

Predictive Value of Early Brain MRI for Neurodevelopmental Outcome at 12 Months of Age in Neonates with Hypoxic Ischaemic Encephalopathy: A Prospective Observational Study from a Tertiary Care Centre

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ABSTRACT

Introduction: Perinatal asphyxia with Hypoxic Ischaemic Encephalopathy (HIE) is a common cause of neonatal mortality and morbidity in Low and Middle Income Countries (LMIC) including India. Early objective assessment of severity of brain injury in these neonates is vital in important prognostication and timely optimisation of early intervention. Early Magnetic Resonance Imaging (MRI) is a tool commonly used to predict neurodevelopmental outcome in these neonates, however, studies are limited to assess this association in the Indian context.

Aim: To determine the association between early MRI brain findings and neurodevelopmental outcome at 12 months of age in neonates with HIE.

Materials and Methods: This prospective observational study was conducted in neonatal intensive care unit FH Medical College and Hospital, Agra, Uttar Pradesh, India. A total of 123 babies admitted with diagnosis of perinatal asphyxia by National Neonatal-Perinatal Database (NNPD) criteria were enrolled between October 2020 to September 2023. HIE staging was done by Sarnat and Sarnat staging. MRI was done at 7 to 14 days of life. Neonates were assessed for anthropometry, neurological

examination and a DDST-II (Denver Developmental screening- II) at 12 months of age. Normally distributed continuous variables were summarised as Mean \pm SD and compared using Analysis of Variance (ANOVA). Categorical variables were analysed using the Chi-square test, and correlations were assessed using Pearson's correlation coefficient and p-value <0.05 was significant.

Results: Out of total 123 participants, 93 (75.6%) were male. A total of 91 (74%) deliveries were vaginal, while 32 (26%) were performed by caesarean section. Of 123, 101 (82%) babies completed the follow-up and DDST-2 was done at 12 month. Correlation of MRI brain with developmental screening was done at 12 months of age showed 100% sensitivity, 51.5% specificity with Positive Predictive Value (PPV) 55% and Negative Predictive Value (NPV) of 100%.

Conclusion: In neonates with HIE, increasing severity was strongly associated with abnormal MRI findings, worse neurological status at discharge, and delayed neurodevelopment at 12 months. Abnormal MRI was common in HIE stage II-III and predicted poor outcomes, while normal MRI was associated with normal development. So MRI is a reliable prognostic tool.

Keywords: Development assessment, Magnetic resonance imaging, Newborn, Neuroimaging, Perinatal asphyxia

INTRODUCTION

Perinatal asphyxia is defined as a condition that leads to progressive hypoxemia, hypercapnia, and metabolic acidosis with multiorgan failure [1]. Globally, 2 to 10 per 1000 term newborns faces perinatal asphyxia [2]. World Health Organisation (WHO) reported approximately nine lac death every year due to birth asphyxia [3]. HIE is the leading cause of neonatal brain injury, morbidity and mortality globally. In developed world, incidence is estimated at 1-8 per 1000 live births. In developing world estimates as high as 26 per 1000 live births [4]. Approximately, 20-30% of infants with HIE (depending on severity) die in neonatal period and 33-50% of survivors are left with permanent neurodevelopment abnormalities such as cerebral palsy, low IQ, learning and cognitive impairment [5].

Perinatal asphyxia is most important cause of HIE, leads to hypoxemia and hypercapnia. Hypotension and the resulting

decrease cerebral blood flow led to a cascade of deleterious events, including acidosis, release of inflammatory mediators and excitatory neurotransmitters, free radical formation, calcium accumulation and lipid peroxidation. These events result in biphasic energy failure, in which initial impairment of cell metabolism is followed by reperfusion prior to eventual neuronal cell death [6].

Accurate identification and characterisation of severity, extent and location of brain injury rely on selection of appropriate neuroimaging modalities. MRI is modality of choice for evaluation of HIE because of excellent Grey white matter resolution, well depiction of myelination pattern and multiplanar imaging capabilities [5]. Hypoxic injury occurring before 35 weeks of gestational age results in periventricular leukomalacia. At 40 weeks of gestational age, the degree of hypoxia correlates to the area of the brain that is injured. Mild hypoxia will affect the parasagittal white matter while severe hypoxia affects the putamen, thalamus and paracentral white matter [7].

The spectrum of brain injury in this group is broad and includes White Matter Injury of Prematurity (WMIP), germinal matrix-intraventricular haemorrhage, or a combination of both. In preterm neonates, severe asphyxia preferentially injures the thalami, dorsal brainstem, and anterior vermis with relative sparing of the basal ganglia and cortex [8]. During mild-to-moderate hypoperfusion, autoregulation causes redistribution of blood flow to the hyper metabolically active deep grey matter structures. This results in injury predominantly to the watershed zones of the cerebrum. The vascular supply of the brain changes with brain maturation. In the full-term, ventriculofugal vessels also extend into the brain from the lateral ventricles and the intervascular border zone moves peripherally to a parasagittal location. This results in subcortical white matter and parasagittal cortical injury during hypotension [9]. In severe hypoperfusion, there is loss of autoregulation. The vulnerable regions are the deep grey matter and the early or actively myelinating fibres with higher concentrations of neurotransmitter receptors. Severe asphyxia in term neonates causes injury to the posterior putamina, ventrolateral thalami, hippocampi and dorsal brainstem, and occasionally the sensorimotor cortex [10].

Eight months appear to be the earliest time at which MRI findings correlate well with the developmental outcome [7]. In predicting neurological outcome MRI findings of the neonatal period had the highest negative predictive value [7]. Previous studies [6,7,11,12] have emphasised the role of MRI in evaluating neonatal brain injury following birth asphyxia. However, limited studies have evaluated these findings in relation to early clinical outcomes, developmental association indicating a need for further research [11, 12].

Hence, present study was conducted to determine the association between early MRI brain findings and neurodevelopmental outcome at 12 months of age in neonates with HIE.

MATERIALS AND METHODS

This prospective observational study was conducted at FH Medical College, Agra, Uttar Pradesh, India during the periods of October 2020 to September 2023. This study was approved by ethical committee of institute (IEC No-FHMC/IEC/R.Cell/2020/18). Written informed consent was obtained from all participants. All eligible birth asphyxia babies admitted during the study period and fulfilling the inclusion and exclusion criteria were included.

Inclusion criteria: Both term and preterm newborns (≥ 28 weeks gestation) admitted to the Neonatal Intensive Care Unit (NICU) with a history of birth asphyxia, meeting American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) criteria including cord pH < 7.0 , Apgar score < 3 at 5 minutes or more, neurological signs (seizures, hypotonia, coma, or HIE), and evidence of multiorgan dysfunction in the immediate neonatal period [13] were included in the study.

Exclusion criteria: Newborn with congenital anomalies, syndromic features, metabolic disorders, gestational age < 28 weeks, or encephalopathy from causes other than HIE were excluded from study.

Study Procedure

After enrolment, staging of HIE was done using Sarnat and Sarnat staging. Sarnat staging is done by clinical neurological examination assessing consciousness, tone, reflexes, seizures, autonomic function, and Electroencephalogram (EEG) findings to classify HIE into Stage I (mild), Stage II (moderate), and Stage III (severe) [10].

MRI was done of all the babies at 1-2 weeks of life. MRI was done on general electronic machine with 1.5 Tesla system with HDXD

SOFTWARE. Sequences were taken in T1W Axial, T2W Axial, and Flair, T1W Sagittal, T2W GRE Axial, DWI Axial and ADC maps. All MRI studies were reviewed by senior radiologist. Some neonates needed sedation for MRI. If required sedation was done by Triclofol (Syp Pediclorol)- 50 mg/kg/dose maximum up to 100 mg/kg in divided doses or Inj. Midazolam- 0.1 mg/kg/dose i.v.

MRI scans were obtained using standard protocols and interpreted by an experienced radiologist. Findings were classified as normal or abnormal based on the presence or absence of radiological abnormalities. First one month post-discharge- weekly examination is done to ascertain whether the infant has settled in the home environment and if he is gaining weight or not. After than monthly/ on vaccination till 12 months of age.

Neuromotor examination- at discharge and at 1, 3 and 6 months and 12 months of age. The discharged newborns were followed till 12 months for neurological assessment using Amiel Tyson Scale [14] and development were assessed by using Denver Development screening test II. The Amiel-Tison Tone Assessment is a clinical neurological examination method used to evaluate muscle tone and neuromotor development in infants, especially during the first year of life. The assessment focuses on active tone, passive tone, postural reactions, primitive reflexes, head control and axial tone. It uses specific maneuvers such as: Scarf sign, Popliteal angle, Heel-to-ear maneuver, Dorsiflexion of the foot, Arm and leg recoil. If the angle was less than normal hypertonia present and if greater than normal hypotonia present. Any asymmetry between extremities was also noted.

Developmental Assessment- Babies were assessed at every visit and recorded. Followed till 12 months of age. Developmental examination was done by using Denver Developmental Screening Test II (DDST). The test includes 125 topics that fall into four groups: Gross motor, Fine motor and adaptive, Language and Personal-social. Interpretation of Results was done as Normal- No delays and/or delay in one domain, Abnormal Two or more cautions and/or one or more delays [15].

STATISTICAL ANALYSIS

Statistical Analysis was done by Statistical Package for the Social Sciences (SPSS) Computer Software version 22.0 for Windows (IBM, Armonk, New York, USA) was used for all statistical analysis. Normally distributed continuous variables were described using mean \pm SD and compared using ANOVA test, Chi-square test and for correlation Pearson's coefficient test. The p-value was interpreted as: Significant if $p < 0.05$, highly significant if $p < 0.01$, very highly significant if $p < 0.001$.

RESULTS

Total 123 babies were enrolled, 22 expired. Among 123 enrolled babies 93 were male and 30 females. A total of 18 were preterm and 105 term babies. Most common mode of delivery was vaginal route. The mean birth weight was 2.2 ± 0.307 kg in HIE stage I, 2.64 ± 0.428 kg in HIE stage II, and 2.88 ± 0.50 kg in HIE stage III [Table/Fig-1].

MRI was done between seven to 14 days of life. Overall, 91 (74%) of MRIs were abnormal. Abnormal MRI findings were observed in 50 (94.3%) of infants with HIE stage III and 36 (69.2%) with HIE stage II, compared with only 5 (27.8%) in HIE stage I [Table/Fig-2].

Most commonly affected part was internal capsule (28%) followed by cerebral hemisphere (20%), periventricular (27%) and others in HIE stage III. In stage II most commonly, affected part was periventricular (18%) [Table/Fig-3].

	Gestation		Mode of delivery		Sex		Mean birth weight
	Preterm	Term	LSCS	VD	Male	Female	
HIE I	6	12	8	10	12	6	2.2±0.307
HIE II	9	43	13	39	41	11	2.64±0.428
HIE III	3	50	11	42	40	13	2.88±0.5
	18 (14.63%)	105 (85.37%)	32 (26%)	91 (74%)	93 (75.6%)	30 (24.4%)	

[Table/Fig-1]: Demographic profile.

MRI brain	Normal	Abnormal	Total
HIE stage I	13 (72.2%)	5 (27.8%)	18
HIE stage II	16 (30.8%)	36 (69.2%)	52
HIE stage III	3 (5.7%)	50 (94.3%)	53
Total	32 (26.0%)	91 (74%)	123

[Table/Fig-2]: MRI finding at 7 to 14 days of life.

Sensitivity and specificity of MRI for predicting developmental outcome was 100% and 51.5, respectively, PPV- 55% and NPV- 100%.

[Table/Fig-7-9] show representative MRI findings demonstrating different patterns of hypoxic-ischaemic brain injury in neonates with perinatal.

	Internal capsules	Basal ganglia	Corpus callosum	Periventricular	Subcortical white matter	Cerebral hemisphere	Others
HIE stage I	0	0	0	0	0	0	5 (28%)
HIE stage II	2 (4%)	9 (17%)	1 (2%)	14 (27%)	3 (6%)	11 (21%)	14 (27%)
HIE stage III	15 (28%)	5 (9%)	5 (9%)	10 (18%)	4 (7%)	11 (20%)	19 (35%)

[Table/Fig-3]: Part of brain affected in MRI.

Multiple part of brain involved as shown in table; Parts affected other than those mentioned in the table are categorised under "Others"

Twenty-two babies of HIE stage III died. All babies of HIE stage I were normal and most of the babies 20 (64.5%) out of 31 surviving) of HIE stage III with poor neurological examination. This was statistically significant [Table/Fig-4].

	Poor neurological examination at discharge	Normal	Total	p-value
HIE stage I	0	18 (100)	18 (100)	0.0003
HIE stage II	18 (35)	34 (65)	52	
HIE stage III	20 (64.5)	11 (35.5)	31	
Total	38 (37.6)	63 (62.4)	101	

[Table/Fig-4]: Neurological development at discharge.

These babies were followed for one year and assessed for development by DDST II. All the babies of HIE stage I were developmentally normal. While in HIE stage II and III 32.7% and 64.5% babies had delayed development [Table/Fig-5].

	Normal development	Delayed development	Total
HIE I	18 (100%)	0	18
HIE II	35 (67.3)	17 (32.7%)	52
HIE III	11 (35.5)	20 (64.5%)	31
	63	38	101

[Table/Fig-5]: Outcome at 12 months of age in different stages of HIE.

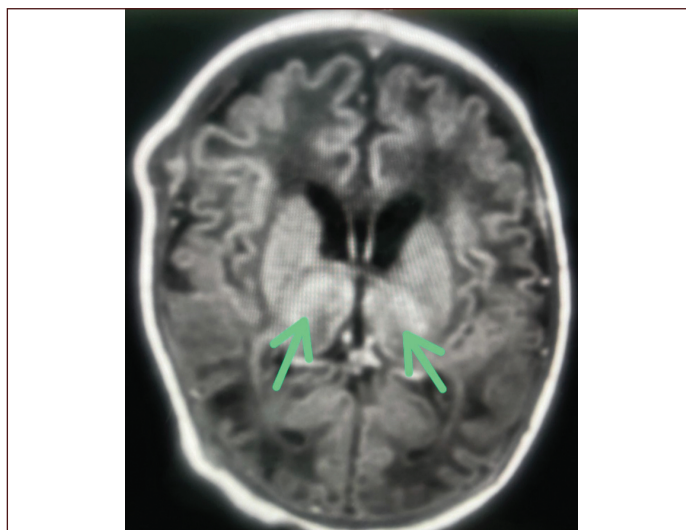
Babies with normal MRI have 100% normal development. However, 44.9% with abnormal MRI have normal development. Association of abnormal MRI with developmental outcome is statistically very highly significant [Table/Fig-6].

	Outcome abnormal	Outcome normal	Total	p-value
MRI abnormal	38	31	69	0.0001
MRI normal	0	32	32	
Total	38	63	101	

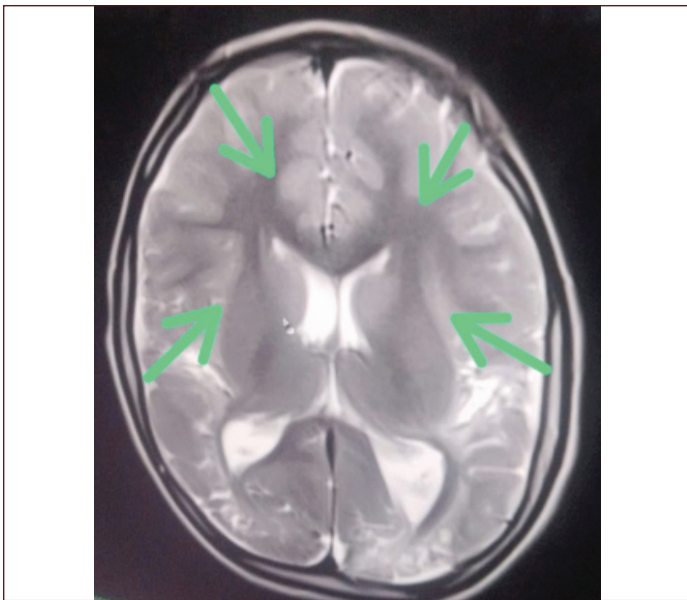
[Table/Fig-6]: Association between MRI done (between 1-2 week of life) and developmental screening by DDST II at 12 months of age.



[Table/Fig-7]: Abnormal diffuse T2 hyperintensity is seen diffusely involving bilateral cerebral white matter.



[Table/Fig-8]: Showing bilateral basal ganglia and thalami show T1/FLAIR hyperintense signal with basal ganglia showing diffusion restriction bilaterally.



[Table/Fig-9]: Axial T2-weighted images demonstrate bilateral, symmetric hyperintense signal abnormalities involving the deep gray nuclei, predominantly the basal ganglia (putamen and globus pallidus) and thalamus.

DISCUSSION

In this study most of the babies admitted with HIE were term and delivered vaginally, with male predominance. Most of the MRI in babies with HIE stage III was abnormal and most commonly affected part was internal capsule. All babies with stage I HIE were normal developmentally, while in HIE stage III showed delayed development. This study demonstrated an association between MRI findings and developmental outcomes at one year of age. Babies with normal MRI findings exhibited normal developmental outcomes. However, it is important to note that abnormal MRI findings did not consistently predict abnormal development. Some infants with abnormal MRI findings still demonstrated normal developmental progress. There is strong association between MRI appearance of birth asphyxia and clinical outcome. Hence, MRI has a strong role in prognosticating developmental outcome.

Total 123 babies were enrolled, among them 22 were died, all are from HIE stage III. In present study, more males were affected with birth asphyxia. The higher prevalence of seeking healthcare for male babies in certain regions and ethnicities may be responsible, similar to findings in a study on babies with birth asphyxia. This aligns with the results of studies conducted by Solayman M et al., in Bangladesh (60%), Aslam HM et al., in Karachi (61%) and Aliyu I et al., in Nigeria (60.3%) [16-18]. The potential protective impact of an additional "x" chromosome might account for this observation.

No mortality seen in HIE stage I and II in this study, which was similar to Behera A et al., and Elder DE et al., for HIE stage I [11,19]. In contrast both study by Levene et al., and Behera A et al., noticed mortality in HIE stage II. Mortality in HIE stage III was 22 (43.1%) which was as compared to Elder DE et al., who reported 80% mortality in this group. As severity of HIE increases mortality increases because of more severe brain injury, need for mechanical ventilation and multiorgan involvement [19]. This study also showed significant statistical association between neuroimaging abnormality and severity of HIE. Thus, neuroimaging may help to predict neurodevelopment outcome in term infants with HIE.

In this study, 37.6% has poor neurological examination at discharge. All the neonates with HIE stage I had normal neurological examination, while 35% and 64.5% had poor neurological examination with HIE stage II and III, respectively.

MRI was done at 7-14 day of life. Ninety-one (74%) MRI were abnormal and 32 (26%) normal. Out of 53 HIE stage three babies only three had normal MRI and rest 50 with abnormal MRI brain. In stage II HIE 36 (69% of stage 2 MRI) were abnormal. Most of the MRI 13 (72.22%) out of 18 were normal in HIE stage I. There is significant association of HIE stages with abnormal neuroimaging suggesting that severe birth asphyxia with HIE stage III have undergone severe neurological damage with hypoxic ischaemic changes seen in neuroimaging. In contrast to study by Behera A et al., none of babies with HIE stage III had normal neuroimaging [19].

In the present study, site of brain injury among HIE stage II and III are almost similar. In both groups area included (watershed area, Thalamus, MCA territory infarct) mainly followed by Cerebral hemisphere region that affected 22% and 20% in HIE stages II and HIE stage III, respectively. The present study observed that internal capsule mostly affected in HIE stage III (28%) as compared to HIE stage II (4%). In contrast Li Y et al., study showed most common brain injury pattern was watershed (22%), deep grey matter (20%), punctate white matter (18%) and atypical lesion (18%) [20].

In another study by De Vries LS and Groenendaal F in severe asphyxia basal ganglia and thalamus were predominant pattern of injury and white matter/watershed area was predominately involved in moderate asphyxia [21]. Study by Cavalleri F et al., noticed that among 23 enrolled infants nine patient had involvement of deep grey matter structure, eight cases with lesion confined to deep grey matter, Peri rolandic cortex, and hippocampus, three patient with watershed pattern, punctate white matter and basal ganglia involvement [22]. All the surviving babies were followed till 12 months of age and developmental assessment was done by using DDST II scale. All the babies are developmentally normal among HIE stage I group. Most of babies in stage III HIE group with poor developmental outcome.

Babies with normal MRI have 100% normal development. However, 44.95% with abnormal MRI had normal development. Association of abnormal MRI with development outcome was statistically significant. Another study was conducted by EL Ayouty M et al., which correlated MRI findings and clinical outcome in neonates with HIE. A total of 25 neonates with HIE were included in the study out of which three had severe HIE, 19 had moderate HIE and three had mild HIE [23].

Sensitivity and specificity of MRI for predicting development outcome was 100% and 51.5%, respectively, PPV- 55% and NPV- 100%. Similarly, in Ramachandran S and Sripathi S, study had sensitivity of 72%, specificity of 71% and PPV and NPV of 92% and 50% for detecting HIE and prognosticating the neurological outcome. They studied role of MRI in infants with suspected HIE and prognosticating neurological outcome at end of one year. Sensitivity of MRI in prognosticating clinical outcome was 72% and specificity was 71% while PPV and NPV was 86% and 50% respectively. The study concluded that MRI is a useful modality to assess early changes in HIE and it can prognosticate clinical outcome [12].

Limitation(s)

First limitation was the evaluation of neurodevelopmental outcome performed at 12 months of age. A neuropsychological examination at later times may highlight alterations in complex cognitive functions that cannot be fully appreciated at 12 months of age. A second limitation was that study do not comprise HIE newborn treated with neuroprotective hypothermia. It will be interesting to analyse with the present approach the predictive value of routine diagnostic tool on the outcome of infant treated with therapeutic hypothermia.

CONCLUSION(S)

In this study, neonates with HIE, the severity of HIE showed a strong correlation with MRI abnormalities, adverse neurological status at discharge, and delayed neurodevelopment at 12 months. Abnormal MRI findings were significantly more frequent in HIE stage II and III and were associated with poorer developmental outcomes. Infants with a normal MRI had uniformly normal neurodevelopment, highlighting MRI as a highly sensitive tool for prognostication. Thus, MRI performed in the second week of life is a valuable predictor of long-term neurodevelopmental outcome in infants with HIE.

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