

Original Research Article

Neurodevelopmental outcome of babies with hypoxic ischemic encephalopathy

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Received: 10 May 2017

Accepted: 05 June 2017

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ABSTRACT

Background: The aim of the study was to find out the neurodevelopmental outcome of babies with hypoxic ischemic encephalopathy at 6 months of age and to predict early markers of abnormal neurological outcome in those babies.

Methods: 50 babies admitted with hypoxic ischemic encephalopathy were enrolled in this prospective study and followed up at 3 and 6 months of age at Mahatma Gandhi Memorial Government Hospital, Trichy. The neurological outcome of the babies was assessed by CDC grading of motor milestones, Trivandrum development screening chart, Amiel Tison angles head circumference and weight measured. USG cranium was done for all the babies and MRI brain was done in babies with abnormal neuro sonogram and abnormal outcome. Vision and hearing were tested clinically.

Results: The incidence of abnormal neurological outcome was 14%. The early markers predicting abnormal neurological sequelae are identified.

Conclusions: Early identification of abnormal neuro behaviour helps in starting early intervention to improve the long term outcome.

Keywords: Amiel Tison angles, CDC grading of motor milestones, Early intervention, Hypoxic ischemic encephalopathy, Neurodevelopmental outcome, Trivandrum development screening chart

INTRODUCTION

Perinatal asphyxia is one of the predominant causes of neonatal mortality third only to sepsis and prematurity.¹ It is also one of the leading causes of morbidity among children.² According to the National Neonatal Perinatal Database (NNPD) network report, the incidence of birth asphyxia is 1.4%.

Babies born with birth asphyxia and showing features of hypoxic ischemic encephalopathy should be followed up at regular intervals to detect neurological abnormalities at the earliest and start early stimulation exercises so that their long-term outcome will be better.

Cerebral palsy, microcephaly, global developmental delay, seizure disorder is some of the neurological sequelae following hypoxic ischemic encephalopathy.³⁻⁷

WHO defines perinatal asphyxia as “failure to initiate and sustain breathing”. NNPD Network- defines

- Moderate perinatal asphyxia- slow/gasping breathing or Apgar of 4 to 6 at 1 minute
- Severe perinatal asphyxia- No breathing or Apgar score of 0-3 at 1 minute of age.

The objective of the study was to study the neurodevelopmental outcome of surviving babies with hypoxic ischemic encephalopathy at 6 months of age in

MGMGH, Trichy and to study the perinatal risk factors in these babies.

METHODS

Prospective analytical cohort study was designed. Babies with birth asphyxia admitted in our NICU are taken under the study. Duration of this study was babies with hypoxic ischemic encephalopathy were followed up for 6 months. Sampling type: simple random sampling with sample size for an alpha error of 0.05 and power of 0.8, 50 cases taken for study.

Inclusion criteria

Term newborn babies, Apgar of ≤ 7 at 5 minutes or babies needing positive pressure ventilation and features of hypoxic ischemic encephalopathy.

Exclusion criteria

Preterm babies <36 weeks, babies with CNS or cardiac malformation and babies died during the hospital stay in the new born period.

A pilot study with 10 babies was first done and the feasibility of the study was analysed and operational errors were understood. Clearance was obtained from the ethical committee.

Term babies with birth asphyxia admitted in our newborn ward are first observed for features of hypoxic ischemic encephalopathy. Staging with HIE done with Sarnat and Sarnat staging. Informed consent obtained from the parents and then babies are enrolled in the study. Course during the hospital stay recorded in the standard proforma.

Babies who died during the hospital stay were excluded. Babies which is found to have CNS malformations in neuroimaging is also excluded. At the time of discharge parents are advised to come for follow up at 3 and 6 months of age.

During the follow up period babies are examined at the child development clinic in our hospital. Anthropometry is measured. Amiel Tison passive angles are measured using the goniometer. Range of the angles is recorded. Active tone of the child is observed. CDC grading of social smile and head control are done at 3 and 6 months of age respectively.

Complete neurological examination of the child is done at every visit-tone, power, reflexes, sensory system, cranial nerves and involuntary movements. Vision is tested clinically by-fixing and following light at 3 months And Recognises mother, able to grasp objects at 6 months of age. Hearing is tested clinically using a simple rattle at 3 months, sound of paper at 6 months, Child alerts to sound at 3 months, turns to sound at 6 months.

USG Cranium is done in all the babies with hypoxic ischemic encephalopathy. If neurological examination is abnormal or USG cranium is abnormal, MRI Brain is also done. In babies with abnormal neurological examination, early stimulation exercises are started in our hospital and these babies are regularly followed up at our high-risk newborn clinic.

RESULTS

50 babies were studied over a period of 6 months and the following observations were noted. In this study, 92% of babies with birth asphyxia delivered via normal vaginal delivery, remaining 8% by caesarean section. 18% babies with birth asphyxia were small for gestational age, 6% were large for gestational age, 76% were appropriate for gestational age. 54% of the babies enrolled were inborn and 46% of the babies enrolled were outborn.

Babies were referred from nearby PHCs, GH, private hospital through neonatal ambulance. 8% of the babies had severe birth asphyxia (Apgar <3 at 5 min), 88% of the babies with moderate asphyxia and 4% had mild birth asphyxia.

Majority of the babies with hypoxic ischemic encephalopathy had apgar scores 4 to 6, this emphasises the need for vigorous resuscitation to improve the Apgar scores, thus reducing the incidence of encephalopathy in the babies.

Gestational ages of the babies were from 36 to 40 weeks, 3 babies with 36 weeks gestation, remaining 47 babies being 37 weeks and above. 18% of the babies had HIE stage I, 78% of the babies had HIE stage II, only 4% of the babies had HIE stage III. Only 4% of the babies enrolled in the study had HIE stage III, as the mortality in the stage is high and such babies are excluded from the study. In this study, the predominant perinatal risk factor was prolonged II stage of labour (34%).

But 48% of the babies had no antenatal risk factors, which still emphasises the need for continuous CTG monitoring to detect fetal distress, umbilical cord compression and appropriate oxytocin administration. The other risk factors were PIH (4%), MSAF (10%) and anaemia complicating pregnancy (4%). 18% of the babies were ventilated, but ventilated babies with refractory seizures and severe hypoxic ischemic encephalopathy had died during the hospital stay and hence was not included in the study.

16% of the babies discharged in <7 days, indicating the early recovery of tone, suck, swallow abnormalities, early direct breast feeding hence early discharge.

60% had 7 to 14 days of hospital stay, 24% had to stay more than 2 weeks, sepsis, refractory seizures, jaundice, acute kidney injury complicating the hospital stay. Babies with failure to thrive at 3 months of age were 28% which

reduced to 4% with proper feeding advice and counselling.

The two babies failed to gain weight in spite of breast feeding even at 6 months and had developmental delay suggesting weight at 3 months of age as an important predictor of neurodevelopmental outcome. In this study, 6 babies had microcephaly at 3 months of age. All the 6 babies had developmental delay, indicating the importance of measurement of head circumference at 3 months for predicting the neurodevelopmental outcome.

Adductor angle measured at 3 months were in the range between 40-90. Three babies had very much restricted angles at 3 months of age and two of these babies showed slight improvement in the tone at 6 months with the adductor angle of 100 due to early stimulation exercises. 4 babies had restricted adductor angles at 6 months of age implicating increased tone. All the 6 babies with restricted adductor angles had abnormal neurodevelopmental outcome.

Popliteal angle measured at 3 months were in the range of 70-90, and at 6 months in the range of 90-120. Six babies had restricted popliteal angles at 3 months and 5 babies with restricted popliteal angles at 6 months. One baby had asymmetry with the angles measured, angle being restricted in the right side.

Heel to ear measured angles were in the range of 70-90 at 3 months and 90 to 130 at 6 months of age. 7 babies had restricted heel to ear measured at 3 months and 6 months of age. Among the seven babies, one baby had asymmetry between the right and left, angle being restricted in the right side.

Among the 50 babies, 7 babies had abnormal tone at 6 months, one baby showed asymmetry, abnormal tone on the right side. Dorsiflexion angle measured were in the range of 60-80, no significant tone abnormalities detected by dorsiflexion angle in this study.

All the 50 babies had attained social smile by 3 months of age, while 6 babies had not attained head control by 6 months of age indicating developmental delay of motor milestone by 6 months of age. Out of the 50 babies, 6 babies had recurrent seizures and were on continuous antiepileptic therapy. Babies who had seizures in the newborn period were discharged with oral phenobarbitone 3-5 mg/kg/day and at 3 months of age if the baby had normal neurological examination and no further seizures, the drug was stopped.

USG cranium was done in all the 50 babies. Babies who had abnormal neurological examination and abnormal USG cranium, MRI Brain was done. Diffuse white matter changes observed in 2 babies, cerebral edema in left parietal region in 1 baby, gliosis changes in 1 baby, porencephalic cystic changes with old infarct in 1 baby, diffuse cerebral atrophy in 1 baby.

Of the 50 babies studied, 7 babies had abnormal tone with hypertonia in 6 babies and tone asymmetry in 1 baby. Asymmetry of tone detected is an important early marker for spastic hemiplegia. Thus detecting it early and starting early intervention can improve the tone and improving the neurological outcome of the baby.

Of the 50 babies studied, 7 babies had abnormal neurodevelopmental outcome-tone abnormalities, developmental delay, microcephaly, seizure disorder with abnormal neuroimaging in 6 babies. Vision and Hearing tested clinically were normal in all the 50 babies.

The mean birth weight of the babies studied was 2.8 kg and mean gestational age was 38 weeks. So, this study can be applied for term newborn babies only. The mean head circumference was 34 cm, and all the babies at birth had normal head size. The mean adductor angle tested at 3 months was 77.2 which increased to 108 at 6 months. The mean popliteal angle was 87.8 at 3 months and 116.2 at 6 months. Computer based analysis of the data done using the SPSS software package. Mean and standard deviation calculated. P value calculated using the chi square test. 6 babies with abnormal neurodevelopmental outcome had recurrent seizures. There is significant association ($p=0.000$) of seizures with the abnormal neurodevelopmental outcome. 6 babies with abnormal neurodevelopmental outcome had abnormal neuroimaging. There is significant association ($p=0.00$) of neuroimaging with the outcome. Thus, neuroimaging is an important predictor of neurodevelopmental outcome. One baby had severe birth asphyxia with hypoxic ischemic encephalopathy stage III, remaining 5 babies had HIE stage II.

There is significant association ($p=0.11$) between HIE stages and abnormal neuroimaging. Babies with HIE stage I had normal neuroimaging findings. All babies with severe birth asphyxia should be screened with USG and then with MRI Brain at 6 weeks of age so that neurodevelopmental outcome of the child can be predicted.

Of the 26 babies with antenatal and intrapartum risk factors, 1 baby had HIE stage III, 22 babies had HIE stage II and 3 babies had HIE stage I. There is significant association ($p=0.42$) between antenatal risk factors and stages of hypoxic ischemic encephalopathy. Of the 7 babies with abnormal neuro developmental outcome, 6 babies had HIE stage II, 1 baby had HIE stage III.

All the 9 babies with HIE stage I have normal neurodevelopmental outcome at 6 months. Of the 50 babies, 15 babies had stayed in the hospital for more than 10 days and of the 15, 5 babies had abnormal neurological outcome. There is significant association ($p=0.10$) between the duration of hospital stay and the abnormal neurological outcome.

Of the 50 babies, both the babies with HIE stage III had apgar 4 to 6 with moderate asphyxia. Both the babies with Apgar of 7/10, had HIE stage I. Babies with severe asphyxia with Apgar of <3, had HIE stage II. 7 babies

with moderate asphyxia had HIE stage I, 35 babies had HIE stage II. There is significant association (p=0.34) between the Apgar score and HIE stages.

Table 1: Early markers predicting neurological outcome.

	Mean	S.D	Statistical inference
Hospital stay			
Normal (n=43)	9.95	4.237	T=-3.551; Df=48; 0.001<0.05; Significant
Abnormal (n=7)	16.57	6.451	
wt3			
Normal (n=43)	4.7512	0.65151	T=1.810; Df=48; 0.077>0.05; Not significant
Abnormal (n=7)	4.2714	0.64217	
wt6			
Normal (n=43)	6.4488	0.62654	T=2.433; Df=48; 0.019<0.05; Significant
Abnormal (n=7)	5.8143	0.72670	
hc3			
Normal (n=43)	38.60	1.050	T=3.118; Df=48; 0.003<0.05; Significant
Abnormal (n=7)	37.29	0.951	
hc6			
Normal (n=43)	41.28	0.826	T=6.131; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	38.57	2.149	
Adductor3			
Normal (n=43)	79.30	3.377	T=5.381; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	64.29	17.182	
Adductor6			
Normal (n=43)	110.47	3.050	T=8.890; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	92.86	11.127	
Popliteal3			
Normal (n=43)	89.77	1.525	T=9.235; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	75.71	9.759	
Popliteal6			
Normal (n=43)	119.53	3.050	T=11.878; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	95.71	11.339	
Heel-ear 3			
Normal (n=43)	89.30	2.578	T=7.920; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	75.71	9.759	
Heel-ear 6			
Normal (n=43)	119.30	4.021	T=10.528; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	95.71	11.339	
Scarf sign 3			
Normal (n=43)	2.00	0.000(a)	T - Test not applicable
Abnormal (n=7)	2.00	0.000(a)	
Scarf sign 6			
Normal (n=43)	1.02	0.152	T=-10.467; Df=48; 0.000<0.05; Significant
Abnormal (n=7)	1.86	0.378	
Dorsiflxn 3			
Normal (n=43)	60.47	2.131	T=-.985; Df=48; 0.330>0.05; Not significant
Abnormal (n=7)	61.43	3.780	
Dorsiflxn 6			
Normal (n=43)	68.14	4.502	T=.537; Df=48; 0.593>0.05; Not significant
Abnormal (n=7)	67.14	4.880	

5 babies with abnormal neurodevelopmental outcome had microcephaly. There is significant association ($p=0.000$) between microcephaly with the abnormal neurodevelopmental outcome.

DISCUSSION

50 babies were followed up till 6 months of age. Incidence of abnormal neuro developmental outcome was 14%. In the study conducted by Baburaj et al, developmental delays due to birth asphyxia was 16.7%.⁸ In another study conducted by Padayachee et al, 11.5% had cerebral palsy and 5.3% had developmental delay.⁹

Follow up was done till 6 months of age as abnormal neurological outcome can be detected early as early as 3 months and starting early intervention can improve the outcome. In a study conducted by Zafar Meenai et al, developmental delay was found in 9.5% of the healthy children as early as 3 months of age using Trivandrum development screening chart and 15% were due to birth asphyxia.¹⁰

There is significant association between the low Apgar score and HIE stages with a p value of 0.034. Babies with Apgar score of 4 to 6 went in for HIE stage III and babies with Apgar score of <3 at 5 minutes had HIE stage II. This implies that Apgar score of 4 to 6 also still needs vigorous resuscitation to improve Apgar score at 10 and 15 min so that severity of encephalopathy can be reduced.

In a study conducted by Misra et al, shows that outcome of babies with low 5 minute Apgar scores was significantly better than those with the same scores at 10 minutes.¹¹ Symptomatic neonates when compared to asymptomatic neonates with same Apgar score showed significantly poorer outcome.

In a study conducted by Gonzalez de Dioz et al, there was a significant association between severity of perinatal asphyxia and neurologic sequelae (RR =2.82).¹²

There is significant association of antenatal risk factors with the severity of HIE stages with a p value of 0.42. Prolonged II stage of labour is the predominant risk factor in this study (34%).

The next predominant risk factor was MSAF (10%). 48% had no antenatal risk factor, this suggests that proper antenatal care with regular antenatal visits should be done to identify the risk factor, and continuous CTG monitoring is essential to detect fetal distress early.

In a study conducted by Kaye et al, antenatal risk factors identified were ante partum hospitalisation, anaemia, ante partum haemorrhage, preeclampsia, and augmentation of labour with oxytocin, MSAF, instrumental delivery and malpresentations.¹³

There is significant association of HIE stages with the abnormal neuro imaging suggesting that severe birth asphyxia with HIE stage III have undergone severe neurological damage with hypoxic ischemic changes seen in the neuro imaging. In a study conducted by Anand et al, none of the babies with HIE stage III had normal scan, and neurosonogram findings correlated well with the stage of HIE.

6 babies of the total 50 babies have abnormal neuroimaging and there is significant association between the neuroimaging and the outcome with the p value of 0.000, suggesting that neuroimaging is an important predictor of neurological sequelae. This finding is similar to the result of a study conducted by Khaled Abdulqawi et al where cranial ultrasound found to have a positive predictive value of 78% and negative predictive value of 58.3% respectively.¹⁴ Neuro imaging correlated well with the abnormal outcome and severity of HIE stages.

Duration of stay in the hospital also predicts abnormal neurodevelopmental outcome as there is significant association with a p value of 0.014. This is similar to the study done by Carli Get al, which showed the significant association between duration of hospital stay and the adverse outcome.¹⁵

There is significant association between seizures and microcephaly with abnormal neuro developmental outcome with p value of 0.000 making recurrence of seizures and slow head growth, important predictors of cerebral palsy.

Amiel Tison angles-adductor angle, popliteal angle, heel to ear sign, scarf sign measured at 3 months and 6 months correlates with the developmental delay. In a study done by Elenjickal et al, correlation between abnormal tone and developmental delay was highly significant.¹⁶ In another study conducted by Godbole et al early predictors of neurodevelopmental outcome were identified as absence of social smile, abnormal neuro behaviour at 3 months and absent pull to sit position, absent voluntary reach and transfer of objects at 6 months.¹⁷

The difference in mean of the weight at 6 months between the normal and abnormal babies is statistically significant. Hence failure to gain weight/failure to thrive is an important predictor of neurodevelopmental outcome.

The mean adductor angle at 3 months was 77.2 which increased to 108 at 6 months. The mean popliteal angle was 87.8 at 3 months and 116.2 at 6 months. In a study done by Chaudhari et al, the mean adductor angle increased from 84.8 at 3 months to 126.6 at 12 months and the mean popliteal angle increased from 100.6 at 3 months to 136 at 12 months.¹⁸

In this study, an attempt was made to detect abnormal neuro behaviour at an early age so that early intervention could be started to improve the outcome. Abnormal tone can be detected at 3 months itself by Amiel Tison passive angles and microcephaly at 3 months by measurement of head circumference. Therefore, proper counselling of the parents regarding the follow up visits should be done to detect abnormalities early. These high-risk babies are followed up even after 6 months to detect subtle neurological abnormalities later.

Limitations of the study should not be over looked. Perinatal risk factors for all the babies could not be studied as continuous CTG monitoring was not done for all the deliveries and administration of oxytocin for acceleration of labour was not recorded.

The mean gestational age of the babies studied was 38 weeks. Hence, the study could be applied only to full term new born babies and further analysis is required to understand the impact of HIE on pre-term babies.

Long term follows up of these babies is necessary to detect subtle neurocognitive abnormalities as the follow up in this study was done only for six months.

CONCLUSION

The incidence of abnormal neurological outcome was 14%, abnormal tone-14%, developmental delay -12%, seizures -12% and microcephaly -12%. The early markers predicting neurologic sequelae identified-antenatal risk factors, low Apgar scores, hypoxic ischemic encephalopathy, duration of hospital stay, slow head growth, abnormal tone, abnormal neuroimaging, recurrent seizures and weight at 6 months of age. It could be inferred from the study that abnormal neurological outcome could be predicted as early as 3 months of age. Hence, early stimulation could be started to improve the outcome. Long term follows up of all these babies is needed to detect subtle neurocognitive abnormalities.

ACKNOWLEDGEMENTS

Authors would like to thank babies and their parents involved in the study. Authors would cardinally thank the Dean of KAPVGMHC, Trichy and the District Early Intervention Clinic MGM GH, Trichy for their entire support in the follow up of babies with birth asphyxia.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Nazeer S, Senthilkumar K, Thangavel A, Uma Maheswari M. Neurodevelopmental outcome of babies with hypoxic ischemic encephalopathy. *Int J Res Med Sci* 2017;5:3197-203.