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Pediatrics

Neurodevelopmental Outcome at 12 Months in Term Babies with Birth Asphyxia and Correlation with MRI Findings and Neonatal Complications

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Abstract: Hypoxic Ischemic Encephalopathy (HIE) in term neonates is a leading cause of neurological disability worldwide. Survivors of severe HIE have longterm neurological disabilities like cerebral palsy, mental retardation and epilepsy. Several (complications with birth asphyxia) factors in immediate neonatal period are associated with adverse neurological outcome in future. MRI is one of the most sensitive and specific tool for assessing the severity of HIE and predicting the long term neurological outcome. The present study aimed to identify the immediate neonatal complications and MRI findings which are associated with adverse neurological outcome.180 term intramural babies with birth asphyxia were enrolled in the study. They were admitted in NICU and managed according to the protocol of the unit. Any complications during hospital stay were recorded. MRI brain was done in all babies with HIE after 2 weeks of age. At followup visits anthropometric data, immunization details and any other problems were recorded. Discharged cases were linked to follow up outpatient department (OPD) of NICU and one year follow up dates were mentioned in discharge summary. A telephonic remainder was given 48 hours prior to follow up date and cases were followed at 1, 3, 6, 9, 12 months of age. Neurodevelopmental screening was done with DDST II. Hearing screening was done by inhouse audiologist. This study tried to correlate the neonatal complications and MRI findings with neurological outcome of discharged babies. Among 180 intramural babies in study population, 154 (85.5%) babies had signs of HIE. Most common neonatal complication in babies with birth asphyxia was seizures (44.18%). The overall mortality rate was 26.7%. 88 babies completed 1 year followup, of them 71 (80%) babies had normal development and 17 (20%) had delayed development. Neonatal complications like hypoglycaemia, shock, respiratory distress and delayed initiation of direct oral feeds (paladai or breast feeds after 7 days of life) were more commonly associated with adverse neurodevelopmental outcome at one year which was statistically significant ($p < 0.05$). Fronto-parietal cortical and sub cortical white matter changes (watershed areas) were the common abnormal MRI findings observed in babies with HIE. MRI brain has a sensitivity of 82.4%, specificity of 92%, PPV of 73.7% and NPV of 94.7%, in predicting abnormal neurodevelopmental outcome at 1 year of age. Complications in new-born period like hypoglycaemia, shock and renal failure adversely affect the neurodevelopmental outcome of babies with HIE. MRI changes especially involving basal ganglia and thalamus can predict poor neurodevelopmental outcome with high sensitivity and specificity.

Keywords: Asphyxia, HIE, MRI brain, Neurodevelopment.

INTRODUCTION

Hypoxic Ischemic Encephalopathy (HIE) in term neonates is a leading cause of neurological

disability worldwide. Survivors of severe HIE have longterm neurological disabilities like cerebral palsy, mental retardation and epilepsy. A variety of clinical and radiological tools help in prognostication which inturn guide the clinician in proper parent counseling and early institution of stimulation therapy for better development of infant.

Several (complications of birth asphyxia) factors in immediate neonatal period like shock, hypoglycemia, renal failure etc are associated with adverse neurological outcome in future. MRI is one of the most sensitive and specific tool for assessing the severity of HIE and predicting the long term neurological outcome. The present study aimed to identify the immediate neonatal complications and MRI findings which are associated with adverse neurological outcome.

MATERIALS AND METHODS

This prospective observational study was conducted in the Neonatal intensive care unit (NICU) of the Department of Pediatrics, Government General Hospital, Kakinada over a period of 18 months from April 2014 to September 2015. Informed consent was taken from parent/attendants. The study was approved by Institutional Ethics committee. 180 intramural babies with birth asphyxia formed the study group.

Inclusion criteria

Term intramural babies with birth asphyxia, according to WHO definition(Failure to initiate and sustain breathing at birth)

Exclusion criteria

- Babies with life threatening congenital anomalies.
- Babies with inborn errors of metabolism.
- Babies with neuromuscular disorder.

180 term babies with birth asphyxia were enrolled in the study. Study population were admitted and evaluated for short term outcome and follow up was done for 1 year for neurodevelopmental outcome. Resuscitation was carried out as per neonatal resuscitation program 2010 by American Heart Association by trained residents. Details of antenatal and natal history and condition of baby at birth (including resuscitation details) were recorded in a structured predesigned proforma. Detailed systemic examination with special reference to muscle tone and primitive reflexes was done and the babies with birth asphyxia were categorized based on Sarnat and Sarnat staging of hypoxic ischemic encephalopathy. Any complications during hospital stay like hypoglycaemia, hypocalcemia, respiratory distress, anaemia, polycythemia, sepsis, shock, jaundice, acute renal failure, necrotizing enterocolitis and feeding difficulties were recorded.

Babies were managed according to the protocol of the unit. MRI brain was done in all babies with hypoxic ischemic encephalopathy (HIE) after 2 weeks of age and correlated with neurodevelopmental outcome. All discharged cases were linked to follow up outpatient department (OPD) of NICU and one year follow up dates were mentioned in discharge summary. A telephonic remainder was given 48 hours prior to follow up date and cases were followed at 1, 3, 6, 9, 12 months of age.

Anthropometric data like weight, length, occipitofrontal circumference were noted and plotted on W.H.O growth charts serially in all follow up visits. During each follow up visit immunisation status, details of seizures, antiepileptic therapy, muscle tone, feeding difficulties, and other relevant problems were recorded and treated accordingly. Neurodevelopmental screening was done with Denver Developmental Screening Test (DDST II).

While doing DDST II the items intersected by and just adjacent to the age line were tested. The items were denoted as P for pass, F for failed, No for no opportunity, and R for refused to cooperate or attempt. The interpretation of the individual items was made as follows:

Advanced

Child passes item that falls completely to the right of the age line

Normal

Child passes, fails, or refuses item on which the age line falls between the 25 & 75 percentile.

Caution

Child fails or refuses item on which the age line falls between the 75 and 90 percentile.

Delayed

Child fails or refuses item that falls completely to the left of the age line.

No opportunity

Child has had no chance to perform the item

DDST II test interpretation was done as

- Normal: Child with no delays and a maximum of 1 caution
- Suspect: Two or more cautions and or one or more delays
- Untestable: Refusal scores on 1 or more items completely to the left of age line or; More than one item intersected by the age line in the 75-90 percentile area. These children were rescreened again.

Cases with 'suspect' or 'untestable' after rescreening were sent for detailed developmental evaluation by Developmental Assessment Scales For Indian Infants (DASII). Muscle tone was assessed in terms of adductor angle, popliteal angle, dorsiflexion angle, scarf sign and were compared against Amiel-Tison muscle tone norms. Cases found with abnormal tone in follow up were managed on outpatient basis at physiotherapy block in NICU with assistance of physiotherapist. Mothers of babies with developmental delay were trained in early stimulation.

Hearing screening was done at discharge by otoacoustic emission (OAE) by inhouse audiologist and all referred cases were reassessed after one month. Cases referred on second OAE test were sent for brainstem evoked response audiometry (BERA) and referred to ENT department for follow up.

STATISTICAL ANALYSIS

All categorical variables were presented as frequencies and percentages. Chi- square test was applied and p values were calculated for the risk factors and outcome of babies. The statistical analysis was carried out at 5% level of significance and p value < 0.05 was considered significant. Data analysis was done by Microsoft Excel and IBM SPSS (version 21) software. Diagnostic statistics viz. sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were computed to find the correlation between abnormal MRI and neurodevelopmental outcome.

RESULTS

Among 180 intramural babies in study population, 154 (85.5%) babies had signs of hypoxic ischemic encephalopathy according to Sarnat and Sarnat staging. Out of the 154 babies with HIE, 67 (43.5%) babies were of stage I, 55 (35.7%) babies were of stage II and 32 (20.8%) babies were of stage III severity. Most common neonatal complication in babies with birth asphyxia was seizures (44.18%) followed by respiratory distress (34.30%), shock (30.81%), hypoglycaemia (25.00%), jaundice requiring treatment (23.25%), sepsis (20.93%), acute renal failure (16.86%), anaemia (16.86%), hypocalcaemia (13.95%) , necrotising enterocolitis (11.04%) and polycythemia (05.81%) in decreasing order of their occurrence. 8 babies left against medical advice and the clinical course was noted in 172 cases. 46 (26.74%) of the 172 cases died during hospital stay and 126 (73.26%) cases were discharged. The mortality rate was 26.7%. The mortality rate in babies with HIE I, HIE II and HIE III was 7.6%, 28.9% and 82% respectively. 3 babies with birth asphyxia but no HIE expired due to other causes like shock and sepsis.

Table-1: Neurodevelopmental Outcome Of Babies With Birth Asphyxia

Age Of Follow Up	DDST Normal	DDST Abnormal	Total	Lost to Follow Up
3 months	102(81%)	24(19%)	126	00
6 months	93(82%)	21(18%)	114	12
9 months	80(82%)	18(18%)	98	16
12 months	71(80%)	17(20%)	88	10

81% of discharged babies had normal development and 19% of babies had delayed development at 3 months follow up. Similar proportion of babies had normal and delayed development at 6 and 9 months follow up. At one year of life 30% babies were lost to follow up and 70% babies were assessed. Among 88 infants with birth asphyxia 17(20%) had delayed neurodevelopment and the remaining 71(80%) babies had normal development (table 1)?

Table 2 depicts severity of HIE and neurodevelopment at 1 year of age. Abnormal neurodevelopment with DDST II was seen in 4(6.5%), 11(42.3%) and 4 (100%) babies with HIE I, HIE II and HIE III respectively. All babies with asphyxia, without signs of encephalopathy had a normal neurodevelopmental outcome at one year of life. Neonatal complications like hypoglycaemia, shock, respiratory distress and delayed initiation of direct oral feeds (paladai or breast feeds for more than 7 days) were more commonly associated with adverse neurodevelopmental outcome at one year which was statistically significant (p < 0.05) as shown in table 3.

Table-2: Severity Of HIE Vs Neurodevelopment at One Year

HIE Stage	NO HIE		HIE I		HIE II		HIE III		Total
DDST	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	
3 mon	23	00	56	05	22	15	0	04	126
6 mon	19	00	52	05	21	13	0	04	114
9 mon	14	00	48	04	17	11	0	04	98
12mon	12	00	43	03	15	11	0	04	88

Table-3: Correlation of Neonatal Complications with Neurodevelopmental Outcome at One Year

DDST II / COMPLICATION	Normal (n=71)	Delay (n=17)	P value
Hypoglycemia	12(16.90)	09(52.94)	0.0037
Hypocalcemia	07(09.85)	03(17.64)	0.3989
Anemia	16(22.53)	01(05.88)	0.1754
Polycythemia	04(05.63)	01(05.88)	1.000
Hyperbilirubinemia	16(22.53)	07(41.17)	0.1327
Shock	10(114.08)	11(64.70)	0.0001
ARF	08(11.26)	04(23.52)	0.2357
NEC	06(08.45)	03(17.64)	0.3669
Respiratory distress	11(15.49)	14(82.35)	0.0001
Sepsis	16(22.53)	03(17.64)	1.000
Seizures(>3)	05(07.04)	03(17.64)	0.1797
Feeding Problems(Delayed Direct Oral Feeds For >7 Days)	05(07.04)	09(52.94)	0.0001

Out of the 126 discharged babies, MRI was done for 103 babies with HIE and out of them 76 babies completed one year followed up. Fronto parietal cortical and sub cortical white matter changes (watershed areas) were the common abnormal MRI findings observed in babies with HIE (table 4). Deep grey nuclei involvement and diffuse encephalomalacia were noted in some cases.

Table-4: MRI Findings and Neurodevelopmental Outcome

MRI Findings	Normal Development	Developmental delay	Total
Normal	54	03	57
Abnormal	05	14	19
Abnormal Cortex BGT Pattern Cortex + BGT	 05 00 00	 08 01 05	
Total	59	17	76

Table 5 depicts the value of MRI brain in predicting the abnormal neurodevelopmental outcome. In the present study MRI brain has a sensitivity of 82.4%, specificity of 92%, PPV of 73.7% and NPV of 94.7%, in predicting abnormal neurodevelopmental outcome at 1 year of age.

Table-5: Value of MRI Brain in Predicting the Abnormal Neurodevelopmental Outcome

Sensitivity	82.4
Specificity	92.0
PPV	73.7
NPV	94.7

DISCUSSION

The present study attempted to associate the severity of HIE and complications during neonatal period with the neurodevelopmental outcome at 12 months age in term babies with birth asphyxia. This study also tried to evaluate the role of MRI in predicting the neurodevelopmental outcome of these babies.

In the present study, 17 out of 88 (20%) babies followed for 1 year had neurodevelopmental abnormalities. Sonali Suman *et al*. [1], Peliowski A *et al.* [2] and Ellis *et al*. [3] reported 12.8%,14.3% and 20% incidence of neurological sequale in babies with HIE at 1 year followup.

In the present study, out of 17 babies with abnormal neurodevelopmental outcome at 12 months only 4 had Sarnat HIE stage III. But all 4 babies with HIE III had abnormal neurological outcome at 1 year. This shows that Sarnat stage III had strong specificity (100%) in predicting poor neurodevelopmental outcome. Mostafa EI-Ayouty *et al*. [4] in their study reported (similar results) that all 3 babies with HIE stage III had abnormal neurodevelopmental outcome.

In the present study, complications like hypoglycaemia, shock and respiratory distress in newborn period were associates with poor neurodevelopmental outcome at 1 year. Prevention, early detection and prompt management of these complications in newborn period helps in better long term neurodevelopmental outcome of babies with HIE.

MRI & neurodevelopmental outcome

Many studies have found the basal ganglia watershed score to be an excellent predictor of the neurological outcome. Two major areas of damage have been identified. Deep grey nuclei (basal ganglia) and the intravascular boundary (watershed) zone. Cases with mild to moderate hypoperfusion are characterized by parasagittal lesions involving vascular border zones between anterior, middle and posterior cerebral arteries whereas profound hypotension involves primary lateral thalami, posterior putamen, hippocampi and perirolandic gyri. Selective vulnerability of the basal ganglia and the thalami could be related to their higher metabolic activity during the first months of life. Studies based on the topographic pattern of the neuronal injury have shown that the term infants with predominant injury to basal ganglion and thalamus have an infavourable neurological outcome. The pattern of injury most easily seen between 1 week & 4 weeks after birth when brain swelling has settled and before atrophy becomes obvious. In the present study, MRI was done after 2 weeks and before discharge.

In the present study out of 76 babies with HIE followed for 1year, 57 had normal MRI and 19 had abnormal MRI. 17 babies had delayed development and 59 babies had normal development. Out of 57 babies with abnormal MRI, 54 had normal neurological outcome but 3 had delayed development. Out of 19 babies with abnormal MRI, 14 showed adverse neurodevelopmental outcome at 1 year.

Out of 13 babies who had fronto-parietal cortical changes in MRI, 8 babies showed adverse neurodevelopmental outcome and 5 had normal development. One baby with basal ganglia abnormality and all 5 babies with cortical and basal ganglia abnormalities showed adverse neurodevelopmental outcome at 1 year. MRI brain had a sensitivity of 82%, specificity of 92%, and positive predictive value of 73.7% and negative predictive value of 94.7% in predicting abnormal neurodevelopmental outcome.

Annu Jose *et al*. [5], Hee Cheol Jo *et al*. [6] reported similar results. The specificity of MRI in predicting neurodevelopmental outcome was 45% and 43% in studies done by Basavaraj Patil *et al*. [7] and Mostafa EI-Ayouty *et al*. [4] respectively. This is much less compared to the present study.

CONCLUSION

Complications in newborn period like hypoglycaemia, shock and renal failure adversely affect the neurodevelopmental outcome of babies with HIE. MRI changes especially involving basal ganglia and thalamus can predict poor neurodevelopmental outcome with high sensitivity and specificity.

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