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Original Research Article

To Study the Clinical Spectrum of Hypoxic Ischemic Encephalopathy and Its Correlation with CK-MB Assay and Electrocardiography in Newborns at Nalanda Medical College and Hospital, Patna

Naz Yasmeen[1], Suman Kumari[2], Bir Prakash Jaiswal[3]

[1]Senior Resident, Department of Paediatrics, Nalanda Medical College & Hospital, Patna, Bihar, India
[2]Senior Resident, Department of Paediatrics, Nalanda Medical College & Hospital, Patna, Bihar, India
[3]Professor, Department of Paediatrics, Nalanda Medical College & Hospital, Patna, Bihar, India

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Corresponding author: Dr. Suman Kumari
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Abstract:

Aim: To study the various causes of encephalopathy and their outcome in newborns admitted in NMCH and to evaluate the myocardial dysfunction in neonates having birth asphyxia from the study of electrocardiography (ECG) and creatine phosphokinase muscle brain fraction (CK-MB) assay.

Methodology: All term neonates with features of encephalopathy admitted in the neonatal ICU of Nalanda Medical College & Hospital for a period of 9 months between August 2023 to May 2024 were included. Babies were admitted in the hospital with the evidence of asphyxia indicated by any three of the following: (i) APGAR <3 at 5 minutes. (ii) Meconium stained amniotic fluid (MSAF) (iii) need for PPV for >1 min at birth. Preterm babies, neonates with sepsis or congenital malformation, neonates whose mothers received opioids or any other form of sedation were excluded. After written consent from parents, the demographic details were taken, maternal history, birth events, APGAR score were recorded. Detailed clinical examination and serum CK-MB assay were done at birth, 24 hours and at 72 hours. Chest X-ray to assess cardiomegaly, and electrocardiography and echocardiographic evaluation were done.

Results: During the study period 90 babies were found to be of neonatal encephalopathy. Out of which 82 babies had hypoxic encephalopathy. Of 82 cases, 35(42.7%) were in mild, 27(32.9%) in moderate and 20(24.4%) belonged to severe HIE. Further 82 babies with HIE were evaluated for transient myocardial ischemia. MSAF was commonly associated with HIE. Common complications were shock and respiratory failure. Mortality was observed to be 31.7 % in cases of HIE. Cardiomegaly in CXR, ST depression in ECG, Tricuspid Regurgitation (TR) in ECHO, and elevated CK- MB were commonly detected in babies with transient myocardial ischemia.

Conclusion: Hypoxic ischemic encephalopathy is the most common cause of neonatal encephalopathy. Routine ECG monitoring of asphyxiated babies helps to detect myocardial dysfunction and hence the identification of shock. Assay of cardiac enzyme markers CPK-MB helps to complement clinical evaluation for early identification of shock.

Keywords: Neonatal Encephalopathy, Birth Asphyxia, Transient Myocardial Ischemia, CK-MB.

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Introduction

Neonatal encephalopathy as a result of birth asphyxia is still a haunting problem for developing countries like India. Neonatal encephalopathy refers to an abnormal neurobehavioral state characterized by decreased consciousness and brainstem or motor dysfunction [1,2].

Hypoxic-ischemic encephalopathy (HIE) or birth asphyxia is the primary cause. Additional causes include birth trauma, hypoglycemia, meningitis, and bilirubin encephalopathy, inborn errors of metabolism, central nervous system defects, accidental local anesthetic intoxication, space-occupying lesions, and intracranial hemorrhage [2]. Despite advancements in fetal and perinatal medicine, birth asphyxia remains a significant cause of prolonged hospitalization and mortality due to multiple organ dysfunctions. Survivors often suffer from developmental delays and spasticity. In India, birth asphyxia accounts for approximately 20% of newborn deaths [2,3]. Perinatal asphyxia affects multiple organs, with clinical manifestations appearing gradually. Critical organ dysfunction drastically worsens vital parameters, making early detection in neonatal intensive care units crucial for

reducing morbidity and mortality [4]. Myocardial ischemia in asphyxiated babies is typically transient. Cardiac dysfunction is a common consequence of perinatal asphyxia, with an incidence of 24-60%. Detection methods include clinical presentation, electrocardiography (ECG), echocardiograms, and cardiac enzyme assays (CK-MB, Troponin I) [5]. Recognition of myocardial ischemia in neonates is challenging, and few studies have focused on myocardial dysfunction using these diagnostic tools. Rajakumar et al. demonstrated the utility of C-Troponin assays in evaluating myocardial damage severity and outcomes in perinatal asphyxia. Kanik et al. assessed myocardial dysfunction in neonates with HIE to predict mortality [15,26]. In countries where mothers often present late with obstetric complications, detecting myocardial dysfunction is vital for early treatment and improved outcomes.

Birth asphyxia impairs the exchange of respiratory gases during parturition, leading to adverse effects on the fetus. It can occur in utero, at birth, or postnatally. The incidence varies from 0.5-2% of live births in developed countries and is significantly higher in low to middle-income countries [6[. Birth asphyxia accounts for 20% of perinatal deaths. During an asphyxic event, physiological mechanisms prioritize vital organs (brain and heart) at the expense of others (kidneys, gastrointestinal tract, skin). Despite compensatory mechanisms, asphyxia can progress to HIE, primarily affecting the brain and heart [7]. The brain, heart, kidneys, gastrointestinal tract, and bone marrow are significantly affected by perinatal asphyxia. The degree of multi-organ dysfunction (MOD) predicts whether an asphyxiated neonate will succumb to organ damage or recover completely. HIE, a major concern in asphyxiated neonates, can lead to serious long-term neurological sequelae among survivors [8, 9].

Two-thirds of neonatal deaths occur within the first seven days of life, making early life critical for survival and future health. MODS and failure due to cardiovascular instability, pulmonary dysfunction, hepatic impairment, gastrointestinal disorders, and acute renal failure are common. Myocardial damage in perinatal asphyxia can be determined by raised serum CK-MB and cardiac troponin levels [10]. HIE is a significant cause of morbidity and mortality, with a global incidence of 1-8 per 1000 live births in developed countries and up to 26 per 1000 in developing regions. Survivors often face high rates of disability [11]. Troponin I and T are cardiac-specific markers of myocardial damage. Several studies indicate that troponin-I is a good marker of myocardial dysfunction and early death in infants with HIE. The inotropic score (IS), based on dopamine, dobutamine, and epinephrine dosages, measures postoperative pharmacologic cardiac support and is a potential marker of disease severity and mortality after heart surgery. Studies have shown that CK-MB levels are significantly elevated in asphyxiated infants compared to healthy ones. Elevated CK-MB values within the first hours of life indicate myocardial involvement. However, CK-MB levels return to normal within days. Troponin-I and CK-MB assays provide valuable insights into myocardial damage and can help predict outcomes in neonates with HIE [12,13].

Materials and Methods:

This was a prospective study conducted at a tertiary care centre of a teaching hospital during the period of August 2023 to May 2024. The study was approved by the Ethics Committee and written informed consent was obtained from the parents. Eighty-two neonates at term gestation, who suffered from perinatal asphyxia and progressed to hypoxic ischemic encephalopathy, as defined by Levene staging were included. APGAR score of newborns was evaluated at 1, 5 and 10 minutes and they were resuscitated as per NRP guidelines. Cases with congenital heart diseases, major central nervous system malformations and neonatal sepsis were excluded. All the neonates were managed in NICU as per hospital protocol. They were given oxygen by hood (5–6 l/min), nasal continuous positive airway pressure, mechanical ventilation (based on saturation of oxygen (SpO2) and Arterial Blood Gas findings), intravenous fluids, vitamin K, inotropes (Dopamine, Dobutamine and Adrenaline) and anticonvulsants (Phenobarbitone 20 mg/kg as loading dose, followed by 3–5 mg/kg/day, and Levetiracetam was also added with 20-40 mg/kg loading dose in non-responder to phenobarbitone), wherever required. Feeding was started once patient showed improvement, initially started as nasogastric feeding and then followed by spoon or breast feeding. A 12-lead ECG was recorded and 4 ml of venous blood was collected for cardiac enzymes estimation in each asphyxiated neonates within 72 hours of life. Infants with ECG changes of grade 1 or 2 were diagnosed to have mild, whereas those with changes of grades 3 or 4 were considered to have severe injuries. The grading was done as per criteria defined by Jedeikin et al. Grade1 with flat or inverted T waves on 1 or 2 leads except AVR. Grade 2 with flat or inverted T waves in 3 or more leads except AVR. Grade 3 with flat or inverted T waves in 3 or more leads and either ST depression or elevation >2 mm in at least two chest leads or >1 mm in at least two standard leads, or a Q wave abnormality of duration >0.02 s or amplitude >25% of R wave in one anterior or three related chest leads. Grad 4 - presence of classical segmental infarction with abnormal Q wave and markedly elevated ST segment or complete left bundle branch block. Creatine kinase-MB (CK-MB) was measured by quantitative determination based on immune-inhibition IFCC methodology using semi auto-

analyzer. A chest X-ray was taken in all patients. The serum which was collected from patient were also analysed for other hematological and biochemical investigations like PCV, total and differential leukocyte count, urea, creatinine, sodium, potassium, calcium and blood sugar.

Statistical Analysis

Data was entered into an Excel Spreadsheet and analysed using SPSS Version 20. Using this software, frequencies, percentages, means, standard deviations, chi square test, paired t test, unpaired t test correlation were applied. A 'p' value less than 0.05 was considered significant. Differences in mean of quantitative data among different stages of HIE were compared by Analysis of Variance (ANOVA) and proportions by Chi-Square tests.

Results

The average gestational age of the newborn babies was 37.95±1.34 weeks. Among the 90 cases of NE, there were 40 males and 50 females. Forty-eight (53.33%) babies were inborn and 42 (46.66%) babies were outborn. Out of 90 babies of NE, 82 were selected as having HIE fulfilling the inclusion criteria. Normal vaginal delivery was the most common mode, while breech and vacuum-assisted vaginal delivery were the least common methods. The amniotic fluid color and delivery methods did not affect the development of different stages of HIE.

However, modes of resuscitation and Apgar scores at 1, 5 and 10 minutes were statistically significant among different stages of HIE. Twenty-four (29.3%) neonates required initial steps of resuscitation and in 58 (70.7%) bag and mask ventilation was given. It was switched over to bag and tube ventilation in 6 cases as they required prolonged ventilation, in addition 4 (6.6%) needed chest compression also. The chest X-ray was abnormal and showed features of meconium aspiration in 11 (13.4%) cases and cardiomegaly in 27 (32.9%) cases. ECG changes were observed in 46 (56.1%) neonates; of these 19 (23.2%) had grade I, 13 (15.8%) grades II and III each and 1 (1.2%) grade IV abnormalities. Six neonates with mild HIE while 20 each in moderate and severe HIE had abnormal ECG and changes among different stages of HIE were significant (P = 0.002). The cardiac enzymes levels were considered abnormal when it were above our reference laboratory values (CK Total > 190 U/l, CK-MB >25 U/l and troponin I > 0.05 ng/ml). The serum level of enzyme CK Total was raised in 54 (65.8%), while CK- MB was raised in 52 (63.4%) neonates with marked elevation (> 100 U/L) in 34 (41.5%). Their levels showed further rise with increasing severity of HIE and the severe HIE group had significantly higher level in comparison to mild and moderate HIE cases (P = 0.02, <0.001 and 0.004, respectively). Sixty-one percent babies had normal echocardiogram, while 22 % had decreased LV contractility and rest 17 % had tricuspid insufficiency.

Twenty-six of 82 (31.7%) neonates died during hospital stay between 24 to 264 hours of post natal life. They belonged to moderate and severe HIE stages and needed mechanical ventilation, inotropes and anticonvulsants in addition to other supportive measures. Sixty-eight of the 82 (82.9%) under study neonates developed complications like shock, respiratory failure, acute kidney injury and necrotizing enterocolitis. About 27% of patients died who developed shock, while mortality was 50%, 40% and 100% in babies progressing to respiratory failure, AKI and NEC respectively. Outcome of newborns with HIE in relation to ECG, CK-Total and CK-MB are shown in Table 6. The non- survivors had significantly high proportion of abnormal ECG (p = 0.01), raised levels of CK-MB (p = 0.03) in comparison to survivors. However, no such relationship was observed with CK-Total level in these neonates.

Table 1: Basic characteristics of neonates and HIE staging

Parameters	Categories		HIE Stage		P value
		Mild (n = 35)	Moderate (n = 27)	Severe(n=20)	
Gender	Male	15 (42.9%)	13 (48.1%)	8 (40%)	0.845
	Female	20 (57.1%)	14 (51.9%)	12 (60%)	
Gestational age	Term	21 (60%)	23 (85.2%)	16 (80%)	0.062
	Post dated	14 (40%)	4 (14.8%)	4 (20%)	
Antenatalcomplications	No	32 (91.4%)	18 (67%)	14 (70%)	0.039
	Yes	3 (8.6%)	9 (33%)	6 (30%)	
Obstetric Problems	No	34 (97.1%)	25 (92.6%)	12 (60%)	0.0003
	Yes	1 (2.9%)	2 (7.4%)	8 (40%)	
Birth weight (g)		2826.92±446.1	3111.11 ± 437.94	2875±331.46	0.06
Length (cm)		49.58 ± 2.02	50.3 ± 3.05	49 ± 2.2	0.241
Head circumference (cm)		34.31 ± 1.49	34.07 ± 1.64	33.75 ± 1.25	0.558
Maternal age (yr)		22.62 ± 3.01	24.15 ± 3.98	23.45 ± 4.55	0.521
Maternal weight (kg)		58 ± 8.11	56.07 ± 5.92	58.0 ± 8.4	0.587

The concentrations of serum CK-MB on day 1 and day 3 were found to be statistically highly significant in the asphyxiated group as compared to the control group ($P < 0.001$).

The mean serum CK-MB concentrations in asphyxiated neonates on day 1 were 133.18 ± 265.24 U/L while on day 3 were 73.91 ± 80.67 U/L. Among the infants having HIE, the mean serum value of CK-MB in HIE I, HIE II and HIE III were found to be 59.89±16.54 U/L, 124.27±133.72 U/L and 293.48±522.31 U/L respectively on day 1. On day 3, the mean serum value of CK-MB in HIE I, HIE II and HIE III were found to be 32.70±14.35 U/L, 73.30±69.32 U/L and 156.40±110.09 U/L respectively (Table 3).

The mean values of CK-MB were found to be decreased in different stages of HIE on day 3 as compared to day 1 in asphyxiated neonates.

Table 2: HIE staging in relation to natal factors

Birth Details	Categories		HIE Stage		P value
		Mild(n=35)	Moderate (n=27)	Severe(n=20)	
Liquor	Clear	26 (74.3%)	16 (59.3%)	10 (50%)	0.171
	Meconium	9 (25.7%)	11 (40.7%)	10 (50%)	
Modes of delivery	Normal	27 (77.2%)	19 (70.4%)	14 (70%)	0.782
	Caesarean	8 (22.8%)	8 (22.2%)	6 (25%)	
	Instrumental	0 (0%)	2 (7.4%)	1 (5%)	
Details of resuscitation	Initial steps	10 (28.6%)	13 (48%)	1 (5%)	0.005
	Bag and Mask & Chest compression	25 (71.4%)	14 (52%)	19 (95%)	
Apgar score-1 min		3.26 ± 0.83	3.21 ± 0.64	2.65 ± 0.6	0.008
Apgar score-5 min		5.08 ± 0.49	4.78 ± 0.58	4.5 ± 0.75	0.002
Apgar score-10 min		7.48 ± 0.88	6.95 ± 0.91	5.5 ± 1.25	0.003

Table 3: Comparison of Mean Values of CK-MB on Day 1 and Day 3 in Different Stages of HIE and their Correlation

Stages of HIE	Day 1 Mean ± SD	Day 3 Mean ± SD	r Value	p Value
I (n=35)	59.89±16.54	32.70±14.35	0.757	0.002
II (n=27)	124.27±133.72	73.30±69.32	0.941	0.001
III (20)	293.48±522.31	156.40±110.09	0.978	0.004

Table 4: Abnormality in chest X ray, ECG & Echo

Investigations	Categories	Number of patients	Percentage
Chest X-ray	Normal	44	53.7
	Meconium aspiration	11	13.4
	Cardiomegaly	27	32.9
E.C.G	Abnormal	46	56.1
	Normal	36	43.9
Grading of E.C.G	Grade1	19	23.2
	Grade2	13	15.8
	Grade3	13	15.8
	Grade4	1	1.2
Echocardiogram	Normal	50	60.9
	Deceased LV contractility	18	21.9
	Tricuspid Regurgitation	14	17.2

Table 5: Demography with clinical final outcome

Characteristics	Frequency (%)
Gender	
Male	40 (44.45)
Female	50 (55.55)
Place of birth	
Inborn	48 (53.3)
Outborn	42 (46.7)
Outcome	
Discharged	56 (68.3)

Expired	26 (31.7)	
Encephalopathy due to Asphyxia		
Present	82 (91.1)	
Absent	8 (8.9)	
Complications	**68 (83%)**	**Death (26)**
Shock	36 (52.9%)	10 (27.7%)
Respiratory Failure	20 (29.5%)	10 (50%)
Acute Kidney Injury	10 (14.7%)	4 (40%)
Necrotizing Enterocolitis	2 (2.9%)	2 (100%)

Discussion

Neonatal hypoxia is a common entity occurring as a result of dysfunctional oxygenation of the various organs in the perinatal period. Hypoxic insult is either due to failure of initiation and maintenance of respiration at birth or due to oxygen deficit at tissue level as a result of fetal distress owing to several factors viz. placental insufficiency, chorioamnionitis, placental abruption, metabolic defects. Perinatal asphyxia can lead to various outcomes, from no neurological injury in mild cases to fatality and extensive neurological sequelae in severe cases. Clinical evaluation terms include low 1-minute and 5-minute Apgar scores, decreased consciousness, neuromotor tone abnormalities, and seizures. Hypoxic-ischemic encephalopathy (HIE) refers to brain injury due to impaired cerebral blood flow, diagnosed through biochemical markers, EEG, neuroimaging, or post-mortem findings.

Perinatal asphyxia occurs in 1-1.5% of live births in the West and about 0.5% of infants >36 weeks gestation, contributing to 20% of perinatal deaths. Risk factors include maternal diabetes, hypertension, and fetal growth restriction. Asphyxia primarily results from impaired gas exchange across the placenta, leading to oxygen deficiency and CO2 buildup. This condition affects multiple organs, with kidneys, CNS, heart, and lungs frequently involved. Early detection in NICUs is crucial to reducing morbidity and mortality. Metabolic derangements such as low calcium and sodium levels, thrombocytopenia, and disseminated intravascular coagulation are common. Brain damage from asphyxia manifests as HIE, which can lead to severe neuromotor sequelae if untreated.

HIE severity is classified by Sarnat and Sarnat into three grades: mild (hyperalertness, no seizures), moderate (seizures, lethargy, hypotonia), and severe (coma, frequent seizures, isoelectric EEG). Levene's classification offers a simplified assessment. Cardiac effects include decreased ventricular contractility and myocardial ischemia, with symptoms like tachycardia and congestive heart failure. Myocardial injury is indicated by elevated CK-MB levels and can be confirmed via histological findings.

The Apgar score, although debated for its prognostic value, is useful for immediate assessment and resuscitation effectiveness. Low scores indicate the need for further neurological observation. Conditions like maternal drug use or prematurity can also cause low Apgar scores. The Apgar score and umbilical artery blood pH together predict neonatal death risk, particularly when both are low. Survivors of severe HIE may suffer from long-term complications like mental retardation, epilepsy, and cerebral palsy, while those with moderate HIE have a variable prognosis. Early intervention and coordinated follow-up care are essential for affected infants.

Table 6: Outcome of neonates with HIE in relation to ECG and cardiac enzymes

Parameters	Categories	Survivors (n = 56)	Non-survivors (n = 26)	P value
ECG	Normal	29 (51.8%)	7 (27%)	0.010
	Abnormal	27 (48.2%)	19 (73%)	
CK-Total(U/L)	Normal	19 (34%)	1 (6.3%)	0.674
	Abnormal	37 (66%)	25 (93.8%)	
CK-MB(U/L)	Normal	25 (44.6%)	2 (0%)	0.030
	Abnormal	31 (55.4%)	24 (100%)	

MSAF occurred in 30 (36.58%) neonates with HIE in the present study, while a study by Reddy S et al., reported MSAF in only 8% of deliveries [16]. Some other studies showed incidence of MSAF of around 18 %. The disparity may be due to the differences in inclusion criteria of the study. LV dysfunction and tricuspid regurgitation were the common ECHO findings which was consistent with the studies by Ranjit MS, Omokhodion SI, and Losekoot TG [17, 18]. The mean CK-MB value at day 1 in the current study was133.18U/L (±264.24). In a study by Omokhodion SI and Losekoot TG, the mean value was 16.36 (±3.0) in the immediate postpartum period [18]. Higher

values of 176.1±243and121±77.4 were obtained in studies by Reddy S and Dutta S, and Rajakumar PS et al., respectively [16,15]. In the present study, shock (53%) and respiratory failure (29.3%) were the leading causes of morbidity and mortality in HIE affected babies. A study by Reddy S and Dutta S reported cardiogenic shock in only16% of cases [16], while Rajakumar PS et al., reported congestive heart failure in 36.7% of cases and respiratory failure in 66.7% of cases [15]. In the present study, out of the 82 HIE babies admitted, 26 expired (31.7%). In the study by Rajakumar PS et al., only 16% of babies expired [15].The high mortality in the present study can be attributed to differences in inclusion criteria and high number of outborn cases who were referred from peripheries. Respiratory failure caused death in 50% of newborns with severe respiratory distress, while cardiac dysfunction resulted in only 29 % of cases. This can be attributed to the transient nature of myocardial ischaemia.

Conclusion

Neonatal encephalopathy, particularly due to birth asphyxia, poses significant risks of multi-organ dysfunction and long-term neurological damage. Early detection and management of myocardial dysfunction are crucial for improving survival and reducing long-term sequelae in affected neonates. Continued research and advances in diagnostic tools are essential for better outcomes in neonatal intensive care.

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