging (MRI) has been found to be most sensitive in detecting lesions in the brain of neonates with HII.

Aim: To evaluate the role of MRI in assessing neurologic damage in newborns with suspected HII and its association with clinical staging.

Materials and Methods: An institution-based descriptive cross-sectional study was conducted in a tertiary care Government Hospital in Guwahati, Assam, India for a duration of 15 months from May 2017 to July 2018 on 50 neonates with history of perinatal asphyxia. Assessment of conventional T1 and T2 weighted images, Diffusion Weighted Imaging (DWI) and Susceptibility Weighted Imaging (SWI) was done and association of MRI findings with gestational maturity, Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores and clinical staging (Sarnat and Sarnat Staging system) was studied.

Results: In majority of cases with clinically mild HII, MRI findings were either normal or of mild degree whereas in cases of clinically advanced stages of HII, MRI findings were moderate-to-severe, suggesting a positive association between clinical grading and severity of brain injury. Term neonates sustained injuries mostly in cortical-subcortical/watershed zones of brain whereas preterm neonates were seen to sustain mainly periventricular lesions. Basal ganglia, thalamic and midbrain lesions were seen to be associated with severe degree of HII in term neonates whereas germinal matrix haemorrhage was observed in preterm neonates with severe HII. A positive association was seen between severity of brain lesions with both low APGAR scores and gestational prematurity.

Conclusion: MRI is helpful to study the pattern of brain involvement in term and preterm neonates with suspected HII and to assess the severity of injury. MRI findings are seen to correlate well with clinical staging.

Keywords: APGAR score, Diffusion weighted imaging, Germinal matrix haemorrhage, Hypoxic ischaemic encephalopathy, Perinatal asphyxia, Sarnat's staging

INTRODUCTION

Hypoxic Ischaemic Injury (HII) or Hypoxic Ischaemic Encephalopathy (HIE) is one of the most common causes of neonatal morbidity and mortality in most of the countries. The most common cause of HII is perinatal asphyxia [1]. Problems during delivery, like a compressed umbilical cord or placental dysfunction, can result in an acute reduction of circulation and gas exchange. Also, after birth, problems with the oxygen supply can occur, if the newborn cannot initiate or sustain effective breathing [2,3]. Perinatal asphyxia is characterised by oxygen and nutrients deficiency in all organs of the newborn, hence called hypoxic ischaemia. Especially to the brain, this injury is reported to have serious consequences for future development [2]. The hypoxic-ischaemic insult can affect large parts of the brain, both in gray and white matter [2,4]. This may have consequences for brain development, both structural and functional, and in the long-term might result in mental retardation, motor deficits and disorders of sensory functions [2,5].

Although, Ultrasonography (USG), Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are all used, MRI is the most sensitive and specific modality for detection of HII. It is safe as it involves no radiation and can be performed during neonate's sleep [6]. Diffusion Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) changes are detected earlier than on conventional T1- and T2-weighted MRI [7].

As neonatal encephalopathy continues to be a cause of high mortality and morbidity worldwide, detection of such injury at an early stage is essential for development of strategies to limit permanent brain damage and for prognostication of neurological development of the newborn [8,9]. Despite a high incidence rate of HII in a developing nation like India, there is scarcity of literature on imaging-based studies on HII conducted. Hence, the present study was an attempt to address such lacunae in literature for better understanding of the imaging-based prognostication of affected neonates as opposed to clinical staging and to determine any association between the two. MRI defines the nature and the extent of injury and also has diagnostic value in excluding unaffected babies from those clinically considered as mildly or moderately asphyxiated.

The aim of this study was to evaluate the role of MRI in assessing neurological damage in newborns with suspected HII and its association with clinical staging.

MATERIALS AND METHODS

The present study was an institution-based descriptive cross-sectional study conducted in a tertiary care Government Hospital in Guwahati, Assam, India for a period of 15 months from May 2017 to July 2018 after obtaining clearance from Institutional Ethical Committee (IEC) vide No. MC/190/2007/Pt-1/EC/99 dated 30/05/2017. A total of 50 neonates were enrolled in the study

who subsequently underwent MRI of brain. This sample size was achieved by including all the eligible neonates based on inclusion and exclusion criteria admitted to the Paediatrics Department within the time frame of study.

Inclusion criteria: All haemodynamically stable newborns irrespective of the gestational age sustaining perinatal asphyxia with clinical diagnosis of HII were included.

Exclusion criteria: Haemodynamically unstable babies who may not tolerate prolonged examination times. Babies with lethal/major congenital malformation, infection and suspected metabolic disease.

MRI was done on Siemens Somatom Tim Avanto 1.5 Tesla MRI System. Sedation was achieved using pedicloryl syrup. (Inj. Propofol 2-3 mg/kg body weight, slow i.v. was used for restless babies). Following plain MRI pulse sequences were obtained with section thickness 3-4 millimeter:

- T1-weighted spin-echo (TR/ TE, 400/13-308),
- T2-FLAIR (TR/TE, 9500/120),
- Axial T2 FSE TR/TE (4000/102),
- DWI (TR/TE 8000/100.7)
- SWI (Susceptibility Weighted Imaging)

A standardised grading system was devised for both MRI findings in term and preterm neonates as well as clinical symptoms.

Procedure

In all cases, after obtaining informed consent, a brief history of mother was taken which included clinical and antenatal details, followed by clinical examination of the neonate, symptoms suspicious for perinatal asphyxia including APGAR score, feeding status, reflexes, presence of seizures, etc. Parameters such as gestational age, birth weight were recorded. The babies were then evaluated with MRI examination of the brain.

Symptoms suspicious for perinatal asphyxia included one or more of the following criteria such as meconeum stained liquor, derangements in prenatal Non Stress Test (NST) or cardiotopography, low APGAR score [10] at birth, poor feeding, abnormal tone/reflexes etc. A score of 7 or <7 at 5 minutes of birth was considered as low APGAR score.

Clinical grading of HII (According to Sarnat and Sarnat Staging System [11]):

- Mild: Irritable/Poor feeding/Exaggerated tendon reflexes/ Normal to increased muscle tone/No seizures.
- Moderate: Lethargic/Exaggerated tendon reflexes/Decreased muscle tone/Early onset seizure.
- Severe: Coma/Seizures/Flaccidity/Brainstem and autonomic dysfunction.

MRI criteria: Lesions or altered signal intensities due to ischaemic injury in the regions of interest for HII, viz.,– Subcortical white matter and/or cortex, Posterior Limb of Internal Capsule (PLIC), Perirolandic White Matter (PRWM), Periventricular White Matter (PVWM), basal ganglia, thalami, brainstem and germinal matrix.

Morphology/pattern of brain lesions was classified as described by Chao CP et al., [12].

Sites of altered signal intensities in term babies:

- Subcortical white matter/cortex- signifies mild injury
- PRWM and PLIC- moderate injury
- Brainstem, Basal ganglia and thalami- severe injury.

Sites of altered signal intensities in preterm babies:

- PVWM- signifies mild injury
- PVWM with or without PLIC/PRWM- moderate injury
- Germinal matrix bleed/basal ganglia and thalamic lesions- severe injury.

STATISTICAL ANALYSIS

Analysis of the study was done as per standardised statistical methods using Statistical Package for the Social Sciences (SPSS) version 16.0. Various clinical and demographic features (variables) were compared with abnormal MRI findings (outcome) using inferential statistics, i.e., Pearson's Chi-square test to find out the association between these. Quantitative variables were handled as frequencies and represented in a tabular and histogram format, whereas categorical variables were represented with the help of bar diagrams. The p-value of <0.05 indicates statistically significant difference.

RESULTS

Frequency distribution of MRI findings according to different variables such as gestational age, APGAR score and clinical staging were studied and observations are shown in [Table/Fig-1-3]. Severity of brain injury was found to be more in preterm babies (50% showed severe involvement), whereas majority of term babies (50%) showed only mild involvement [Table/Fig-1]. Babies with low APGAR score at 5 minutes of birth were found to be more commonly affected and more likely to show severe MRI abnormalities [Table/Fig-2].

Foetal maturity	MRI				Total n (%)
	Normal	Mild	Moderate	Severe	
Preterm	1	1	2	4	8 (16)
Term	12	21	6	3	42 (84)
Total	13	22	8	7	50 (100)

[Table/Fig-1]: Showing distribution of MRI findings according to gestational age. Pearson Chi-square test, p-value=0.007 i.e., statistically significant

APGAR score	MRI				Total n (%)
	Normal	Mild	Moderate	Severe	
7 or <7	2	4	5	7	18 (36)
> 7	11	18	3	0	32 (64)
Total	13	22	8	7	50 (100)

[Table/Fig-2]: Showing distribution of MRI findings according to APGAR score. Pearson Chi-square test, p-value <0.001 statistically significant

Sarnat's staging	Frequency (N=50)	Percentage (%)
Stage 1 (Mild)	13	26
Stage 2 (Moderate)	28	56
Stage 3 (Severe)	9	18
Total	50	100

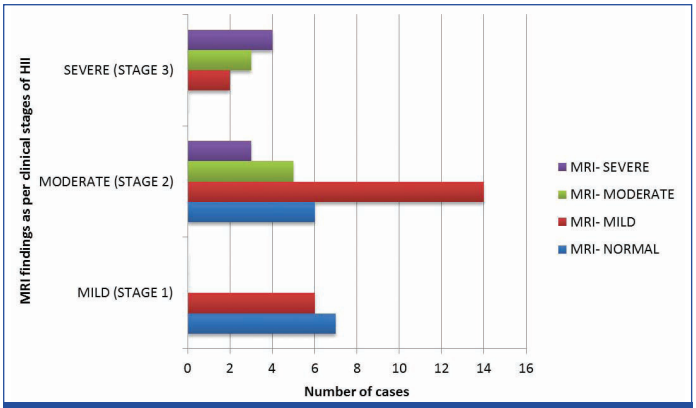
[Table/Fig-3]: Case distribution of clinical grading of Hypoxic Ischaemic Injury.

Out of 13 cases clinically classified as stage 1 HII, 7 cases had a normal MRI study. Also, within this group less than half of the cases (46%) showed mild brain injury [Table/Fig-4]. In patients clinically having moderate HII (stage 2), a normal MRI study was found in 6 cases (21.4%) and mild involvement was seen in 14 cases (50%). In babies classified as clinically severe (stage 3), 4 cases (44.4%) showed severe involvement in MRI study and none of these cases showed a normal MRI findings [Table/Fig-4].

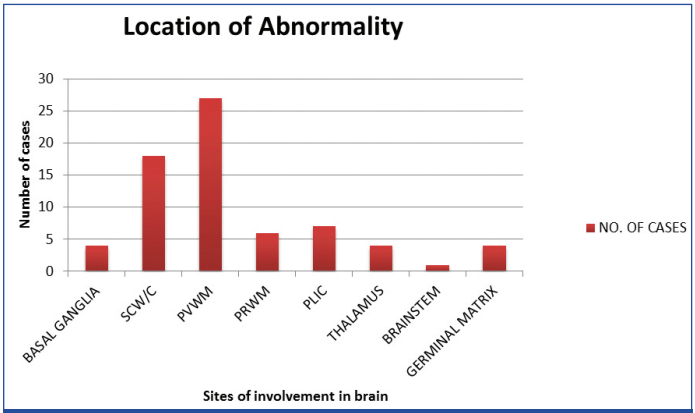
PVWM was observed to be the most commonly affected area (54% cases), followed by cortex/subcortical white matter (36% cases) [Table/Fig-5].

Periventricular White Matter (PVWM): PVWM abnormality was seen in 27 cases (54%), in the form of T2 and FLAIR hyperintensity with evidence of restricted diffusion on DWI in 8 cases [Table/Fig-6,7]. Of these, 21 (50%) were term neonates while 6 (75%) were preterm.

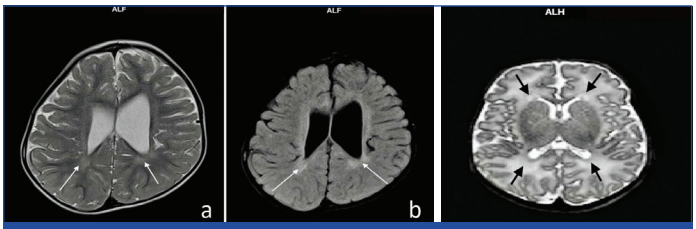
Cortex/Subcortical white matter: Cortex and/or subcortical white matter abnormality was observed in 18 cases (36%). All of these cases were found to be term babies (42 cases). In majority of cases, changes were observed in the form of T2 and FLAIR hyperintensities in the cortex, especially watershed portions between Anterior



[Table/Fig-4]: Bar diagram depicting association between clinical grading of HII (Sarnat's Grading) with MRI grading.
Pearson Chi-square test, p-value=0.003 statistically significant

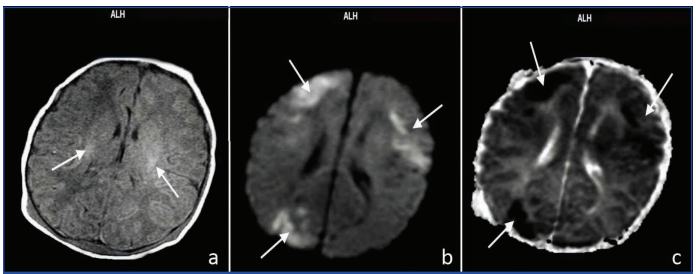


[Table/Fig-5]: Bar diagram showing frequency of involvement of different regions of brain in HII.
n=50. SCW/C: Subcortical white matter/cortex; PVWM: Periventricular white matter; PRWM: Perirolandic white matter; PLIC: Posterior limb of internal capsule



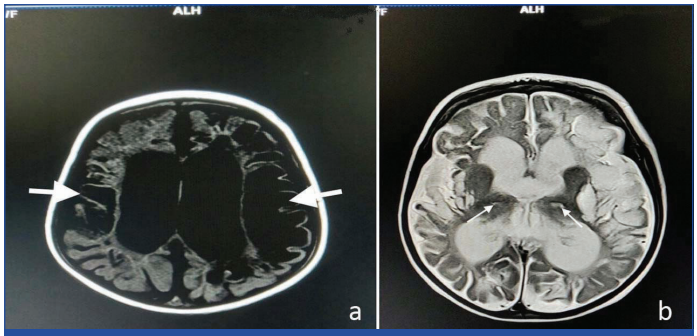
[Table/Fig-6]: Axial T2WI (a) and FLAIR (b) sequences showing periventricular leukomalacia (white arrows) with ventriculomegaly in a 20-day-old preterm neonate with mild HII. **[Table/Fig-7]:** Axial T2WI image showing exaggerated signals in Periventricular White Matter (PVWM) suggestive of periventricular leukomalacia in a preterm neonate with mild HII. (Images from left to right)

Cerebral Artery (ACA)- Middle Cerebral Artery (MCA) and Middle Cerebral Artery (MCA)- Posterior Cerebral Artery (PCA) territories, and the underlying subcortical white matter. Diffusion restriction was seen in three cases [Table/Fig-8]. Two of the cases had changes of multicystic encephalomalacia [Table/Fig-9].



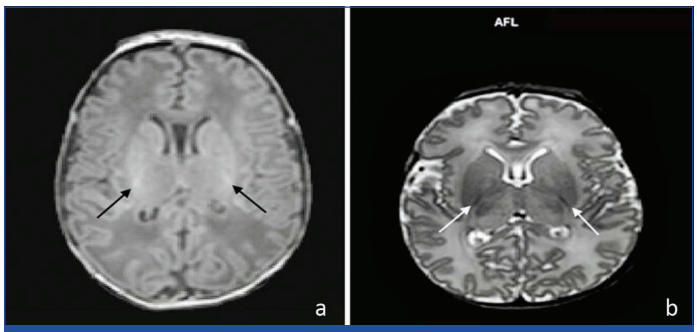
[Table/Fig-8]: Axial T1WI (a) showing hyperintensities in bilateral basal ganglia (white arrows) in a seven-day-old term neonate with moderate HII. DWI (b) and corresponding ADC map (c) in the same patient showing restricted diffusion (white arrows) in cortical and subcortical watershed territories between Anterior Cerebral Artery (ACA)- Middle Cerebral Artery (MCA) and Middle Cerebral Artery (MCA)- Posterior Cerebral Artery (PCA).

Posterior Limb of Internal Capsule (PLIC): PLIC involvement was found in seven cases (14%) in the form of absence of the (or



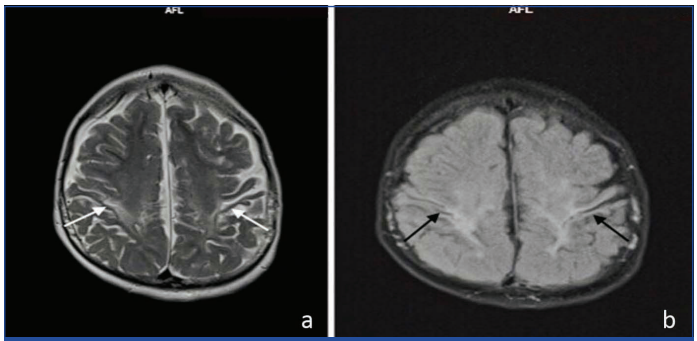
[Table/Fig-9]: Axial T1WI (a) and T2WI (b) sequences showing cystic encephalomalacia (thick white arrows in a) with ulegyria involving bilateral fronto-parieto- temporal lobes and ventricular dilatation in a 13-day-old term neonate with profound HII. Hyperintensities with cystic changes noted in bilateral thalami (thin white arrows in b).

incomplete) normal T1 hyperintensity and T2/FLAIR hypointensity in the PLIC [Table/Fig-10]. Restricted diffusion on DWI was seen in two cases. Six cases (14.2%) were term neonates while one case (12.5%) was preterm.



[Table/Fig-10]: Axial T1WI (a) and T2WI (b) showing abnormal appearance of bilateral PLIC with incomplete T1 hyperintensity (black arrows) and T2 hypointensity (white arrows) in a 20-day-old term neonate with moderate HII.

Perirolandic White Matter (PRWM): Signal changes in the form of T1, T2 and FLAIR hyperintensity involving the PRWM was seen in six cases (12%) [Table/Fig-11]. Of these, five cases (11.9%) were term babies while one case (12.5%) was preterm. Diffusion restriction was present in two cases.

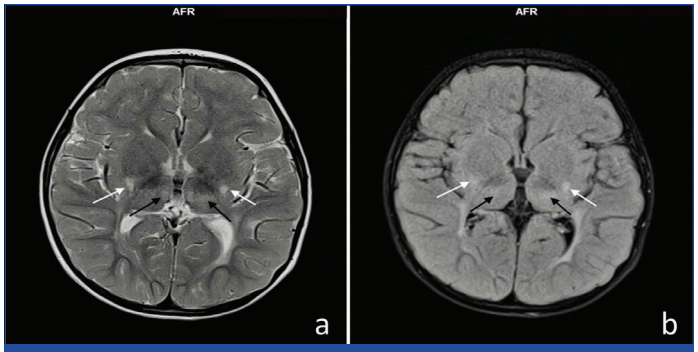


[Table/Fig-11]: Axial T2WI (a) and FLAIR (b) images showing hyperintensities in bilateral perirolandic cortex (arrows) with mild volume loss in a 20-day-old term neonate with moderate HII.

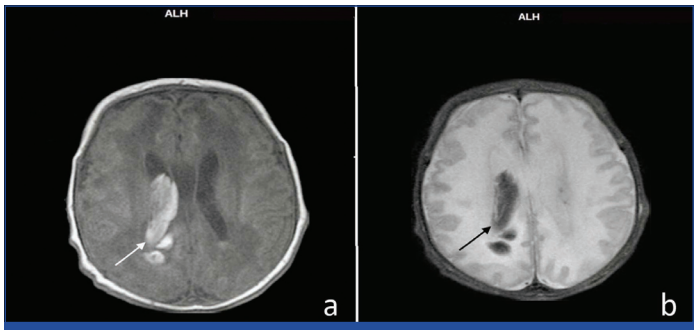
Basal ganglia and thalamus: Abnormality in the basal ganglia and thalami was observed in four cases (8%) each. Of these, three were term babies and one was preterm, in each category. The signal changes were in the form of T1, T2 and FLAIR hyperintensities [Table/Fig-12]. Three of the cases showed restricted diffusion.

Brainstem: Brainstem signal changes were seen in one case (2%), who was a term neonate. T1, T2 and FLAIR hyperintensities were seen along with mild diffusion restriction on DWI.

Germinal matrix: Germinal matrix haemorrhage was seen in four cases (8%), all of whom were preterm babies. Signal changes were observed in the form of T1 hyperintensity in the ventricles along with presence of susceptibility foci on SWI in the corresponding regions in two cases [Table/Fig-13]. In the other two cases, only susceptibility foci were seen in the ventricles without the presence of corresponding T1 hyperintensity.



[Table/Fig-12]: Axial T2WI (a) and FLAIR (b) sequences showing hyperintensities in bilateral basal ganglia (white arrows) and thalami (black arrows) in a 24-day-old term neonate with severe HII.



[Table/Fig-13]: Axial T1WI (a) showing intraventricular bleed (germinal matrix haemorrhage) in right lateral ventricle (white arrow) and corresponding SWI image (b) showing blooming artifacts (black arrow) in a 12-day-old preterm infant with severe HII.

DISCUSSION

Gestational age: In the present study, more severe brain involvement was seen in preterm babies compared to term babies, with a statistically significant association between these variables. Therefore according to this study, there was significant association between maturity of foetus and brain injury in birth asphyxia and the chance of finding a severe MRI abnormality was high. This finding corroborates with that of the study conducted by Moore T et al., according to which infants born prematurely have a high incidence of neonatal brain injury, with detrimental effects on motor, cognitive, behavioural, social, attentional, and sensory outcomes [13]. Hintz SR et al., in their study also find that preterm neonates are more prone to sustaining HII as compared to term babies [14]. Also, Cooper DJ, and Bryce J et al., in their studies concluded that premature neonates are particularly at risk of suffering HII, with the incidence being a significant 60% higher [15,16].

APGAR score: In present study, significant association was found between low APGAR score and brain injury. It was seen that babies with low APGAR at 5 minutes of birth, majority (88.8%) were affected and almost half (43.7%) of them showed severe involvement in MRI. Of the babies having normal APGAR and showing MRI changes, majority (85.7%) were mild and none of them showed severe involvement. These findings corroborated with study conducted by Mercuri E et al., which observed that cerebral infarction and scattered white matter changes were most common findings in infants with low APGAR (4 and above) score whereas severe and moderate basal ganglia and thalamic lesions were observed in babies with very low APGAR (3 or below) [17]. Similarly Ayrapetyan M et al., in their study found that in infants with low APGAR scores approximately 35% showed severe and 41% showed mild-to-moderate MRI abnormalities [18].

Clinical severity (Sarnat's classification): In this study, it was found that there is >50% chance of getting a normal MRI even in neonates who are clinically graded as mildly affected (stage 1). Whereas in clinically severe (stage 3) babies, almost half (44.4%) of them showed severe MRI abnormalities. These findings corroborated with those of the study conducted by Kaufman SA et al., in which more than half of the cases with clinically mild hypotension showed a normal MRI study [19]. Of those babies clinically having moderate hypotension, 20% were normal at MRI, 52% showed only mild changes and 12% showed severe involvement. More than half of the babies having clinically severe hypotension showed involvement of thalamus, basal ganglia and brainstem. It was concluded that mild encephalopathy correlates with normal MRI result, and severe encephalopathy correlates with abnormalities in the basal ganglia/thalami [19].

In present study, majority of newborns who had HII were found to have mild involvement on brain MRI (44%). This was similar to a study done by Lally PJ et al., in South India where the proportion of newborns with mild HII was 56% and also to another study conducted in Rotunda hospital in Ireland by Hayes BC et al., where of the 237 newborns assessed, 65.4% had the mild form of HII [20,21].

Location of abnormality in brain: Present study found that in term babies with mild HII, 16 cases (76.1%) showed signal changes in cortex/subcortical white matter. This observation was similar to study by Van Den BR, and Takashima S and Tanaka K who concluded that term infants suffering from mild ischaemic insult mostly sustain injury in the watershed regions of cerebral cortex and underlying subcortical white matter and PVWM [22,23]. This pattern of injury will lead to gliosis in the cortical subcortical region and atrophy of parasagittal watershed areas in term neonates.

In a significant proportion (77%) of term babies manifesting clinically mild HII, signal changes were found in PVWM. According to Rutherford M et al., such periventricular signal changes are sometimes difficult to differentiate from delayed myelination, due to immature white matter in infants under one year of age [24]. These changes may however become more obvious with time in some infants and hence, such infants are to be followed-up with repeat imaging.

Among those neonates having clinically severe asphyxia, 57% showed involvement of thalamus and basal ganglia each and 14.28% showed involvement of brainstem. According to a study by Sie LT et al., in babies having severe asphyxia, 50% showed thalamic involvement, 25% basal ganglia involvement and 25% brainstem involvement [25]. Bharat MP et al., in their study found that in babies with clinical stage 3 HII, 55% had bilateral basal ganglia involvement and 30% had bilateral thalamic involvement [26]. Voit T et al., has observed that thalamic-striatal damage is the hallmark of more widespread brain damage, more frequently observed in asphyxiated term babies [27]. Barkovich AJ and Truwit CL also observed that primary brainstem, thalamus and basal ganglia involvement is seen in those with cardio-circulatory arrest, indicating severe birth asphyxia [28]. Chang PD et al., in their study concluded that lesions in the basal ganglia-thalamus, posterior or anterior limb of internal capsule or watershed infarction corresponded with subsequent abnormal neurodevelopmental outcome at 18-24 months of age and accounted for about 45% of the total abnormal cases [29].

Among those suffering from clinically moderate asphyxia in present study, signal changes were frequently observed in perirolandic white matter and PLIC (75% and 87%, respectively), majority of whom were term babies. Rutherford MA et al., had observed that MRI lesions in internal capsule predict poor neurodevelopmental outcome in infants with HII [30].

Present study found that in preterm babies with mild-to-moderate hypotension, all three cases (1 mild and 2 moderate) showed PVWM involvement and it was also the most common area to be affected. Germinal matrix haemorrhage was seen in four preterm babies (50%) out of which three had severe hypotension and one had moderate hypotension. Therefore, germinal matrix was found to be most commonly affected in severe hypotension. These findings were corroborated in the study by Sie LT et al., where periventricular leukomalacia was seen in majority of neonates (82%) after subacute or chronic hypoxia in preterm babies, and also in the study by

Bharat MP et al., where 23.3% of preterm babies with HII showed periventricular leucomalacia and all cases showing haemorrhage were seen in preterm babies only [25,26].

Limitation(s)

The sample size was small. Also, no follow-up imaging in neurodevelopmental assessment of study population at a later age could be done for comparison of clinical outcomes with initial MRI studies. Another limitation is possible under detection of brain lesions in preterm babies due to immature myelination in brain. Follow-up of long-term data of affected infants to assess unreported milder disabilities such as attention deficit disorders needs to be taken up. Further work needs to be done on a larger study population and with newer advances like Diffusion Tensor Imaging (DTI) perfusion MRI and MRI spectroscopy to firmly establish guidelines on use of neuroimaging in babies with birth asphyxia.

CONCLUSION(S)

MRI is an excellent non invasive imaging technique for the assessment of severity of brain injury in children affected with HII. The use of MRI has resulted in identification of a higher rate of abnormalities compared to other modalities. PVWM is found to be the most frequently affected area for ischaemic lesions in both term and preterm babies. Severely asphyxiated cases shows involvement of thalamus-basal ganglia in term and germinal matrix haemorrhage in preterm babies. Neonates who are prematurely born and those with a low APGAR score are prone to show more severe injury. Early diagnosis of HII would help to identify neonates who require early rehabilitation for the improvement of long-term outcome and reduction of disability.

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