Original Article
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Paediatrics Section

Cranial Colour Doppler and Electroencephalogram as Early Prognostic Markers in Babies with Hypoxic Ischaemic Encephalopathy: A Prospective Cohort Study

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ABSTRACT

Introduction: Birth asphyxia continues to be a leading cause of neonatal morbidity and mortality globally. Early detection of ischaemic changes through Doppler ultrasound and Electroencephalography (EEG) may play a crucial role in prompt management, timely referral and effective parental counseling.

Aim: To evaluate role of Cranial colour doppler and EEG background activity in prediction of short and long-term outcome in term newborn with Hypoxic–Ischaemic Encephalopathy (HIE).

Materials and Methods: The present prospective cohort study was carried out in S.S. Medical College and SGM Hospital in central India during January 2020 to June 2022. A total of 71 full term neonates with HIE gone through Cranial Doppler and conventional EEG minimum for 1 hour within 6 hours of birth. Hammersmith Neonatal Neurological Examination (HNNE) was performed at the time of discharge and neurodevelopmental assessment at follow-up visit was done using Hammersmith Infant Neurological Examination (HINE) and Developmental Assessment Scales for Indian Infant (DASII). Association between EEG background activity and HNNE score, HINE score and neurodevelopmental outcome (cerebral palsy, epilepsy and developmental delay) was calculated. Chi-square test and Analysis of Variance (ANOVA) test was done and p-value <0.05 was considered significant.

Results: Among babies with abnormal Doppler scan, 26 (92.8%) have bad short-term outcome, similar result were seen with abnormal Doppler and abnormal EEG in which 26 (94%) and 11 (84%) have bad short-term outcome (abnormal HNNE) respectively. After combining all modalities 23 (100%} babies showed bad outcme on short-term basis with p-value <0.05. Mean HNNE and HINE score was significantly lower (p-value=0.001) in newborns with abnormal doppler and severely abnormal EEG as compared to normal Doppler and normal EEG group. A severely abnormal EEG at birth was significantly associated with cerebral palsy (p-value=0.0005), epilepsy (p-value=0.04) and developmental delay (p-value=0.001).

Conclusion: Cranial colour doppler with EEG within 6 hours of birth in term HIE babies had high sensitivity and negative predictive value in predicting neurodevelopmental outcome.

Keywords: Cerebral palsy, Developmental delay, Epilepsy, Neurodevelopmental outcome

INTRODUCTION

The HIE is one of the most common cause of neonatal mortality and morbidity globally; it accounts for 26 out of every 1000 live births in developed and developing country respectively. In US population incidence of perinatal HIE was 1.7 per 1000 [1-3]. In India, estimated incidence of birth asphyxia is 12-16% [4]. In newer study the incidence was 5.26% that is, 92 out of 1749 live births in northern India [5].

Traditionally, the severity grading of HIE along with advanced neuroimaging techniques like Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) has been utilised to assess the extent of cerebral injury during the neonatal period and to predict long-term neuromotor outcomes. However, the grading of HIE alone is not always reliable for prognostication and advanced imaging modalities are often not readily available in many neonatal care units in resource-limited settings such as India. Moreover, performing such investigations in clinically unstable neonates during the immediate postnatal period is frequently not feasible [6]. The EEG has been extensively used for the diagnosis of neonatal seizures and for monitoring of neonates on antiseizure therapy [7]. A previous study have shown that EEG provides excellent predictive value for both short-term and long-term outcomes in infants with HIE, with good sensitivity. In addition, cranial colour Doppler has emerged as a valuable tool in evaluating the neurological prognosis of HIE-affected neonates [8]. It is a cost-effective, non invasive and easily accessible modality that can be initiated very early, even immediately after birth, making it particularly suitable for low-resource settings [9].

The above mentioned modalities have been studied separately in past for prognostication of HIE in babies [10-12]. In a study by Alfaifi J, cranial USG played crucial role in treatment for HIE [10]. Similar study done by Annink KV et al., showed validated Cranial Ultrasonography (CUS) scoring system is associated with neurodevelopmental outcome in neonates with HIE [11]. A study by Bourel-Ponchel E et al., showed that cranial EEG is also important tool for HIE prognostic value [12]. These previous studies focused mainly on EEG and Doppler separately, in present study combined use of cranial colour doppler and EEG with structured neurological examination was used. Early detection of ischaemic changes from Doppler and EEG will provide timely management, referral and parental counseling regarding HIE.

The combined use of cranial colour doppler and EEG with structured neurological examination may have a better sensitivity and predictive value for outcome of HIE babies. Hence this study aimed to assess the role of cranial color doppler as early prognostic marker of babies with HIE short-term and long-term outcome and also to investigate the role of EEG background activity and its severity in HIE short-term and long-term outcome.

MATERIAL AND METHODS

The present prospective cohort study was conducted at S.S. Medical College and SGM Hospital, Rewa in central India during January 2020 to June 2022. This study was approved by the Institutional Ethics Committee (IEC) Shyam Shah Medical College, Rewa, Madhya Pradesh, India (No. 4249/SS/PG/MC/2020).

Inclusion criteria: Neonates with following: (a) Gestational Age (GA) of 37-42 weeks, postnatal age <6 hours, © any one of the following: Foetal distress at delivery, need for resuscitation at birth or Apgar score <6 at 5 min, metabolic acidosis PH <7.1 or base deficit >10.8 [13] were included in the study.

Exclusion criteria: Babies with congenital heart disease and other major congenital anomaly inborn errors of metabolism; genetic syndromes were excluded from the study.

Sample size: The present study included 71 neonates admitted for HIE in Neonatal Intensive Care Unit (NICU) of tertiary care centre within the study duration.

Data collection: Parents of infants who met the inclusion criteria were approached and written informed consent was obtained. EEG was performed for all enrolled neonates within 6 hours of birth using an RMS electronic EEG machine. Each recording lasted a minimum of one hour and electrode placement followed the International 10-20 system, modified appropriately for neonates [10].

The EEG background activity was classified into three categories based on previously established criteria, with modifications according to the updated American Clinical Neurophysiology Society (ACNS) guidelines. Interpretation was done by a trained paediatric neurologist experienced in neonatal EEGs [10,11]:

- **Normal/mildly abnormal:** Continuous background activity with minor abnormalities such as mild asymmetry, slight voltage depression, or poorly defined sleep-wake cycling.
- **Moderately abnormal:** Discontinuous activity with interburst intervals of around 10 seconds, absence of clear sleep-wake cycling and evident asymmetry or asynchrony.
- **Severely abnormal:** Discontinuous background with interburst intervals ranging from 10 to 60 seconds, severe attenuation of background activity and absent sleep-wake cycles.
- **Isoelectric EEG:** Background activity with interburst intervals greater than 60 seconds.

Cranial color doppler was conducted within 72 hours of birth [12]. A 2-5 MHz convex or phased array transducer of a computed sonography system was used. The transducer was positioned between the eye socket and the ear, just above the zygomatic arch, to capture flow signals from the Middle Cerebral Artery (MCA). Haemodynamic parameters such as Pulsatility Index (PI) and Resistive Index (RI) of the right MCA were recorded. In this study, an RI <0.50 or >0.90 and a PI <1.0 were considered abnormal and indicative of cerebral hypoxia [13,7].

Many tools are available for neurological follow-up of newborns, among them, the HINE has emerged as one of the most reliable and easy-to-use methods for early detection of neurological impairments in both high-risk and low-risk infants [14,15]. It can be effectively administered even by trained non specialist staff [16]. The HINE evaluates several neurological domains, including cranial nerve function, posture, spontaneous movements, muscle tone, primitive reflexes and behaviour. Beyond identifying motor deficits, it also provides valuable insight into the type and severity of overall neurological dysfunction [15]. An optimality score is calculated by comparing the infant's scores to those typically observed in a normal population, with scores occurring in at least 90% of healthy infants considered optimal. The total score ranges from 0 to 78. At 9 and 12 months of age, a score of ≥73 is considered optimal, while scores below 73 are regarded as suboptimal [15].

Neurodevelopmental assessment was done using the Developmental Assessment Scale for Indian Infants (DASII) by a single trained examiner at the time of admission, prior to initiation of any intervention. DASII is an Indian adaptation of the Bayley Scale of Infant Development and consists of two components: a motor scale with 67 items and a mental scale with 163 items. It is suitable for evaluating children up to the age of 30 months [17]. After assessing the infants, the Motor Development Quotient (MoDQ) and Mental Development Quotient (MeDQ) were calculated according to the DASII manual. A developmental delay was defined as a Development Quotient (DQ) of ≤70, which corresponds to 2 standard deviations below the mean in either the motor or mental domain [18,19]. Furthermore, the infants from both groups were categorised based on the degree of delay as follows:

- Mild delay: DQ 51-70
- Moderate delay: DQ 36-50
- Severe delay: DQ ≤35

Short-term outcome assessment: At the time of discharge, short-term outcome was evaluated. A poor outcome was defined as either neonatal death or a suboptimal score on the HNNE. The HNNE was conducted and optimality scores were calculated for each domain (e.g., posture, tone, reflexes, movements, behaviour) as well as a composite score by summing all component scores. A composite score greater than 30.5 was considered optimal, based on criteria established by the scale developers [20]. In addition to the composite score, individual items were also analysed for suboptimal scores, using specific cut-off values provided in the original HNNE scale guidelines. Any infant who either died during the neonatal period or had a suboptimal composite HNNE score was classified as having a poor short-term outcome [20].

Long-term outcome: On follow-up from 3 months to 9 months of age visit, HINE was performed and age specific cut-off value was used to categorise optimal and suboptimal specific for age [21]. DASII scale (Indian modification of Bayley's scale for infant development) was used for developmental assessment and MoDQ and MeDQ was calculated. A DQ <70 was considered as delayed. Average of mental development quotient and motor development quotient <70% was considered abnormal [22]. On the basis of clinical history and EEG–doppler, on follow-up epilepsy and cerebral palsy was diagnosed. Patients having clinical features of cerebral palsy were diagnosed and classified accordingly [23]. Tone assessment was done using modified Ashworth scale [24]. An abnormal long-term outcome was defined as abnormal HINE, DASII, presence of CP or Epilepsy.

STATISTICAL ANALYSIS

The association of cranial colour doppler findings (classified as hypoxic or normal) and EEG background activity (categorised as normal/mildly abnormal, moderately abnormal and severely abnormal) was analysed with respect to the following outcomes: mortality, HNNE score (optimal/suboptimal), HINE score (optimal/suboptimal), cerebral palsy, epilepsy and developmental delay. Categorical variables were assessed using the Chi-square test, while continuous variables were analysed using ANOVA and Student's t-test, as appropriate. Data analysis was conducted using Statistical Package for the Social Sciences (SPSS) software, version 18.0. The predictive utility of early neonatal EEG was evaluated by calculating the Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity and specificity based on binary classification of outcomes. A p-value of <0.05 was considered statistically significant.

RESULT

General baseline characteristics of subjects are listed in [Table/Fig-1]. A total of 71 neonates were enrolled for study out of which 47 were discharged and 28 babies came for follow-up. Out of them 53 (74.6%) were male and 18 (25.4%) were female, 53 neonates belong to rural population and remaining 18 belongs to urban and 57 (80%) neonates belongs to joint family.

Characteristics	n (%)		Survivors n=47	Non survivors n=24
Gender				
Male	53 (74.6)		35	18
Female	18 (25.4)		12	6
Mean gestational age (weeks)	38.15±0.74		38.15±0.74	38.25±0.79
Socio-economic status				
Lower	1 (1.87)		1	0
Lower middle	41 (57.75)		26	15
Upper lower	11 (15.49)		6	5
Upper middle	18 (25.35)		14	04
Residence				
Rural	53 (74.7)		33	20
Urban	18 (25.3)		14	04
Joint family	57 (80.3)		35	22
Nuclear family	14 (20)		12	02
>4 Number of family member	53 (74.7)		32	21
<4 number of family member	18 (25)		15	03
Mode of delivery				
NVD	59 (83.1)		38	21
LSCS	12 (16.9)		9	3
>1 Birth order	37 (52.1)		22	15
Antenatal complication	16 (22.5)		12	4
Mean Birth weight M±SD	3.1±3.2		3.18±0.24	3.16±0.28
EEG finding, n (%)	Mildly abnormal	36 (50.7)	29	7
	Moderately abnormal	13 (18.3)	8	5
	Severely abnormal	22 (31.0)	10	12
Abnormal Doppler finding, n (%)		28 (39.4)	12	16
Mean±SD duration of stay (days)			4.7±0.55	4.7±0.65
Outcome n (%)	Discharge	47 (66.2)	47	0
	Death	24 (33.8)	0	24

[Table/Fig-1]: General characteristics of the patients.

The results of the cohort study reveal a strong association between abnormal EEG and Doppler findings with adverse patient outcomes. In the short-term analysis, individuals with severely abnormal EEG results had a 100% incidence of bad outcomes, while moderate abnormalities led to bad outcomes in 85% of cases. Similarly, abnormal Doppler results significantly predicted poor outcomes, with 93% of individuals exhibiting adverse effects. The combined presence of abnormal EEG and Doppler findings further exacerbated the risk, indicating a 100% probability of bad outcomes. These association were statistically significant, as evidenced by p-values less than 0.0001 for both EEG and Doppler results independently predicting short-term outcomes [Table/Fig-2].

		Good outcome	Bad outcome	p-Value
EEG n (%)	Mild n=36	22 (61%)	14 (39%)	<0.001
	Moderate n=13	2 (15%)	11 (85%)	
	Severe n=22	0	22 (100%)	
Doppler Results n (%)	Normal n=43	22 (51%)	21 (49%)	<0.001
	Abnormal n=28	2 (7%)	26 (93%)	
Doppler and EEG both abnormal n=23 (%)		0	23 (100)	<0.001
HNNE (at the time of discharge)				
Suboptimal		-	23	
Optimal		24	-	

[Table/Fig-2]: Short-term outcome of the studied cohort.

Long-term outcomes mirrored these trends, where severe EEG abnormalities consistently resulted in 100% bad outcomes. However, the doppler findings showed a less pronounced effect on long-term prognosis compared to the short-term results. The statistical significance of these observations was robust for EEG abnormalities (p-value <0.001) as well as for Doppler results in the long-term outcomes (p-value=<0.001) [Table/Fig-3,4]. Furthermore, the sensitivity, specificity and predictive values of these markers were significant. For example, the combined assessment of EEG and Doppler in predicting short-term outcomes showed a sensitivity of 78.7% and a specificity of 67%, with a positive predictive value of 82.2%. These diagnostic markers are crucial in determining the prognosis and guiding the clinical management of patients in both short and long-term scenarios [Table/Fig-5].

The study reveals significant neurological outcomes among infants with severe EEG abnormalities in the neonatal period, where 100% subsequently developed epilepsy during long-term follow-up and 70% were diagnosed with cerebral palsy upon follow-up. Additionally, all infants who developed epilepsy had hypoxic changes in their Doppler results at birth [Table/Fig-6]. The data also shows differing developmental outcomes related to Doppler results at birth: only 16.67% of those with abnormal Doppler findings achieved a Developmental Quotient (DQ) above 70%, while 83.33% scored below 70 [Table/Fig-7].

DISSCUSSION

The present study highlights crucial relationships between EEG findings, Doppler results and patient outcomes over both short-

		Good outcome, n (%)	Bad outcome, n (%)	p-value
EEG n (%)	Mild	12 (80)	3 (20)	<0.001
	Moderate	0	3 (100)	
	Severe	0	10 (100)	
Doppler Results n (%)	Normal	10 (52.6)	9 (47.4)	<0.001
	Abnormal	2 (22.2)	7 (77.8)	
EEG and doppler abnormal n (%)		4 (22.2)	14 (77.8)	<0.001
HINE score				
Optimal		12 (42.8)	-	-
Suboptimal		-	16 (57.2)	
DASII				
Normal		11	-	-
abnormal		-	17	

[Table/Fig-3]: Long-term outcome of the studied cohort (n=28).

		Survivors n=47	Non survivors n=24
EEG n (%)	Mild	29 (61.7)	7 (29.2)
	Moderate	8 (17)	5 (20.8)
	Severe	10 (21.3)	12 (50)
Doppler Results n (%)	Normal	35 (74.5)	8 (33.3)
	Abnormal	12 (25.5)	16 (66.7)
Doppler and EEG both abnormal n=23 (%)		9	14
HNNE			
Suboptimal		23	0
Optimal		24	0

[Table/Fig-4]: Short-term outcome of the studied cohort in survivors and non survivors.

	Sensitivity	Specificity	PPV	NPV
Short-term outcome				
EEG	70.2	91.7	94.3	61.1
Color doppler	55.3	91.7	92.8	51.2
Combined	78.7	67	82.2	61.5
Long-term outcome				
EEG	81.3	100	100	80
Color doppler	62.5	83.3	93,3	62.5
Combined	100	75	84.2	100

[Table/Fig-5]: Markers for poor long-term and short-term outcome.

term and long-term periods. Abnormal EEG results, especially severe cases, are strongly correlated with negative outcomes, a pattern that holds true in the analysis of doppler results where abnormal findings are similarly linked to poorer health outcomes. This relationship is further quantified through statistical significance in the data, underscoring the reliability of these diagnostic tools in predicting patient prognosis. Additionally, the assessment of sensitivity, specificity and predictive values for both EEG and Doppler indicates their effectiveness for predicting short-term outcomes and when combined with HNNE scores they had excellent predictive capability for long-term outcomes also.

Hamelin S et al., [25] concluded that worse EEG background categories associated with unfavourable neurologic outcome. Previous studies [26] concluded that patients having normal/mildly abnormal EEG at

Cerebral palsy	EEG finding: Normal/Mildly abnormal n (%)	Moderately abnormal n (%)	Severely abnormal n (%)	Total no. of patients	p-value
Yes	0	2 (66)	7 (70)	9	0.0005
No	15 100)	1 (34)	3 (30)	19	
Total no. of patients	15 (100)	3 (100)	10 (100)	28	
Epilepsy	**EEG finding: Normal/Mildly abnormal n (%)**	**Moderately abnormal n (%)**	**Severely abnormal n (%)**	**Total no. of patients**	**p-value**
Yes	0	0	3 (100)	3	0.04
No	15 (60)	3 (12)	7 (28)	25	

[Table/Fig-6]: There were statistically significant association between Epilepsy and cerebral palsy with EEG abnormality of Neonates, with p-value (p<0.05).

Development quotient (DQ) (n=28)	Doppler abnormality: Normal (n=16)	Hypoxia (n=12)	p-value
Mean±standard	78.69±16.49	54.57±21.31	0.0023
No. of patients with low DQ (<70%)	07 (43.75%)	10 (83.33%)	0.0371
No. of patients with normal DQ (>70%)	09 (56.25%)	02 (16.67%)	

[Table/Fig-7]: There were statistically significant difference according to association between development quotients With Doppler abnormality of Neonates, with p-value (p<0.05).

birth had a excellent PPV for normal long-term outcome similar to results of present study. A structured review by Awal MA et al., also concluded a sensitivity of 87 for severe EEG predicting poor outcome [27] which was also seen in present study. Colour doppler was also used as predictor for outcome of HIE babies in previous studies with good sentivity and specifity by Guan B et al., [28].

Though EEG and colour doppler are good enough in predicting outcome of HIE babies, combining both modalities increased the sensitivity and predictive values for short-term in previous studies Enhesari A et al., [29]. EEG and colour doppler alone has been studied as a prognostic marker for long-term outcome of HIE babies with good sensitivity like in Murray DM et al., and Wazir S et al., [30,31] present study proves that in combination with colour doppler and structured neurological exam at birth significantly improves sensitivity for prediction of outomes.

Limitation(s)

Major limitation was small sample size; lack of continuous EEG monitoring and poor follow-up rate of patients which maybe attribute to Coronavirus Disease-2019 (COVID-19) pandemic during period of study.

CONCLUSION(S)

Present study concludes that combined use of EEG, Doppler and structured neurological examiantion in term HIE babies had improved sensitivity and NPV predicting short and long-term outcome in babies with HIE. Henceforth in order to predict outcome of a asphyxiated newborn for early intervention and better utilisation of resources in developing countries like India a bed side EEG and cranial colour doppler is very useful tool.

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