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Original Article

Paediatrics Section

Patterns of Magnetic Resonance Imaging and Early Detection via Diffusion-weighted Imaging of Neonatal Hypoxic Brain Injury: A Cross-sectional Study

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ABSTRACT

Introduction: Hypoxic-ischaemic Encephalopathy (HIE) is caused by a hypoxic or ischaemic event, resulting in hypoxemia and hypercapnia. Magnetic Resonance Imaging (MRI) is the most sensitive and specific imaging technology for newborns with HIE. Diffusion-Weighted Imaging (DWI) can detect ischaemic changes in the first days after birth.

Aim: To assess various MRI findings and their distribution patterns in neonates with HIE, as well as the importance of DWI in the early detection of HIE.

Materials and Methods: A hospital-based cross-sectional study was performed in the Department of Radiology at Assam Medical College, Dibrugarh, Assam, India over a period of one year, from August 2021 to July 2022. The study included 88 neonates with HIE diagnosed using the Sarnat staging system (stages II and III). The MRI protocol comprised T2-weighted (axial and coronal), T1-weighted (axial), T2 Fluild Attenuated Inversion Recovery (FLAIR) (axial), DWI (axial), Apparent Diffusion Coefficient (ADC) map, and Gradient eco sequences (GRE) (axial). The Analysis of Variance (ANOVA) test or Student's t-test was used for the association tests for continuous variables, with a p-value <0.05 considered statistically significant.

Results: Most babies underwent MRI between 4 and 7 days of life, and the male-to-female ratio was 1.3:1. The MRI patterns observed included deep grey matter injury in 39 (44%), cortical injury in 17 (19.3%), periventricular injury in 11 (12.5%), and a mixed pattern in 21 (23.9%). The most common patterns observed in preterm and term babies were periventricular leukomalacia and central patterns of injury, respectively. DWI detected ischaemic changes in less than seven-day-old neonates (73.7%) before conventional MRI (50.9%) could identify these changes.

Conclusion: The MRI offers excellent differentiation between grey and white matter and provides a good depiction of the pattern of myelination. MR-DWI adds sensitivity and provides information not seen in the other conventional sequences. MRI can predict severe brain injury in preterm infants who may exhibit less obvious clinical signs of HIE.

Keywords: Encephalopathy, Ischaemia, Neuroimaging, Perinatal asphyxia

INTRODUCTION

The HIE is a dreaded neonatal condition caused by an impairment of cerebral blood flow and oxygen delivery during the perinatal period, resulting in hypoxemia and hypercapnia [1]. The incidence is higher in countries with socioeconomic deprivation, a lack of skilled obstetric care, high birth rates, and geographical constraints [2]. Globally, perinatal asphyxia has an incidence of 2-10 per 1,000 term newborns, resulting in four million deaths [3]. In developed countries, birth asphyxia contributes to less than 0.1% of neonatal deaths, whereas the numbers are significantly higher in the developing world [3]. Recent data from India reports an incidence of 2 to 16.2%, with a quite high case fatality rate of 38.5 to 74%. Upto 80% of survivors of severe HIE and about 30-50% of survivors of moderate HIE end up with substantial complications [4].

While cranial ultrasound is a relatively simple, cost-effective, non invasive, point-of-care imaging modality [5], MRI has emerged as a superior technique for detecting HIE changes, offering better grey-white matter resolution and intricate detailing of neurodevelopment and long-term prognostication [6]. Moreover, the predictive value of MRI is not influenced by treatment modalities such as therapeutic hypothermia [6]. The optimal timing for conventional MRI techniques is around 1-4 weeks in term babies [7,8]. Very early scans during the first 72 hours of life might result in misinterpretation due to cytotoxic brain oedema. However, established changes at this time indicate a prenatal insult [9]. DWI can be used in the first days after birth, and with improved sequences and measurements of apparent diffusion coefficient values, the specificity and sensitivity of very early scans for predicting outcomes are likely improved [10-12]. This is a definite advantage of DW-MRI over conventional techniques, as earlier neuroimaging helps clinicians in quicker prognostication and planning for early stimulation.

Although MRI findings of perinatal asphyxia have been well studied in developed countries, data from low-to-middle-income countries [13-17], which unfortunately have a high prevalence of birth asphyxia due to poor antenatal care, is scarce. Additionally, DW-MRI has been suggested to be better than the conventional T1 and T2-weighted sequences, which tend to underestimate brain injury during the first week of life [18]. Hence, the present study was conducted to assess various MRI findings and their distribution patterns in neonates with HIE, as well as the importance of DWI in the early detection of HIE.

MATERIALS AND METHODS

This hospital-based cross-sectional study was conducted in the Department of Radiology at Assam Medical College, Dilbrugarh, Assam, India over a period of one year, from August 2021 to July 2022. Permission was obtained from the Institutional Ethics

Committee (IEC-H NO.AMC/EC/PG5533), and informed written consent was obtained from the concerned parents or guardians.

Inclusion criteria: All haemodynamically stable infants with HIE belonging to Sarnat and Sarnat stages II and III [19] were eligible for inclusion.

Exclusion criteria: Infants with HIE stage I, those who were haemodynamically unstable, those on respiratory support, and parents who did not consent to the study were excluded.

Sample size calculation: With a 95% confidence interval and an absolute precision of 10%, and considering the perirolandic area to be the most common distribution pattern (65%) [20], the minimum calculated sample size was 88.

Study Procedure

All eligible infants with HIE admitted to the Neonatal Intensive Care Unit (NICU) were assessed by the on-duty paediatric resident assigned to the NICU on a rotational basis, and modified Sarnat and Sarnat staging [14] was performed. During the study period, out of the total newborns admitted with HIE, 88 were enrolled in the study after necessary exclusions. A detailed clinical history, including birth order, gravida-parity, maternal medical history, mode of delivery, duration and progress of labour, Apperance, Pulse, Grimace, Activity, Respiration (APGAR) score as recorded by the attending paediatric resident, details of resuscitation if any, documented injuries, as well as neurological examination findings, were reported on a predesigned proforma.

The MRI was performed in all cases using the Siemens Magnetom Avanto 1.5 Tesla, with the infant positioned supine on the MR table under the head coil. On conventional MRI, ischaemic brain injury to the cortex and deep gray matter reveals T1 hyperintensity and variable T2 hyperintensity. However, this can be affected by factors such as haemorrhage, which is often associated with traumatic delivery. These findings reflect ischaemia-induced oedema or cystic encephalomalacia. DWI may demonstrate cytotoxic oedema (due to hypoxic brain injury) in the acute phase before the signal intensity changes are evident on conventional T1- or T2-Weighted Images (WI). Cytotoxic oedema can be observed as diffusion restriction on DWI, evidenced by increased signal intensity.

The MRI protocol was in accordance with the routine protocol followed by the department. The sequence and imaging parameters were as follows: the conventional sequence had a matrix of 256×256, a Field of Vision (FOV) of 240×240 mm, a layer thickness of 5 mm, and a layer spacing of 2.25 mm. The T1-Weighted Image (T1WI) spin echo sequence had a Repeat Time (TR) of 550 ms and an Echo Time (TE) of 8.4 ms. The fast spin echo sequence with T2WI had a TR of 3800 ms and a TE of 90 ms. The axial T2 Fluid Attenuated Inversion Recovery (FLAIR) sequence had a TR of 9020 ms and a TE of 87 ms. The axial DWI sequence had a TR of 3550 ms, a TE of 61.0 ms, B values of 0 s/mm^2 and 1000 s/mm^2, a matrix of 160×160, a FOV of 240×240 mm, a layer thickness of 5 mm, and a layer spacing of 2.25 mm.

Reporting was conducted by the Principal Investigator (PI), who has 12 years of experience in neuroimaging, and a radiology resident trained by the PI after thorough discussion. The total imaging time of the 1.5 T whole-body MR imager was approximately 20 minutes.

STATISTICAL ANALYSIS

The continuous data were presented in terms of frequency, percentages, and mean±standard deviation, while categorical variables were expressed as number percentages. The Chi-square test was used to assess the association between categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

The demographics of the mothers and infants were as follows: most of the mothers were primiparous with singleton pregnancies delivering vaginally. Medical complications were present in 49 mothers [Table/Fig-1]. Most of the babies were between four to seven days old, with male babies outnumbering females by 55 (62.5%) males and 33 (37.5%) females. Out of 88 babies, 72 were term and 16 were preterm. A total of 69 (78.4%) patients included in our study had a normal birth weight (2500-3800 g). Only 19 (21.6%) patients were classified as low birth weight (<2500 g).

Parameters		Number of mothers n (%)
Maternal age (years)	<20 years	25 (28.4)
	20-35 years	28 (31.8)
	>35 years	35 (39.8)
Parity	Primi	58 (65.9)
	Multi	30 (34.1)
Mode of delivery	Vaginal	72 (81.8)
	LSCS	16 (18.2)
Type of pregnancy	Singleton	84 (95.5)
	Multiple	4 (4.5)
Maternal medical complications present		49 (55.7)
Maternal obstetric complications present		34 (38.6)

[Table/Fig-1]: Maternal demographics.
LSCS; Lower segment caesarean section

Total 78 (88.6%) babies had APGAR scores above seven at five minutes of life. During the course of resuscitation, 45 babies (51.1%) required only positive pressure ventilation, while 31 (35.2%) required additional intubation. Total 8 (9.1%) required chest compressions after positive pressure ventilation and endotracheal intubation, while 4 (4.5%) required intravenous epinephrine as well [Table/Fig-2]. Stage II patients were more numerous 80 (90.9%) than Stage III patients 8 (9.1%). This was due to the unstable clinical condition of patients in Stage III and the difficulty in performing MRI on patients receiving respiratory support.

Parameters		n (%)
Age	<72 hours	2 (2.3%)
	4-7 days	78 (88.6%)
	>7 days	8 (9.1%)
Gender	Male	55 (62.5%)
	Female	33 (37.5%)
Gestation	Term	72 (81.8%)
	Preterm	16 (18.2%)
Birth weight	<2.5 kg	69 (78.4%)
	2500 kg and above	19 (21.6%)
Birth order	1	47 (53.4%)
	>/= 2	41 (46.6%)
APGAR score	>/= 7	78 (88.6%)
	4-6	10 (11.4%)
	</= 3	0

Details of resuscitation	Positive pressure ventilation	45 (51.1%)
	Endotracheal intubation	31 (35.2%)
	Chest compressions	8 (9.1%)
	i.v. epinephrine	4 (4.5%)
HIE staging	HIE stage 2	80 (90.9%)
	HIE stage 3	8 (9.1%)
Term	Term	72 (81.8%)
	Preterm	16 (18.2%)

[Table/Fig-2]: Demographics of neonatal population (N=88).

Overall, the most common MRI finding in the present study was deep grey matter involvement in 39 cases (44.3%), followed by mixed pattern injury in 21 cases (23.9%) [Table/Fig-3]. The most common pattern in preterm babies was periventricular leukomalacia, affecting 9 (56.25%) [Table/Fig-4]. Among term babies, the central pattern of injury was most commonly seen, involving 36 cases (50%). Other lesions detected included three subarachnoid haemorrhages, three subdural haemorrhages, one cerebellar haemorrhage, and one intraparenchymal haemorrhage [Table/Fig-5].

MRI patterns	Number (n)	Percentage (%)
Deep grey matter	39	44.3
Cortical injury	17	19.3
Periventricular injury	11	12.5
Mixed pattern injury	21	23.9
Total	88	100

[Table/Fig-3]: Distribution of patterns of HIE in study group.

MRI patterns	Number (n)	Percentage (%)
Periventricular Leukomalacia (PVL)	9	56.25
Germinal Matrix Haemorrhage (GMH)	3	18.75
Deep Grey Matter (DGM)	4	25
Others	0	0
Total	16	100

[Table/Fig-4]: Distribution of patterns of HIE among preterm patients in the study group.

Type	Number (n)	Percentage (%)
Central	36	50
Watershed	7	9.7
Mixed	21	29.2
Others	8	11.1
Total	72	100

[Table/Fig-5]: Distribution of patterns of HIE in term patients in the study group.

In the first week of life, DWI was able to detect evidence of HIE in 42 patients compared to 11 via conventional MRI. Beyond the first week of life, conventional MRI could detect lesions in 18 patients compared to nine patients via DWI [Table/Fig-6]. Among the abnormal findings found in the study participants, 22 (43%) were found to be normal on conventional MRI, while 29 (57%) were found to be abnormal. The proportion of abnormal findings was higher with DWI compared to conventional MRI in the early days [Table/Fig-7].

DISCUSSION

Most of the neonates included in present study belonged to the age group of 4 to 7 days (48.9%). The present study recognised the limitations imposed by selection bias, as diffusion findings have been classically known to pseudo-normalise after a period of seven days. Out of a total of 88 patients, 55 (62.5%) were male and 33 (37.5%) were female, showing a slight male preponderance for HIE. No causal relationship was noted with gender. A total of 69 (78.4%) patients included in our study had normal birth weight, while only 19 (21.6%) patients were classified as low birth weight. A total of 72 patients were term patients (81.8%), and 16 (18.2%) were preterm, indicating that HIE was more common in term patients in our study. Diagnosing neonatal brain injury in premature infants is challenging due to either the absence of obvious signs or, if present, their attribution to developmental immaturity. This may be the reason for the lower number of preterm patients in our study. The distribution patterns of age, gender, weight, and gestation were comparable with those of similar studies [21-23].

Days	DWI		Conventional MRI	
	Abnormal	%	Abnormal	%
1-3 days	12	85.7	2	14.3
4-7 days	30	69.8	9	62.8
8-15 days	9	30	17	56.7
16-28 days	0	0	1	100

[Table/Fig-6]: Distribution of lesions of HIE in conventional and diffusion-weighted MR imaging in study group.

DWI	Conventional MRI		Total	Chi-square	p-value
	Abnormal	Normal			
Abnormal	29 (57%)	22 (43%)	51 (100%)	31.38	<0.001*
Normal	0	37 (100%)	37 (100%)		
Total	29 (33%)	59 (67%)	88 (100%)		

[Table/Fig-7]: Association between DWI and conventional MRI.

Out of 88 babies who were part of the study, 80 babies (90.9%) were clinically staged as Stage II, while 8 out of 88 were categorised as Stage III, corresponding to 9.1% of the total study population. The number of subjects with Stage III injuries included in the study was limited due to the unstable clinical picture associated with these injuries and the difficulties in obtaining MRI scans for patients on respiratory support.

The most common MRI finding in our study group was deep grey matter injury, followed by mixed pattern injury, cortical injury, and periventricular injury. Periventricular leukomalacia changes constituted the most common finding in 56% of the preterm babies in our study group, followed by germinal matrix haemorrhage and basal ganglia-thalamic patterns. A similar study found white matter changes as the most common finding in 89% of cases, followed by basal ganglia-thalamic injury [24].

The central pattern of injury is the most common finding in term babies (50%), followed by the mixed pattern of injury and the watershed pattern. A similar study found that 14.7% of cases had an isolated Basal-Ganglia/Thalamic (BGT) pattern of injury, 10.2% had an isolated watershed pattern of injury, and a mixed pattern of BGT and watershed injury was found in 15.9% [23]. Another study involving a total of 173 term newborns with neonatal encephalopathy found that while normal MRI findings were observed in 51 newborns (30%), among the remaining 122 affected newborns (70%), the most common finding was the watershed pattern of injury, affecting 78 newborns (45%), followed by the basal ganglia/thalamus pattern in 44 newborns (25%) [25]. The findings of present study did not correlate well with the above study, likely due to the difference in sample size.

The usefulness of DWI for acute stroke has been reported in many clinical settings [26-29]. The apparent diffusion coefficient, which is the parameter measured and mapped to compose the diffusion-weighted images, is hypothesised to be sensitive to acute cytotoxic oedema. In the less than seven days age group, DWI was better at detecting lesions in 42 patients compared to conventional MRI, which detected lesions in 29 patients. In the more than seven days age group, conventional MRI detected lesions better than DWI in our study.

In one study, DWI performed at the 6th hour detected ischaemic changes that became even more significant by the 32nd hour, whereas conventional MRI showed no findings at the 6th hour, with initial findings only detectable at the 32nd hour [30]. Another study concluded that diffusion changes, which were evident as early as day two of life when the asphyxiated newborns were still being treated with hypothermia, were associated with later abnormal neurodevelopmental outcomes [31].

Our study has certain strengths, considering it is the first-of-its-kind study from the region, to the best of our knowledge based on the literature review. The results can be used to form guidelines regarding neuroimaging within the first week of life for asphyxiated newborns and will assist in subsequent neurodevelopmental follow-up.

Limitation(s)

Our study was a single-centre study with a small sample size. Due to logistical issues and prolonged scan times, we were only able to scan a limited number of cases. Author also encountered difficulties in obtaining scans for patients with severe birth asphyxia who required respiratory support, as MRI has a prolonged scan duration. We could not include a significant number of neonates under three days old, as most of these neonates were unstable due to respiratory distress. Follow-up assessments were not conducted, and we could not trace the neurodevelopmental outcomes.

CONCLUSION(S)

The DWI is better than the conventional sequence for early neuroprognostication and may help clinicians explore therapeutic options sooner. MRI can predict severe brain injury in preterm infants who exhibit less obvious clinical signs of HIE, aiding in prognosticating outcomes and planning neurodevelopmental therapy. Further studies can be planned to compare the findings with point-of-care cranial ultrasound and to ascertain the influence of therapeutic hypothermia in such cases.

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