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Original Research Article

Correlation between early magnetic resonance imaging brain abnormalities in term infants with perinatal asphyxia and neuro developmental outcome at one year

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ABSTRACT

Background: Hypoxic ischemic encephalopathy is an important cause of permanent brain damage in neonates with perinatal asphyxia. Magnetic resonance imaging (MRI) is valuable in predicting prognosis following HIE.
Methods: Prospective observational cohort study was conducted in tertiary level referral hospital in term infants born with perinatal asphyxia. MRI brain was done between 5 to 14 days of age. Anthropometry and neurological examinations were recorded at birth, discharge and follow-up. Denver developmental screening test II was performed at follow up.
Results: Out of 174 neonates born with PA, enrolled 64 underwent MRI brain. Out of these 14% had stage I, 70% stage II and 16 % stage III HIE as per Sarnat staging. At follow up, abnormalities in tone were noted in 36% infants, which included spastic quadriplegia in 34% and atonic cerebral palsy in 2%. DDST II was normal in 32 and suspect in 18 (36%) infants; with global developmental delay in 14 (28%) and predominantly motor development delay in 4 (8%). Abnormal lesions were seen in the corpus callosum in 34 (68%), posterior limb of internal capsule in 14 (28%), basal ganglia in 11 (22%), watershed region in 6 (12%), thalamus in 4 (8%) and corticospinal tract in 1 (2%) infants were associated with statistical significant poor neurodevelopment outcome $p<0.05$. Diffusion weighted MRI showed abnormalities in the posterior limb of internal capsule (PLIC) in 27 (54%), BG in 8 (16%) and thalamus in 2 (4%) infants was associated with statistically significant poor neurodevelopmental outcome (NDO) ($p<0.05$).
Conclusions: Lesion in BG, thalamic region and PLIC in conventional MRI and abnormality in DW imaging in PLIC and BG were found to correlate with poor NDO at one year of life.

Keywords: Perinatal asphyxia, MRI, Brain, Abnormality, Neurodevelopmental outcome

INTRODUCTION

An important cause of permanent damage to CNS in newborn babies is hypoxic ischemic encephalopathy.[1] The incidence of HIE is higher in developing countries compared to developed countries and has significant mortality (20-30%) and morbidity like permanent neuro developmental abnormalities (33-50%).[1]

Among imaging modalities, magnetic resonance imaging (MRI) is most accurate in the diagnosis of hypoxic ischemic injury in the newborn.[2] In the first 3 to 4 days conventional MRI shows the abnormalities where as diffusion weighted MRI (DWI), based on the molecular diffusion of water can show the abnormalities within 24-48 hours after birth. MRI is also valuable in predicting prognosis following hypoxic ischemic encephalopathy (HIE).

In this study, we have made an attempt to correlate findings of MRI in the neonatal period in babies with HIE as a prognostic tool for predicting neurodevelopmental outcome at 1 year of life.

METHODS

This was a prospective observational cohort study conducted at tertiary level referral hospital's neonatal intensive care unit (NICU) in a tier 2 city in South India between November 2016 to November 2018.

Term newborns (gestational age ≥37 weeks) with perinatal asphyxia (PA) admitted to the NICU after being resuscitated as per neonatal resuscitation program 2015 guidelines were included in the study. Perinatal asphyxia was defined as failure to initiate spontaneous respirations and/or 5 minute Apgar score <6. The study excluded infants with gestational age <37 weeks, birth weight <2kg, babies with major congenital anomaly, and chromosomal abnormality/inborn errors of metabolism. Informed parental consent was obtained before initiating any study related procedures. The study was approved by the institute ethics committee.

Details of maternal antenatal history, intrapartum variables and mode of delivery were recorded. The neonates were admitted immediately after resuscitation to the NICU and managed according to standard NICU protocols, which did not include therapeutic hypothermia. Sepsis screening was performed on all infants at admission and at age 3 days; intravenous antibiotics were given if clinically indicated. Clinical staging of hypoxic-ischaemic encephalopathy was done according to Sarnat and Sarnat (1976) classification to three categories (mild, moderate and severe).[3]

Neuroimaging

MRI brain was done between 5 and 14 days of birth with 1.5 Tesla Philips Acheva Unit. Sequences used were T1W Axial, T2W Axial, and Flair, T1W Sagittal, T2W GRE Axial, DW1 Axial and ADC maps. The MRI scan was reported by a single senior radiologist who was blinded to clinical details of enrolled neonates. Based on the MRI report provided, presence or absence of radiologic abnormalities in specific anatomic locations was recorded in the subject's case report form.

Developmental examinations

Neurological examination was performed regularly and also at the time of discharge. Infants were classified as having abnormal immediate outcome if they displayed alterations in alertness or tone, or had neurological deficits at the time of discharge examination. The parameters recorded at the time of discharge included: weight and occipito-frontal circumference and tone (active and passive). The parents were instructed about the visit schedule for the next one year. Follow-up visits were scheduled once in fortnight for the initial 3 months, once in a month for subsequent 3 months and once in 2 months for next 6 months. At each of these visits, detailed physical examination, growth monitoring (height, weight, occipito-frontal circumference) and neuro-developmental assessment using DDST II (Denver developmental screening test II, 1992) was performed.

DDST II test is designed to compare a given child's performance on a variety of tasks to the performance of other children of the same age. Denver II consists of 125 tasks/items which are arranged in the test forms into 4 areas; personal-social, fine motor-adaptive, language and gross Motor. The findings of DDST II were interpreted as either normal (no delays and a maximum of one caution in the various test items) or suspect (2 or more cautions and/or 1 or more delays). Suspect cases were rescreened after 1 or 2 weeks to confirm the finding and rule out any temporary factors such as fatigue, fear, illness, etc.[4] Neuro developmental outcome (NDO) at the completion of 1 year was the primary outcome measure. At one year, the child was diagnosed to have abnormal outcome if any of the following were present: cerebral palsy of any severity, microcephaly (reduction of 3 standard deviations from head circumference centile at birth assessed using WHO 2006 head circumference charts, corrected for sex) or "Suspect" according to the DDST II assessment. The study schematic is presented in Figure 1.

Data analysis

IBM SPSS statistics version 20.0 (IBM corporation, USA) was used for the statistical analysis. The student-t test was used to compare numerical scales. Univariate analyses on categorical data were performed by Chi square test and Fisher's exact test, $p<0.05$ was considered a statistically significant.

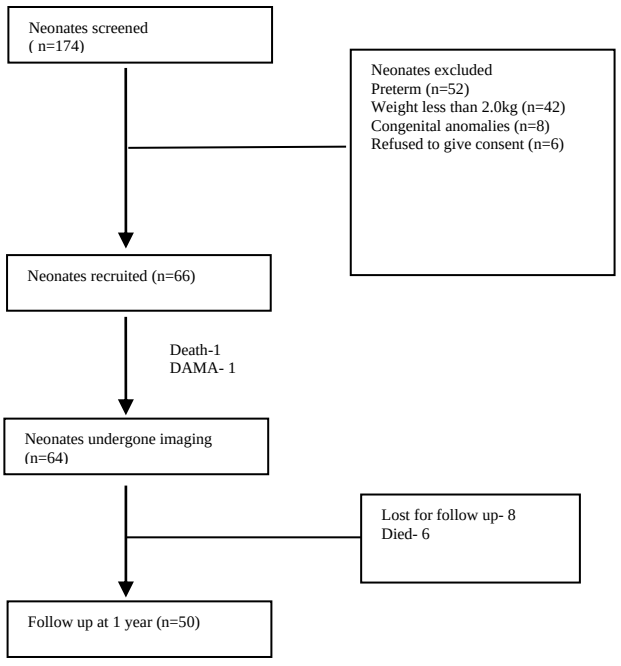

Figure 1: Study flow.

RESULTS

A total of 16,822 neonates were live born during the study period. Summary of the antenatal, perinatal and postnatal clinical characteristics of the study subjects have been summarized in (Table 1).

Table 1: Clinical characteristics of the study subjects.

Antenatal	N (%)
Parity	
Primiparous	31 (62)
Multiparous	19 (38)
Maternal complications	
Pre-eclampsia	10 (20)
Gestational diabetes	3 (6)
Breech presentation	2 (4)
Perinatal	
Prolonged second stage	6 (12)
Mode of delivery	
Normal vaginal delivery	36 (72)
LSCS	9 (18)
Breech extraction	2 (4)
Forceps delivery	3 (6)
Meconium staining of amniotic fluid	14 (28)
Mode of resuscitation	
Initial steps	10 (20)
Bag and mask	19 (38)
Bag and tube	21 (42)
Postnatal	
Gestational age* (weeks±days)	38±3
Male: Female	36 (72):14 (28)
Birth weight* (kg)	2.72±0.3
Head circumference* (cm)	33.74±0.6
Apgar scores#	
1 minute	3 (2,5)
5 minutes	4 (3,5)
HIE Stage (Sarnat & Sarnat)	
Stage 1	7 (14)
Stage 2	35 (70)
Stage 3	8 (16)

*mean(±SD), # median (IQR).

Clinical features

Among the 43 neonates with HIE stage 2 and 3, seizure onset occurred in <12 hours in 29 (58%), between 12-24 hours in 10 (20%) and after 24 hours in 4 (8%). Of these, 28 (56%) received single anticonvulsant agent, 14 (28%) needed two, and 1 (2%) required three anticonvulsant medications.

Developmental outcomes

Abnormal immediate outcomes (alterations in alertness, tone, presence of neurological deficits) were noted in 24 infants (48%) at the time of discharge examination. Final follow-up examination at 12 months revealed abnormal outcomes in 18 (36%) of the 50 infants. Microcephaly was seen in 14 (28%) infants. Abnormalities in tone were noted in 18 (36%) infants, which included spastic quadriplegia in 17 (34%) and atonic cerebral palsy in 1 (2%). DDST II was normal in 32 and suspect in 18 (36%) infants; with global developmental delay in 14 (28%) and predominantly motor development delay in 4 (8%). The correlation between neurodevelopmental outcomes and various perinatal factors have been presented in (Table 2).

MRI brain

Conventional MRI scanning was normal in 13 infants, while abnormal signals were noted in different anatomical locations in 37 infants. Abnormal lesions were seen in the corpus callosum in 34 (68%), posterior limb of internal capsule (PLIC) in 14 (28%), basal ganglia (BG) in 11 (22%), watershed region in 6 (12%), thalamus in 4 (8%) and corticospinal tract (CST) in 1 (2%) infant. Lesions in PLIC, BG, Thalamus and corpus callosum had abnormal immediate and abnormal NDO at 1 year age. Lesions in CST and watershed regions were not associated with abnormal immediate and abnormal NDO at 1 year age.

Diffusion weighted MRI showed abnormalities in the PLIC in 27 (54%), basal ganglia in 8 (16%) and thalamus in 2 (4%) infants was associated with statistically significant poor neurodevelopment outcome ($p<0.05$).

The association and value of various abnormal MRI findings and neuro developmental outcomes at 1 year age has been presented in (Table 3).

DISCUSSION

In our study we found that MR Imaging in the neonatal period in babies with HIE is able to show different pattern of injury due to HIE. MRI has a vital role in prediction of outcomes in babies with HIE. We observed that lesions involving basal ganglia and thalamus on MR imaging in asphyxiated neonates predicted adverse neurological outcome at completion of study period.

Similar data was seen in a study was conducted by Martinez-Biarge et al with 175 term babies with birth asphyxia. They found that the severity of BGT lesions was strongly associated with the severity of motor impairment.[5] In this study, we observed that posterior limb of internal capsule insults in asphyxiated neonates resulted in poor neurological outcome at the end of 1 year. In a study conducted by Rutherford et al to establish whether abnormal signal intensity in the posterior limb of the internal capsule (PLIC) on magnetic resonance imaging is an accurate predictor of neuro-developmental outcome at 1 year of age in infants with hypoxic-ischemic encephalopathy (HIE), they found that abnormal signal intensity in the PLIC is an accurate predictor of neuro-

developmental outcome in term infants suffering from HIE.[6] In another study conducted by Martinez-Biarge et al found that the abnormal PLIC signal intensity predicted the inability to walk independently by 2 years.[5] Most common imaging abnormality detected in our study was lesions involving corpus callosum. Presence of these lesions had predictive value for adverse long term outcome.

Table 2. Comparison of neurodevelopmental outcomes according to perinatal characteristics.

MRI abnormality (location of lesions)	Immediate neurological outcome			Neurodevelopment outcome (1 year)		
	Normal N=26	Abnormal N=24	p value†	Normal N=32	Abnormal N=18	p value†
Apgar score at 1 minute #	4 (3,5)	3 (2,4)	0.006**	3 (2,4)	2 (1,3)	0.001**
Apgar score at 5 minutes #	5 (4,6)	4 (3,5)	0.006**	5 (4,6)	4 (3,5)	0.001**
Born through meconium stained amniotic fluid(n)	4	10	0.039*	5	9	0.009*
Resuscitation step						
Initial	6	4		8	2	
B&M	13	6	0.073	17	2	0.001**
B&T	7	14		7	14	
HIE						
Stage1	7	0	0.001*	7	0	
Stage 2	19	16		25	10	0.001**
Stage 3	0	8		0	8	
Time to seizure onset						
Nil	7	0		7	0	
< 12 hrs	11	18	0.022*	13	16	0.001**
12 - 24 hrs	5	5		8	2	
>24 hrs	3	1		4	0	
No of anticonvulsant						
Nil	7	0		7	0	
One	19	9	0.001**	23	5	0.001**
Two	0	14		2	12	
Three	0	1		0	1	

† Student-t test and Chi-square test, *p<0.05, **p<0.01, # median(IQR)

Table 3. Correlation of brain MRI abnormalities with Neurodevelopmental.

MRI abnormality (location of lesions)	Immediate neurological outcome			Neurodevelpopment outcome (1 year)		
	Normal N=26	Abnormal N=24	P value	Normal N=32	Abnormal V=18	p<0.01**
PLIC	3	11	0.007**	5	9	0.009**
Basal ganglia	3	8	0.063	3	8	0.004**
Thalamus	0	4	0.03*	0	4	0.005**
Corpus callosum	12	22	<0.001**	17	17	0.003**
Watershed region	3	3	0.917	4	2	0.885
Corticospinal tract	0	1	0.293	0	1	0.175
Diffusion weighted brain MRI						
MRI abnormality (location of lesions)	Immediate outcome			Neurodevelpopmen outcome (1 year)		
	Normal N=26	Abnormal N=24	p value	Normal N=32	Abnormal N=18	p<0.05*
PLIC	10	17	0.022*	14	13	0.049*
Basal ganglia	2	6	0.095	0	2	0.054
Thalamus	0	2	0.133	2	6	0.012*

We observed that diffusion weighted MR imaging of asphyxiated neonates with poor long term outcome correlated with insults in basal ganglia and PLIC. In a study conducted by Hunt et al measured ADC values within the PLIC in 28 term infants with a clinical diagnosis of hypoxic ischaemic encephalopathy (HIE), ADC values were significantly associated with poor survival and motor outcome.[7,8] Thalamic and PLIC lesions on MRI of asphyxiated neonates had high predictive value for occurrence of microcephaly at the end of 1 year study period. In a study conducted by Cavalleri et al found that ADC in some regions brain (basal ganglia) is an excellent predictor of poor neuro developmental outcome in babies with HIE.[9]

We did not find any correlation between watershed lesions and neurodevelopment outcome in our study. In contrast to our observation a study conducted by Miller et al were first able to conclude that cognitive deficits associated with the watershed pattern of injury at 30 months.[10]

Early MR imaging of the brain and good follow up rate of the enrolled infants were the strengths of our study. The main limitation of our study was the small sample size and not having classification of the MRI findings as per existing MR Scoring systems.

CONCLUSION

In conclusion, this preliminary study shows the feasibility of utilizing early neuroimaging to predict immediate and neuro-development outcome in asphyxiated neonates. Timely imaging will help identify neonates at risk of abnormal neuro-developmental outcome at the time of discharge based on which initiation of early stimulation programme and physiotherapy can decrease the neurodeficits in this group of asphyxiated infants.

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